TREATMENT OF DIABETES MELLITUS

JOSLIN

(Photo by Bachrach)

Case No. 1469, a Junior in college who celebrated her tenth diabetic anniversary in December, 1927.

Age twenty years. Height 69 inches (175.3 cm.).
Weight 160 pounds (72.7 kilog).

For references, see Case Index.

THE TREATMENT

OF

DIABETES MELLITUS

BY

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TO

GEORGE F. BAKER

BANKER AND PHILANTHROPIST

AND

BY EFFICIENT LENGTH OF DAYS

A STIMULUS TO THE MIDDLE AGED

FOUNDER OF THE GEORGE F. BAKER CLINIC FOR CHRONIC DISEASE

AT THE NEW ENGLAND DEACONESS HOSPITAL

BOSTON, MASS.

PREFACE.

Diabetics and especially diabetic children are here to stay. Years ago I longed to buy them an island or a continent where they could grow up without realizing what they missed, but they would resent such an habitat today, because modern medicine has made them superior to their disease. Furthermore, we should miss them dreadfully, and scientifically we cannot spare them, until we learn how to prevent those complications which their one-sided diet develops both in them and even more subtly in ourselves. Diabetic Utopia, therefore, we want in our midst and I cannot help being happy that one of the islands of that blessed archipelago will be at the New England Deaconess Hospital and near the Harvard Medical School.

The point of view toward the diabetic has changed and in this edition I have tried to present this to the reader. The book has been rewritten, much omitted and replaced, and material added to illustrate how the patient should be treated taking advantage of our newer knowledge. The former edition appeared when insulin therapy was in its infancy; today it approaches stabilization and if in its use the doctor applies intelligently the advances in physiology, chemistry and pathology, as well as the evidence derived from statistics, his cases will seldom be severe or even moderately severe, but can usually be mild. Information from all these sources, therefore, has been brought together to bear upon the problem of treatment. Synthalin, myrtillin, the use of liver, the utilization of exercise, the cultivation of morale and advanced ideas upon diet all receive consideration. In fact, during the last five years whenever I have read, heard or seen anything which I felt would be of value in the treatment of my diabetic patients I have recorded it and later, if on second and third perusal it has seemed worth while, inserted it into this book.

Private statistics foreshadow future public statistics. I have taken the greatest pains, therefore, to transcribe my own records, and hope that others will find the results of the first 3000 cases fully as valuable as those which have been gained from the second 3000. I believe that the accumulation of clinical facts is as important as the presentation of laboratory data, and trust these will be as advantageous to the surgeons, the physicians, the sanitarians and the

medical directors of insurance companies as to diabetics in general. One can see how freely private records have been drawn upon because 895 cases have received individual citation. The purpose of yearly inventories of cases has been to learn which methods of treatment yielded the best results and then to recommend these methods.

The section on children has grown to fifty pages, because children now constitute a vital problem for the doctor's care. Few will question the propriety of the frontispiece, if they count the number of children they know who have survived diabetes ten years. The methods for the prevention and treatment of coma are given *in extenso*, because of the favorable results they have produced. Likewise arteriosclerosis and the plan employed to delay its approach are described and the delicate handling of these only too commonly seen arteriosclerotic patients is given in detail. The routine removal of infected foci, so harmful to the diabetic, and the best methods of accomplishing this are indicated. In short, I have sought to emphasize what hurts the diabetic and what helps him and in each instance to tell how the one state can be avoided and the other secured as demonstrated by the practices followed in the care of my own patients at the New England Deaconess Hospital.

Complications of diabetes were formerly of minor importance, but they are now of major significance. Through the coöperation of many colleagues and friends I have been able to write upon many of these far more extensively than before. Along with the data of my own cases I have sought to include much of the literature, so that this volume might be of greater value for reference, not only to practitioners, but to medical students and all students of diabetes. Certain portions of the book are written as summaries to inveigle the doctor into a search for details. This will explain the unconventional medical diction of "The Diabetes of Today," the story of the Hédon dog, the few pages upon modern diabetic theories and various introductory or concluding paragraphs upon causes of death, coma, gangrene and diabetic surgery in general. In this way I hope I have shown the drift of diabetic thought or at least of my thoughts upon diabetes.

The book is large, but the diabetic patient today, fresh with knowledge based upon his multitude of diabetic primers and manuals, has many queries. The aim has been to provide for all of these questions, so that the doctor will have at his elbow their answers and thus ever be in advance of his patients and so retain their respect.

To all who have lent their aid in the preparation of the present revision I am deeply grateful—the professors who have given me counsel, the doctors and patients who year after year consent to answer my annual letters, the friends who have given me material

aid, and the Editors of *The Boston Medical and Surgical Journal*, of *California and Western Medicine*, of *The Annals of Medicine*, of *The Medical Clinics of North America*, of *The Journal of the American Medical Association* and of *The American Journal of the Medical Sciences*, for the privilege of using sentences and paragraphs with little or no change. I am especially indebted to Professor Hédon and the Editors of the *Journal de Physiologie et Pathologie Générale*, for the photographs of his Montpellier dog and his descriptive words which I have attempted to translate, although every student should consult the original. To the erstwhile students, A. Marble, R. Middleton and R. Miller, to my associates, Drs. H. F. Root, W. S. Curtis and P. White, to Dr. H. Clare Shepardson who read the proof, to Miss H. Hunt and Miss A. McElroy who made the index, to Mrs. M. C. Schmitz who supervised the preparation of the manuscript, to Miss A. Holt who certified the references, to Miss A. Hamblen who made the statistical tables exact, to my secretaries, the Misses G. Sargent, A. Cunningham, A. Warner and M. Bruce, to Prof. E. M. Bailey whose kindness allows the presentation of what is probably the most complete list of diabetic foods yet compiled, and last of all to my kind and long-suffering publishers, I can only offer my heartfelt thanks, for without such assistance there would be no book.

E. P. J.

Boston, Mass.

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TREATMENT OF DIABETES MELLITUS.

SECTION I.

THE DIABETES OF TODAY.

THE outstanding features of the diabetes of today are the prolongation of the lives of diabetic children and the replacement of coma by arteriosclerosis as a cause of death. Diabetes is no longer fatal and the diabetic has ceased to die of his disease. Next in importance are: (*a*) statistically, the increasing incidence of diabetes among women throughout the entire world wherever data are available and the precipitous decline in Massachusetts of deaths from diabetes under the age of fifty years; (*b*) physiologically, the influence of insulin, first upon the storage of glycogen in the muscles as well as in the liver, and second its probable regulation of the katabolism of protein and fat and the formation of sugar therefrom; (*c*) pathologically, the involvement of the whole pancreas in the diabetic process as confirmed by clinical observation on depancreatized dogs and human beings; (*d*) therapeutically, the explanation of what has been empirically the best in treatment in the past by scientific work, the continued efficacy of insulin despite long use, its adequacy in emergencies surgical and otherwise, and the possibility of new medicinal aids in treatment.

In the Naunyn Era children seldom survived the disease for more than two years, but now already their duration of life has trebled and their physical appearance is assurance for the future to practitioner and specialist alike. One cannot look at the happy faces of groups of diabetic children in Boston or at the pictures of similar groups in Vienna without belief that life for them is worth while.

Death is now unusual in the early years of diabetes, particularly in childhood. Of 245 children alive two years ago or seen since only 7, 2.9 per cent, have succumbed to the disease, which is hardly more than 3.4 times the incidence of childhood mortality in the

community at large. So contrary to old conceptions are these facts that it is difficult to become accustomed to the new idea that the diabetic child of today is a living and not a dying diabetic, and that in our program for the treatment of his disease we must plan for many years ahead.

The increased duration of the disease in children has its counterpart in adults between the ages of twenty and fifty years. Indeed, 86 per cent of the patients who died of diabetes in Massachusetts during 1925 were above the age of fifty years.

The significance of the lengthening lives of diabetic children is apparent in various directions. Above all diabetes in a child is pure diabetes untainted by disease in the past and free from the effects of the degeneration of old age. Whatever influence lessens or makes more severe the severity of diabetes in a child should exert a similar effect in older diabetics. Clear inferences can therefore be drawn from treatment of the young while such inferences will always be confused in the old. Then, too, opportunity is offered by diabetes in children to observe the effects produced by the prolonged duration of the uncomplicated disease itself. Finally and best of all, in the child regenerations of the islands of Langerhans should take place far more readily than in the adult, because processes of regeneration and growth go hand in hand with youth, whereas processes of degeneration are the characteristics of senescence.

The danger of growing old, whether diabetic or non-diabetic, is now double what it was in 1860 and hence it is the part of wisdom that all prepare for a long life. Mr. Harold Vanderbilt recognized this and made provision for it in the new dormitory of the Harvard Medical School which bears his name and was opened last fall. In this building he placed a gymnasium to promote the health of doctors-in-the-making. Hitherto in universities interest in exercise ceased with the acquirement of the college degree. Now it is hoped that while these college graduates, our medical students, are acquiring the habit of healthful exercise themselves they will be so impressed with its desirability that later on they will prescribe it for their adult patients. No one worried about the development of old age or arteriosclerosis in the diabetic a generation ago, but today this is the foremost factor in the treatment of the disease, because approximately one-half of those who have diabetes suffer with and ultimately succumb to arteriosclerosis.

Diabetes as its duration lengthens progressively loses its early symptomatology. Many cases after a series of years can scarcely be recognized as true diabetics save from their history, and a doctor unacquainted with this fact might easily doubt the diagnosis or overlook the presence of diabetes. In others the diabetes appears arrested and to the uninitiated suggests a cure. It will not be

strange if diabetes largely disappears from the death certificate, and in fact Miss Hamblen tells me that for six months ending July, 1927, in Massachusetts, exclusive of Boston, 11 per cent of the 340 cases she has so far examined will escape enumeration by international rules of tabulation. These considerations have seemed of enough weight to warrant an investigation of the end-results of treatment in private practice and to discover the causes of death in the fatal cases. As a result of this study definite information has been obtained concerning 94 per cent of all of my patients treated to July 1, 1926, and the causes of death are known for 99 per cent of the 1756 cases who have died. It is this statistical inquiry which permits the statement that whereas in the Naunyn Era over 60 per cent of the diabetics died of coma, today this has been reduced to 10 per cent and arteriosclerosis in its various forms has advanced from 15 per cent to 47 per cent as a cause of death.[1]

Arteriosclerosis in the future, not coma, is the challenge which the doctor must meet. Fortunately for the diabetic, and the non-diabetic, too, the careful methods of study which have been carried out upon diabetics, and especially the peculiar dietetic treatments to which they have been subjected, may be of service not only in the prevention of arteriosclerosis but in deferring the advent of its partner, old age, among diabetics and non-diabetics. In succeeding pages one will meet this arteriosclerotic factor frequently.

New views upon the physiology of diabetes have arisen, stimulated to a large extent by insulin. These views are still in part theoretical, but they have a better basis in fact than the older theories, and though they may change their form again they are of the utmost service to the doctor in his practical treatment of a case. It is only within the last few years that reports of *acutely fatal* diabetes and *complete* diabetes have disappeared from the literature. Today when a diabetic patient dies suddenly we physicians cannot hide our inefficient treatment behind the use of these convenient terms. It is true that these facts in themselves are compelling evidence that the diabetic has not lost all his power to utilize carbohydrate, and it is becoming more and more evident that it is not so much his lack of power to utilize carbohydrate as lack of carbohydrate to utilize. The dog without a pancreas lives upon protein and fat and has a respiratory quotient consistent with that of protein and fat, but if his liver is also taken away, one is confronted with the surprising result that he is living upon carbohydrate, because his respiratory quotient is unity. How can this happen? There is an analogy in the case of the athlete under prolonged and severe strain. He, too, like the depancreatized dog has presumably

[1] No death from diabetic coma occurred between July 1, 1926 and July 1, 1927, among 1241 diabetics traced, constituting 93 per cent of the total seen in that period.

exhausted his meagre carbohydrate store and yet, like the depancreatized dog whose liver has been removed, exhibits a respiratory quotient approaching 1. If I sense the drift of the time in scientific circles, the diabetic is able to burn carbohydrate only in the form of glycogen. Glycogen is all important to the organism and its storage in the liver and muscles is what insulin brings about. Without it the organism is thrown back upon fat and protein to supply bodily needs, and in their metabolism if the sugar resulting therefrom cannot be converted into glycogen and so become available, it is excreted in the urine and the intermediary ketone acids take control, cause acidosis, coma, and death. Insulin has two main functions: (1) the promotion of the storage of glycogen, and (2) although not yet completely proved, the regulation of the premature katabolism of fat. One can almost hear Pflüger say: "I knew it all along," and Geelmuyden echo his words. Insulin, by promoting the storage of glycogen and by preventing the premature breakdown of the fat and protein molecules, allows the patient to take his calories partly in carbohydrate rather than almost exclusively as non-carbohydrate food. This has already led to the prevention of lipemia and may prevent the deposition of cholesterol in the bloodvessels. Furthermore, the importance of the muscles as a storehouse of glycogen is brought to the fore and exercise has now become a rule for the diabetic, not only in his daily occupation, but when confined to bed by a surgical operation. It is as important for a diabetic patient to utilize the glycogen storing power of his muscles as his liver.

The treatment of the diabetic has not been simplified by insulin, but has been made complex. The diabetic taking insulin is like a rapidly moving machine which a slight swerve of the wheel will bring to disaster. This was not true of old-fashioned treatment without insulin. Little changes in treatment then made little differences in condition. The diabetic today must become the master of a more complicated art of diabetic living through knowledge and education.

Knowledge comes from the schools, but wisdom is the gift of the gods, and most of us have had to go to school, the diabetic along with the rest. More and more the schools for diabetics will be in evidence. Already the diabetic school has driven the simple diabetic from the hospital and his bed has been usurped by the diabetic with complications. Class teaching has accomplished this change, and already an aim of the Chemical Foundation is being fulfilled by the diabetic, namely, fewer hospitals rather than more.

The diabetic has made another contribution to medicine in that he has enabled the doctor to absorb the surgeon by bringing him to the medical wards, there to treat his wonderfully interesting complications under medical surroundings. The diabetic has introduced border-line wards of medicine and surgery. Now it is the worst dia-

betic, not the best, who is sought by the hospital, and among these the surgical diabetic heads the list. The surgical diabetic is the serious diabetic, the diabetic who dies. The mortality for surgical diabetics is six times that of medical diabetics and hence they deserve our best care, and that means surgical care in a medical ward.

How dependent the diabetics are upon surgeons! Every other diabetic patient consults a surgeon before he dies, and it goes without saying that every diabetic should have a pathological surgeon after he dies. The surgeon who removes a gall-bladder today little knows how often he prevents the diabetes of tomorrow. To the surgeon a diabetic turns for relief from acidosis. His infection makes his diabetes worse, and it is the surgeon who cures the infection. The physician can tell his patient not to over-eat, but it is the surgeon alone who can prevent the harmful over-eating of hyperthyroidism. As yet the surgeon cannot alleviate atherosis in the heart or brain, but his technical skill already saves a diabetic his legs, and who knows how long it will be before the surgeon will attack the pituitary problem of overgrowth in the prediabetic child. No wonder the doctor and the diabetic welcome the surgeon to the medical wards, because the surgeon is the diabetics' friend.

Dogs without a pancreas, whether they live in Montpellier, France or in Toronto, Canada, require no more insulin today than when it was removed three years ago. If the dose of insulin need not be raised in dogs without any pancreas, why should it be raised in a patient who has some pancreas? Presumably it is not the diseased process itself working in the pancreas which is responsible for an extra demand for insulin by some of our patients, but rather other factors, such as gain in weight and increased diet which insulin itself allows.

Hédon's Dog. I hope the reader will glance at his story and look at his pictures on page 23 and not forget that 668 of my patients went through most of the stages of that dog *except that of recovery*. Fat diabetic dogs in Canada and France have less chance for recovery from coma than thin dogs even with the help of insulin!

Severe diabetes. Is there such an entity? Surely the cases we used to call acutely fatal diabetes and complete diabetes do not represent this state. I cannot call my faithful children severe any more than I would call a diphtheritic case severe when protected by antitoxin. With adjustment of diet these patients usually become manageable, and the more one thinks about them now the more it is manifest that they grew worse in the old days, not because of the disease, but because of your and my honest, but misdirected, dietetic advice. On account of insulin it is hard to find a diabetic who looks severe or whom an audience will believe to be severe. At any rate it is a comfort for a diabetic undergoing proper treatment to

know that he does not look severe and that if rules are followed he will not become severe. The time has arrived when all recognize that diabetes is fatal only from its complications, which in turn are generally avoidable accidents.

Is diabetes curable? At present the verdict is: "Not proven!" But I am wondering what is going to happen to Case No. 632. At the age of thirty he contracted diabetes, and I could not get him sugar-free the next year and only did so the following with fasting. Undernutrition preserved him eight years for the era of insulin which he began when his tolerance for carbohydrate was 15 grams. Now after fifteen years of diabetes his general health is perfect, he is free from glycosuria, free from lipemia, glycemia is almost normal, his insulin is still 22 units, but he tolerates 138 grams carbohydrate. The clinical evidence of regeneration of the pancreas is growing.

THE DEPANCREATIZED DOG.

The Strassburg dog whose pancreas von Mering and Minkowski removed in 1889 taught us the cause of diabetes. In consequence of that epoch-making experiment it was also learned that carbohydrate is formed out of protein in a fairly definite ratio, as shown by the excretion of nitrogen and sugar in the urine, that levulose is the one type of carbohydrate which, when administered to such an animal, will lead to the deposition of glycogen in the liver when other forms fail to do so, and that the factor of safety of the pancreas is so great that more than nine-tenths can be removed before diabetes results.

With dogs in New York Allen increased our knowledge of diabetes still more by demonstrating that they simulated all the features of diabetes in man provided they were partially depancreatized in various states of nutrition. Undernutrition prolonged the life of such animals, whereas overnutrition with any kind of food shortened it. Even acidosis resulted provided the pancreas was largely removed when the previously partially depancreatized animal was fat. In consequence treatment of diabetes became simpler and was put on a more scientific basis.

Now in the age of insulin depancreatized dogs have again come to the aid of the clinician. On this occasion they are the dogs of Macleod in Toronto and of Hédon in Montpellier, France. And what a wealth of information through them has been disclosed for the world's diabetics. The Toronto dogs were depancreatized in November, 1923, and February, 1924; and on September 8, 1923, Hédon depancreatized his dog save for a subcutaneous graft from the tail of the pancreas which in turn was extirpated on January 4, 1924. (Fig. 1.)

Hitherto the life of the completely depancreatized dog was measured by a few days, and his human counterpart by a few years, but already these dogs of Toronto and Montpellier have survived more than half the span of life of their race and remain in good health. Thus they have demonstrated that diabetes in man, which is never quite so complete as in these dogs, builds no barrier to continued existence. What a gift these dogs have bestowed on diabetic mankind through the instrumentality of insulin and its discoverers Banting and Best and their associates Macleod and Collip.

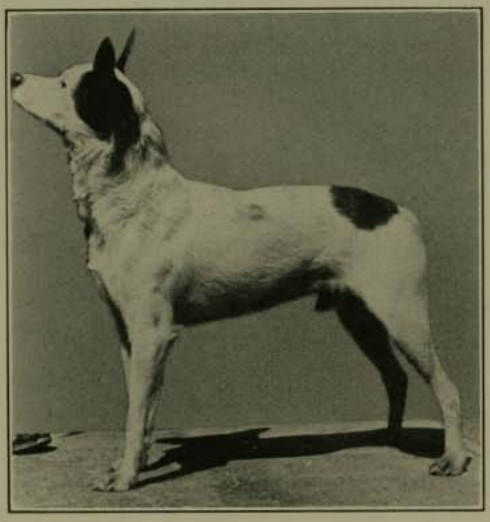


FIG. 1.—Dog. No. 440, April 16, 1924, four months after depancreatization and one hundred days after the beginning of insulin treatment. Weight 7 kilos, appearance normal. Appearance after three months is exactly the same. (After Hédon, Jour. de Physiologie et Pathologie Générale.)

The dosage of insulin which keeps these dogs alive has not been increased or could it be diminished. Insulin therefore does not lose its power in the course of time, but on the other hand no organ of the body can assume the function of the pancreas and produce it. But this is not quite the whole story. Regularity in administration has allowed a gradual reduction in dosage and conversely the dosage had to be notably increased when a deficiency of insulin developed in the body either as a result of insufficient doses or because of voluntary suspension of treatment.

Likewise the character of the diet was important. From the beginning it was evident that when the diet of the Montpellier dog consisted of 25 per cent carbohydrate he was lively, in good spirits and gained weight and strength, but when the ration was exclu-

sively meat the reverse took place. The animal needed carbohydrate and so it came about that for practical purposes carbohydrate and two daily injections of insulin were regulated by permitting a slight glycosuria in order to prevent hypoglycemia.

"The apparently normal condition of these animals, despite the high level to which the blood sugar rises during certain periods of each day (postabsorptive), would seem to contradict the view of clinical observers that hyperglycemia *per se* can be the cause of degenerative changes in the arteries, the kidneys, the eyes, and other tissues. No indications of such changes have been observed, nor do the animals appear to be susceptible to those catarrhal infections which are often observed in dogs kept in confinement." (Macleod.[1]) Professor Hédon writes me that the bloodvessels of his dog show no arteriosclerosis by Roentgen-ray.

Insulin alone, however, does not suffice to protect a depancreatized dog in Canada or France. Such an animal requires trypsin in addition. This he can obtain by eating raw pancreas, or the products of the digestion of casein by trypsin, or the pancreatic juice of another dog with a pancreatic fistula. In this respect the depancreatized dog differs from the human diabetic. The dog has no pancreas but the human diabetic retains pancreatic tissue which still functions though the work of Jones and his confreres has made us aware that it is often lacking in full strength. With a pancreas a dog can live on a meat diet, not so when the gland is removed.

Attempts to treat the depancreatized dog with insulin alone failed both in Europe and America. Fischer was unable to maintain life with his dogs for more than eight months. Such dogs succumb to a fatty degeneration of the liver and arterial atheroma, which Macleod noted occurred more frequently if the animals were fed exclusively with meat, but more slowly when cane sugar was added to the meat diet. The latter attributes these hepatic alterations to improper digestion of protein, because of loss of pancreatic juice and the absorption of toxic substances such as amines. Hédon agrees with him. According to his observations, trypsin must be indispensable to life for if the pancreatectomy has been complete the absence of trypsin not only leads to intestinal putrefaction, but brings about the loss of certain amino-acids such as tryptophan and cystine, as well as others which are known to be indispensable. This would appear to be the explanation for the need of trypsin by these dogs and not that the insulin is toxic either of itself or through the admixture of some impurity. Penau and Simonnet[2] have taken a some-

[1] Macleod, J. J. R.: "Carbohydrate Metabolism and Insulin," Longmans, Green & Co., Ltd., London, 1926, p. 88.

[2] Penau and Simonnet: Acad. de Sciences, Compt. Rend., 1924, **178**, 2208; Ann. des Méd., 1926, **19**, 401.

what different view, and it is possible that a vicarious ferment action can be established in some dogs and not in others.

The failure of lipase contributes to the wasting away of the dog, because the food fat is almost completely eliminated in the feces. The absence of lipase is less important than trypsin because other glands can furnish it and furthermore a totally depancreatized animal can absorb a sufficient fraction of fat from milk. Then, too, it now appears that he can live on his own body fat, which thanks to insulin, in the stage of intermediary metabolism changes to carbohydrate. As for amylase enough can be furnished by the remaining digestive tract. The external secretion of the pancreas, therefore, appears indispensable to life. Although it may not be equal in importance to the internal secretion during a short period at least it is just as important in a long period.

The sexual power of the depancreatized dog persists. The Montpellier dog impregnated various other dogs and in one instance six puppies were born and four developed normally. Sexual power has been noticed also with depancreatized female dogs treated with insulin by Penau and Simonnet, and Macleod and his colleagues. They have not been able to confirm the work of Carlson and Drennan that toward the end of the pregnancy the internal secretion of the fetal pancreas benefited the mother.

Pruritus and alopecia developed at one time in Hédon's dog. He was covered with scratch marks and his hair fell off in large areas. When cystine was added to the diet with flowers of sulphur and later with sodium arsenate the animal was completely cured and the fur came back. (Fig. 2.) From here on I often use Hédon's words.[1]

Later another malady developed probably due to a loss of fat-soluble vitamine and this was xerophthalmia. The conjunctivitis was intense with photophobia and opacity of the cornea although the general state of the animal remained good. This condition healed rapidly when scraps from the kitchen were added, but most of all by the addition of bone. The reappearance of the malady with several tests proved that the organic substances in the bones were responsible for this cure since tricalcium phosphate alone was not effective. Cod-liver oil was not of value, presumably because not absorbed. The disappearance of corneal trouble was striking when the bones were added to the diet and in fact was a matter of only a few hours. (Fig. 3.)

The boulimia was the symptom which showed most clearly that the dog did not have a perfectly normal nutrition. From the beginning of the experiment he never ceased to have an exaggerated appetite. This was greater when on a meat diet when his weight fell below 7 kilos, but it persisted even when he received a mixed diet. He was never satisfied although his reserve of fat deposit was

[1] For ref., see p. 32.

superabundant. The animal was constantly in quest of food remains, licked the floor to obtain any remnant of sawdust, and even swallowed such indigestible objects as paper, cotton, rubber, cork. One would say that his instinct made him seek for some dietary sub-

FIG. 2.—Dermatosis, falling of the hair, in June, 1925. (After Hédon, Jour. de Physiologie et Pathologie Générale.)

FIG. 3.—The animal completely cured of the skin disease and in good general health, but suffering from "xerophthalmia," September, 1925. (After Hédon, Jour. de Physiologie et Pathologie Générale.)

stance which was lacking. Even after feeding he would eat food in immoderate quantities which other dogs would obstinately refuse. This perversion of hunger one often observes in untreated dogs with cachexia, but it is strange to see it in an animal who presents all

the external appearance of health and is living on a mixed diet. Every attempt to overcome it by the addition of various foods and amino-acids failed. One might impute it to hypoglycemia caused by insulin, but that is improbable because the blood sugars were above normal. Furthermore the boulimia persisted in those periods when there was a moderate glycosuria.

So soon as insulin was omitted the latent diabetes returned with full force. In a few days a state of severe acidosis developed which led to coma of typical character from which the animal was rescued while in extremis by the subcutaneous injection of insulin supplemented by the intravenous injection of sodium bicarbonate. On January 29, 1925, thirteen months after depancreatization while

FIG. 4.—The animal in perfect health, three hundred and ninety days after the removal of the pancreas. On this day treatment ceased. (After Hédon, Jour. de Physiologie et Pathologie Générale.)

the animal was in perfect health (Fig. 4) insulin was omitted. The very next day 10 per cent of sugar appeared in the urine accompanied by extreme polyuria and thirst. The diet was then reduced to 400 cc. of milk and 300 grams of meat. On the fifth day 53 grams of sugar were excreted. Although the animal suddenly grew thin he withstood his diabetes very well, but on the fifth day his aspect was completely changed. He was sad and downcast, moved slowly and his muscles were stiff, his appetite was lost and there was difficulty in swallowing. Diacetic acid, granular and fatty casts, and free fat appeared in the urine, as well as albumin

and bile pigment, and it was evident that he was entering into a state of acidosis. The following day these symptoms were such that he refused his food, was no longer able to raise himself, fell

FIG. 5.—Beginning of symptoms, five days after the omission of insulin. (After Hédon, Jour. de Physiologie et Pathologie Générale.)

FIG. 6.—Increased severity the morning of the sixth day. (After Hédon, Jour. de Physiologie et Pathologie Générale.)

into a somnolent state, and finally into a deep coma with slow respiration. He was given injections of insulin, but they were powerless to bring him out of the coma although the hyperglycemia

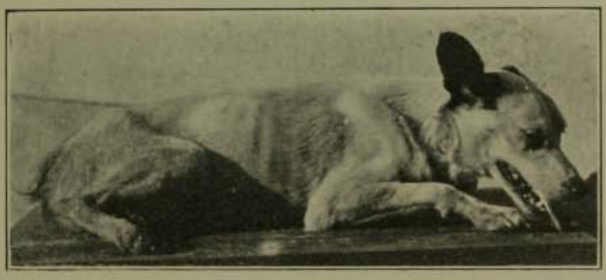


FIG. 7.—Semi-comatose state during the sixth day. (After Hédon, Jour. de Physiologie et Pathologie General.)

FIG. 8.—Complete coma the evening of the same day, notwithstanding the resumption of insulin injections. (After Hédon, Jour. de Physiologie et Pathologie Générale.)

FIG. 9.—The following morning (seventh day) the animal restored by intravenous injections of bicarbonate of soda the preceding night.[1] (After Hédon, Jour. de Physiologie et Pathologie Générale.)

FIGS. 5 to 9.—Development of accidents of acidosis caused by the cessation of treatment.

[1] Figs. 4, 6, 8 and 9 are reprinted from "*Traite de Physiologie normale et pathologue*, t, IV, in preparation, Masson, edit.

and the glycosuria were suppressed. The animal was moribund. The alkaline reserve had fallen to 11 per cent. He was then given an intravenous injection of 2 grams of sodium bicarbonate and the effect was most happy. An immediate amelioration of symptoms was produced which was strikingly apparent to all present. The dog raised his head and became conscious. A second injection a little later reanimated him still more, so that he began to take morsels of meat to which was added a little more of the alkali. He was, however, unable to get up from his bed, but a third injection literally resuscitated him, and the dog which four hours before was about to die raised himself spontaneously, walked around the laboratory with rigid steps like an automaton in order to come to us for food. The next morning his condition was still better and he had eaten during the night all the food placed at his disposal. Fig. 9 shows how he looked, active, the muscles still weak, but yet restored. The return of health, therefore, was accomplished very quickly with the help of insulin and the addition of carbohydrate. The trouble with the urine disappeared completely, the hemoglobinuria immediately, the albuminuria and lipuria more slowly. The body weight was regained in a few weeks. (Figs. 5–9.)

Treatment with insulin alone did not heal the coma of this dog. Can it be that the salt solution I give my patients acts just as effectively as sodium bicarbonate? It would seem to be so.

Why do dogs treated with insulin acquire acidosis when depancreatized dogs not so treated only rarely develop it? One could explain this by reason of the suddenness and intensity with which the change in metabolism is produced in an animal suddenly and completely deprived of pancreatic hormone while reserves of fat are abundant. The rapid breaking down of fat as shown by the lipuria and its imperfect metabolism inundates the organism with intermediary products which it has no time to master. Perhaps according to Petrén's theory the ordinary depancreatized dog lives too short a time for this perversion of metabolism to develop but the insulin dog lives long enough for such to occur.

The metabolism of this dog during his state of acidosis was greatly augmented above the periods without acidosis, while the respiratory quotient fell to a lower value than usual. As for the elevation of the basal metabolism Hédon writes it does not seem that one can relate it simply to the increase in protein disintegration.

Comments upon Table 1. The respiratory quotient before the diabetes began was 0.74. Upon a meat diet with insulin it later was about the same, 0.74 to 0.75, but on a mixed diet it was 0.79. When insulin was omitted the respiratory quotient fell to 0.71, with a mixed diet. When insulin was omitted and the animal was allowed to go into acidosis, by the sixth day the respiratory quotient had fallen to 0.69. It will be observed that a prompt elevation of metabolism followed the pancreatectomy.

TABLE 1.—THE RESPIRATORY QUOTIENT AND CHANGE IN WEIGHT OF THE HÉDON DOG UNDER VARIOUS EXPERIMENTAL CONDITIONS.

Dates.	R. Q.	Urea mgs. per kilo hour.	Calories per kilo hour.	Weight of animal, kgs.	Conditions of the animal and data of the experiment. Food preceding the day of the experiment.
1924					
Jan. 2	0.74	39	2.40	6.438	Before extirpation of the graft; no diabetes; meat diet.
Jan. 4	0.74	92	2.62	6.436	Following extirpation of the graft;
Jan. 5	0.70	97	2.73	6.224	diabetes; meat diet.
Jan. 7	0.75	93	2.72	6.035	Insulin; meat diet.
Jan. 8	0.75	99	2.78	6.033	" "
Jan. 10	0.75	106	2.54	5.993	" "
Jan. 14	0.74	85	2.80	5.768	" "
Jan. 18	0.79	37	2.48	6.026	Insulin after 4 days, mixed diet (milk, bread, meat).
Feb. 2	0.77	38	2.31	6.514	Insulin after 15 days, mixed diet.
Feb. 15	0.74	46	2.36	6.796	Insulin after mixed diet, but meat diet night before.
Feb. 22	0.75	54	2.27	6.407	Insulin after mixed diet, then meat diet three days.
April 12	0.74	41	2.20	7.083	Insulin after long period, mixed diet, meat diet night before.
April 15	0.71	107	2.65	6.914	After discontinuing insulin 48 hours; diabetes severe.
May 26	0.77	52	2.15	6.857	Insulin treatment allowing slight
Dec. 9	0.81	50	2.15	6.929	glycosuria to persist.
1925					
Jan. 29	0.84	52	2.14	7.122	Insulin discontinued for 18 hours; no glycosuria; mixed diet preceding.
Jan. 30	0.74	158	3.01	6.877	Insulin still discontinued; diabetes severe; mixed diet preceding.
Jan. 31	0.71	93	2.97	6.755	Same; no insulin; diabetes severe; mixed diet preceding.
Feb. 3	0.71	118	3.52	6.423	Same; diabetes severe; same diet minus bread.
	0.69	99	3.27	6.294	Same; diabetes severe; state of pronounced acidosis.

From the table one can also discern the change in weight which fell on a meat diet, but increased with the addition of carbohydrate; the rise in metabolism coincident with the meat diet and its fall when carbohydrate was added and its subsequent rise during acidosis; the excretion of urea in the thousandths of a milligram per kilo hour which rises with a meat diet, falls with a mixed diet which includes carbohydrates, greatly increases when insulin is omitted, and remains high during acidosis.

The external appearance of the Montpellier dog, and this is also true of his Toronto friends, is at present just the same as it was at the beginning of experiment. Weight and strength are maintained at a constant level and one would expect the continuance of treat-

ment to procure for him a greater longevity. There is a modification of his disposition dependent upon age and manner of life and the development of the symptoms of parorexia already described, but these are the only traits which indicate a variation produced in the dog in the course of years. The power of insulin to maintain the totally depancreatized dog for an indefinite survival in good condition is thus proved, provided it is associated with the administration of pancreatic ferments by mouth.

The story of 440, the Montpellier dog without a pancreas, is shown by nine of his pictures. For permission to insert these I am indebted to Professor Hédon and he has kindly added a tracing of the femoral pulse (Fig. 10) which was made upon June 13, 1927.

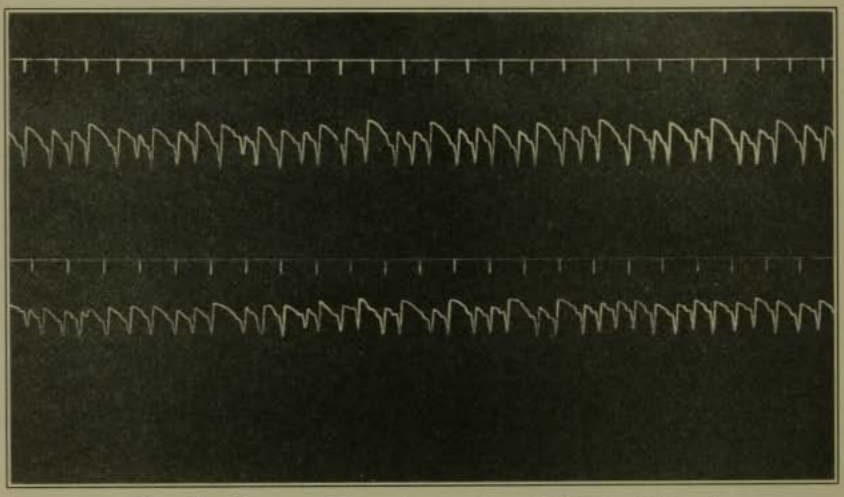


Fig. 10.—Tracing of femoral pulse, June 13, 1927. (Hédon.)

The original article describing the experiments with this dog was published by Hédon in the *Journal de Physiologie et de Pathologie Générale*, 1927, **25**, No. 1, page 1. Like the articles of von Mering and Minkowski, Allen and The Toronto School it is a classic and should be read by every student of medicine.

The pictures of these dogs show the stages of diabetes which other doctors and I must treat. It is pathetic to record that prior to July 1, 1926, I alone have had 668 patients scattered throughout all the world who failed to recover from the eighth stage of this dog. If dogs in Montpellier and Toronto can recover from such a state, is it strange after what I have lived through these twenty-nine years that I should lay emphasis in this book upon the needlessness of deaths from diabetic coma, and record here my indebtedness to the dogs who have helped to save my patients' lives?

SECTION II.

INSULIN.

A. HISTORICAL.

Insulin, the hormone of the pancreas which regulates carbohydrate metabolism, was discovered in 1921 by F. G. Banting with the assistance of C. H. Best[1] while working under the direction of Professor J. J. R. Macleod in the Physiological Laboratory of the University of Toronto. Thus, just a generation elapsed since that other epoch-making discovery in diabetes by von Mering and Minkowski[2] was announced, when they proved that fatal diabetes would follow complete removal of the same gland.

Langerhans[3] discovered the islands which bear his name in 1869, but Laguesse[4] in 1893 was the first to suspect that they produced an internal secretion. Laguesse also noted that they were more numerous in the fetus and new-born. The demonstration by Opie[5] in 1901 and Ssobolew[6] in 1902 that they were the elements of the gland involved in pancreatic diabetes gave a new impetus to the search for a pancreatic ferment. Ssobolew was the first to point out that the atrophy of the pancreas which was known to follow ligation of the pancreatic duct was confined to the acinous tissue and hence did not result in glycosuria, but that when in the course of time the islands became involved glycosuria developed. He also suggested that the pancreas of new-born calves would prove to be a fruitful source of the hypothetical internal secretion to which fourteen years later in 1916 Schafer[7] proposed the name of insulin.

The literature upon insulin is so voluminous that this entire book could be filled several times over with abstracts. Here I have been obliged to deal largely with end-results of investigations although

[1] Banting and Best: Jour. Lab. and Clin. Med., 1922, **7**, 251.
[2] von Mering and Minkowski: Arch. f. exp. Path. u. Pharm., 1889–1890, **26**, 371.
[3] Langerhans: Beiträge zur microskopischen Anatomie der Bauchspeicheldrüse, Inaug. Dissert., Berlin, 1869.
[4] Laguesse: Compt. rend. Soc. Biol., 1893, **45**, 819.
[5] Opie: Johns Hopkins Hosp. Bull., 1901, **12**, 263.
[6] Ssobolew: Zentralbl. f. allg. Path. u. Path. Anat., 1900, **11**, 202; also Virchow's Arch. f. Path. Anat., 1902, **168**, 91.
[7] Schafer: The Endocrine Organs, Longmans, Green & Co., 1916, p. 125.

no one more than I realizes that the early steps in studies which seemed to lead nowhere really form the basis for the completed stairway. For details not here given the reader is referred to Campbell and Macleod,[1] to a monograph "Insulin" by Grevenstuk and Laqueur,[2] another entitled "La Secretion Interne du Pancreas et l'Insuline" by Choay,[3] and still another L'Insuline by Aubertin.[4]

Early Extraction of Insulin.—In accord with Ssobolew's idea Banting and Best first sought insulin in the pancreas of dogs in whom they had ligated the ducts some seven to ten weeks previously. They first employed Ringer's solution for the extraction of the ferment and with it obtained an extract from the atrophied gland, which lowered the sugar in the blood and urine of a depancreatized dog and proved that the extent and duration of the reduction varied directly with the amount of extract injected. With Ringer's solution they also obtained an active extract from the entire pancreas as well, though this was less powerful. On the other hand an extract of the pancreas of a fetal calf, suggested by the discovery of Laguesse of the abundant islands in the fetus, furnished large quantities of the latter secretion. An extract made with 0.1 per cent hydrochloric acid also proved effectual. Later it was proved that the active principle of the gland remained in solution in alcohol percentages below 92 per cent and by using percentages below this much of the protein could be removed.

The use of 0.7 per cent tricresol to prevent sepsis aided greatly in securing a sterile preparation which was safe for both intravenous and subcutaneous use. Extracts were soon obtainable which were practically free from protein, salts, and alcohol-soluble substances. These could be made isotonic and injected subcutaneously without local reactions. In this refinement of the extract Banting and Best were assisted by J. B. Collip who injected the crude extract into normal rabbits and found that the blood sugar became reduced. This gave a method for testing the potency of the various procedures which he devised for its purification.

Subsequently improvements were made in the original methods of extraction of the insulin. Sodium sulphate as well as ammonium sulphate with a carefully adjusted pH between five and six and picric acid have been employed to remove the protein and loss of extract has been retarded by placing the pancreas immediately in a freezing mixture. From the insoluble combination with picric acid it is possible with hydrochloric acid to obtain a soluble salt of insulin hydrochlorate. Dodds and Dickens[5] introduced the

[1] Campbell and Macleod: Medicine, 1924, **3**, 195.
[2] Grevenstuk and Laquer: Munich, Bergmann, 1925; also: Ergebn. d. Physiol, 1925, **23**, Abt. 2, 1.
[3] Choay: Paris, Masson et Cie, 1926.
[4] Aubertin: Paris, Gaston Doin et Cie, 1926.
[5] Dodds and Dickens: Lancet, 1924, **206**, 330.

use of formic acid in aqueous solution for the extraction of insulin as a preliminary step to the precipitation of the protein with picric acid. The insulin picrate was dissolved with acetone. These procedures greatly simplified the extraction by making it unnecessary to use so much alcohol. In the various extractions fat was removed with sulphuric ether.

Abel and Geiling[1] used the commercial insulin prepared by the Lilly Research Laboratories as a basis for their work. Dry insulin powder so prepared was evaluated at 8 rabbit units per milligram: a later preparation which was furnished was valued at 12 units per milligram.

B. NATURE OF INSULIN.

Composition of Insulin.—Purification of the extracted insulin has further progressed in the hands of Abel and Geiling. They have separated from Iletin (Eli Lilly Company), protein-like fractions from which active insulin can be removed. In this way they have greatly raised the potency of insulin. According to Abel and Geiling sulphur is an integral part of the insulin molecule and the activity of a preparation of insulin is directly proportional to the amount of sulphur which it contains. Phosphorus is not a constituent of insulin. The nitrogen content of different preparations varies between 13 and 20 per cent. The same methods of preparation show a marked variation in the carbon, hydrogen, and nitrogen content according to Shonle and Waldo.[2]

Blatherwick, *et al.*[3] have also investigated the composition of insulin. They believe that they have separated a preparation fully as potent as that of Abel but devoid of sulphur. This preparation is almost crystalline when combined as a phosphate or tungstate. Insulin has certain resemblances to guanidine.

Insulin is a hydroscopic powder, soluble in water and 80 per cent alcohol, but insoluble in 92 per cent alcohol and acetone, and precipitated by half saturation with ammonium sulphate, by kaolin, charcoal, and ammonium sulphate. Its solubility depends largely on the hydrogen-ion concentration. The iso-electric point of precipitation lies between 5.5 and 6.

Insulin is a protein according to Dudley[4] and he is led to this conclusion because of: (1) its ready adsorption, (2) its failure to pass through an ultra filter, and (3) its rapid digestion by trypsin and particularly by pepsin. All these qualities indicate a complex protein-like structure. It must be a large molecule and hence its

[1] Abel and Geiling: Jour. Pharm. and Exp. Therap., 1925, **25**, 423.
[2] Shonle and Waldo (cited by Abel and Geiling): Jour. Pharm. and Exp. Therap., 1925, **25**, 423.
[3] Blatherwick, *et al.*: Jour. Biol. Chem., 1927, **72**, 57.
[4] Dudley: Biochem. Jour., 1923, **17**, 376.

absorption and passage through mucous membranes must be difficult. Yet after all it may not be a protein and the protein so intimately connected with it may be simply an impurity.

Insulin will keep for a year or more even in warm climate. It can even be boiled if the acidity is about pH 5; neutral solutions are destroyed by boiling and alkaline solutions still more rapidly. Insulin does not readily lose its power even if the solution in which it is placed should decompose with bacteria and yeast, and smell of hydrogen sulphide. See Shonle and Waldo.[1]

Abel and Geiling were able to separate commercial insulin into a number of different fractions, each of which is capable of further fractionation, but only one of which contains the true insulin or pancreatic hormone. All of their active preparations were characterized by the presence in them of sulphur in a remarkably labile form of combination and they sought to correlate the hypoglycemic action of a given fraction with this instability of its constituent sulphur. They hope that by determination of the sulphur it may be unnecessary to resort to an assay of insulin with animals save for an occasional verification. They obtained a rabbit unitage of 40 units per milligram with one of their preparations.

They consider that this unstable sulphur is an integral part of the insulin molecule.[2] In a later communication they report having obtained the insulin compound in crystalline form with constant melting point. The compound gives a biuret reaction, a weakly positive Mellon's reaction as well as Pauly and ninhydrin reactions. It is very sensitive to alkali. One hundredth of a milligram lowered the blood sugar of a rabbit to 0.045 per cent. Evidently "we are dealing with a hormone which, in very high dilution, influences carbohydrate metabolism acting, as it were, like a catalyst in a chemical reaction."

Quantity and Distribution of Insulin. — Sources of Insulin. — Before entering upon a description of the action of insulin reference will be made to the amount of insulin which exists in the pancreas and the source from which it can be obtained. As a measure of insulin, agreement has been reached upon a unit of strength. The physiological unit at present is the amount of insulin necessary to reduce the blood sugar of a 2-kilogram rabbit, deprived of food for twenty-four hours, to the convulsive level, 0.045 per cent, within five hours. The clinical unit is one-third of the strength of the physiological unit.

Our knowledge of the amount of insulin which exists in the pancreas is obviously changing with the improvement of the methods adopted for its extraction. Estimates vary from 15 to 22 physio-

[1] Shonle and Waldo: Jour. Biol. Chem., 1924, **58**, 731.
[2] Abel: Proc. Nat. Acad. Sci., 1926, **12**, 132.

logical rabbit units per kilogram of the fresh gland of domestic animals to 5000 or even 10,000 (Fenger and Wilson), and to 40,000 units per kilogram of the principal islets of cod (Dudley). In April, 1922, Best and Scott obtained 15 units of insulin per kilogram from the pancreas whereas in July, 1923, methods of extraction had improved so markedly that they were obtaining 400 units per kilogram. The most insulin could be obtained per kilogram from the pancreas of a horse, then from hogs, then from beef. One can extract enough insulin from the pancreas removed from a dog so that when this is injected into the same animal he becomes aglycosuric, and actually can be killed while exhibiting the picture of excessive hypoglycemia. Therefore, the pancreas is a storehouse for insulin. Some indications show that insulin exists in the pancreas, but must be activated in order to become potent. Insulin may not act the first day after being extracted from the pancreas, but will act after standing for one or two days. Insulin appears to be present in every living cell where carbohydrate metabolism is going on, but the islands of Langerhans are the cells in which insulin is most abundant in the body.

The common source of insulin is the pancreas of domestic animals (hogs and cattle). Insulin is also to be obtained from fish. In certain of the teleostal fishes (angler fish, sculpin, cod, pollock, and halibut) the islet tissue is collected into nodules separated from the zymogenous tissue. This so-called "principal" islet may attain the size of the adrenal gland of the rabbit. Although insulin can be obtained in more concentrated form in fish than in domestic animals, so far as I am aware no resort to this source has been made commercially.

Insulin is found in tissues other than the pancreas but the pancreas appears to be the one and only original source. Best and Scott prepared insulin from the submaxillary, thymus, and thyroid glands, and from liver, spleen, and muscle tissue and in fact insulin was present in every tissue they investigated. It is not reported as having been found in the hypophysis. The total muscular system of a dog contains at least twenty times as much insulin as his pancreas, his blood at least five times as much, the liver fully as much as the pancreas. It is remarkable that the tissues of non-diabetic animals narcotized with ether produce far less insulin than normal or even diabetic animals. This may explain some of the untoward effects which in the past have followed the abundant use of ether. Best and Scott also found it in the urine and believe it excreted in somewhat greater amounts by pregnant women than by normal men. They did not find it in the urine of diabetics and Nothmann observed that it disappeared within a few days from the urine of dogs after extirpation of the pancreas.[1]

[1] Nothmann: Cited by Jour. Am. Med. Assn., 1927, 89, 47.

In Table 2 are given the results of analysis of various tissues[1] in 3 of my diabetic cases and of the pancreas in 1 non-diabetic case compared with analyses of 1 diabetic and 2 non-diabetic cases reported by Baker, Dickens, and Dodds,[2] autopsied within three hours of death.

TABLE 2.—INSULIN CONTENT OF HUMAN TISSUES.

Case number.	Cause of death.	Units of insulin per 100 grams tissue.					
		Pancreas.	Liver.	Kidneys.	Heart.	Thyroid.	Spleen.
Diabetic[3]							
127 . . .	Gangrene, coronary thrombosis	14.7	1.2	1.6	1.1		1.0
3592 . . .	Multiple abscesses	2.5	0.9	1.9	2.2		2.2
4289 . . .	Septicemia	25.0	3.0	10.0	3.0	9.0	
Non-diabetic[1] .	Cancer of pancreas	70.0					
Baker, Dickens and Dodds	Pulmonary embolism	87.0	25.0	116.6			90.0
	Myocardial degeneration	108.0		11.5			
	Diabetic coma	42.5	16.3				

From so small a series of analyses carried out under the handicap of transporting specimens a great distance we cannot attempt to draw general conclusions. It is, however, striking that although greatly reduced in amount, insulin was present in both Cases Nos. 127 and 3592, whose pancreases showed marked degenerative change. The duration of diabetes in Case No. 127 was known to have been twenty-five years and of Case No. 3592 was 0.5 years. In Case No. 4289, a young woman with diabetes of recent onset but complicated by primary hyperthyroidism, coma, and septicemia, the pancreas showed almost no pathological change, and insulin was present in considerable amount. It is true that she had received large doses of insulin during the three weeks preceding death. Because of concurrent hyperthyroidism she had also received Lugol's solution, 30 cc. in fifteen days. Whether this treatment had improved the production of insulin, either directly or indirectly, is of great interest. Certainly great clinical improvement in both her diabetes and thyroidism occurred coincidently with the use of insulin and Lugol's solution.

The presence of insulin in the other tissues is clearly shown, presumably due to transfer from the pancreas rather than by production within these other tissues. Best, Smith, and Scott[4] conclude

[1] Root and Warren: Boston Med. and Surg. Jour., 1926, **194**, 45.
[2] Baker, Dickens, and Dodds: British Jour. Exp. Path., 1924, **5**, 327.
[3] I am indebted to Dr. C. H. Best, Toronto Canada, for these analyses.
[4] Best, Smith, and Scott: Am. Jour. Phys., 1924, **68**, 161.

that insulin may be a constituent of every cell which metabolizes carbohydrate and that the islands of Langerhans may be specially developed structures which supply active material when the demand is too great to be met by the insulin-producing power of the individual cell. It remains to be seen whether any diabetic is so severe as to have lost entirely the power of producing insulin.

Clinically no case of "complete" diabetes, save of a transitory nature, has come under my supervision. As a result of our studies of the respiratory metabolism of 118 cases of severe diabetes Benedict and I reached the conclusion that no case was so severe that it did not react to carbohydrate. It is significant that von Noorden with his large clinical experience, over 20,000 cases of diabetes, coincides with this view. Pathological evidence confirms the chemical and clinical evidence above reported, because no pancreas of a diabetic at autopsy has yet been shown to be entirely devoid of islands.

Insulin injected into the body is in part excreted in the urine. It can be injected into dogs during narcosis and recovered in urine in almost quantitative amounts while exercising its full effect. It is evidently not destroyed in the body. From diabetics and dogs one can recover one-third if given by stomach tube and with one dog who was given 700 units by stomach tube one-half was recovered from urine. The only symptoms manifested by this dog was a slight chill. A healthy man is said to excrete a couple of units of insulin a day, a pregnant woman excretes more. The insulin which is excreted is exactly like that obtained from the pancreas.

There appears to be no peculiar specificity in insulin from one species of animal.

A substance similar to insulin has been prepared from yeast by Winter and Smith,[1] Rincones and Gomez[2] and from various vegetable sources, including potatoes and onions, to which Collip[3] has given the name glucokinin. There is no assurance, however, that insulin of pancreatic origin is identical with any of these other types of insulin. Glucokinin is obtained from all sorts of plants. There are strong and even fatal effects obtained from its use and even its action is transferable from animal to animal. The animals to which its action is transferred through injection of blood cannot be revived from the hypoglycemic convulsive stage by means of glucose. With the aid of glucokinin a totally depancreatized dog was kept alive sixty-six days.

Diabetic patients show the presence of insulin both in the tissues generally and also in the pancreas. It is, however, reduced in

[1] Winter and Smith: Jour. Physiol., 1923, **57**, 40.
[2] Rincones and Gomez: Gaceta med. de Carácas, 1923, **30**, 289.
[3] Collip: Proc. Soc. Exp. Biol. and Med., 1923, **20**, 321.

quantity, but reliable data of the amount of insulin are not available. To secure such information the pancreas should be removed immediately after death and either promptly chilled to prevent decomposition and loss of insulin or the extraction of the insulin should be begun at once. Even if this is accomplished one's labor is but begun for the extracted insulin must then be tested as to its strength.

Insulin is said to stimulate the flow of bile and the external pancreatic juice.

The completely diabetic dog contains insulin though the amount is reduced to somewhat more than one-half that existing in the tissues of a normal animal. Insulin obtained from the blood of such dogs will cause hypoglycemia in normal animals, but will not prevent the symptoms of diabetes in the animal. Macleod suggests the occurrence of insulin in depancreatized dogs "can only mean that it exists as some precursor, for the final conversion of which into insulin in the body, the pancreas, or something derived from it, is necessary, although outside the body this conversion can be partially effected by the chemical reagents which are used as extractives."

It is only when the pancreas is present in a dog that he obtains enough insulin to be protected from diabetes. The insulin which may be found in depancreatized animals never suffices to ward off diabetes.

Action of Insulin.—(*a*) **The Blood Sugar Lowered.**—When insulin is injected subcutaneously or intravenously into an animal the sugar in the blood is lowered, the sugar in the urine is reduced, and if acetone bodies or fat have been present in blood and urine they likewise are decreased. The action of insulin is immediate, but the full effect of an injection does not reach a maximum for about sixty minutes or cease for some six to eight or even ten hours. The extent of the lowering of the blood sugar is dependent upon the quantity of insulin injected.

The diabetic and the normal individual as well react to insulin. Moreover, all types of experimental hyperglycemia, such as that produced by puncture of the floor of the fourth ventricle, asphyxia, poisoning by carbon monoxide gas, ether, adrenalin, pituitrin, are counteracted by appropriate doses of insulin and conversely the action of all those agencies which tend to lower the blood sugar, such as a low carbohydrate diet, undernutrition, diarrhea, exercise, is intensified by insulin. Thus insulin is involved in carbohydrate metabolism under all aspects, in the normal, the diabetic, and the experimental diabetic as well as in the physiological effects which diet, drugs, or exercise produce.

The life of depancreatized dogs was preserved for seven months

with the aid of insulin, but eventually they succumbed to symptoms of hepatic intoxicants, such as bile in the urine, jaundice, anorexia, and great bodily weakness. In all cases the liver was found at autopsy to be invaded by large quantities of fat—over 35 per cent of the moist weight being found in one case.[1] The fat absorption was greatly impaired. Fortunately it was found in Toronto that such deaths were unnecessary and that they were prevented by the feeding of raw pancreas. Furthermore, what is of the greatest interest and clinical significance was also discovered: namely, that as time progressed no increase in the dose of insulin was found necessary.

The diabetic patient almost becomes a normal individual when properly under treatment with insulin, save that this state is temporary. In order to prolong this period and to avoid an over- as well as an underdosage of insulin, it is desirable to describe more in detail what insulin does even though an explanation of how it acts is still unsatisfactory.

The most striking effect of insulin is the fall which it produces in the percentage of blood sugar. This is most easily studied. Case No. 3129 entered the hospital on April 20, 1923, with 5 per cent sugar in the urine, four plus acidosis, and a blood sugar of 0.40 per cent two hours after food. Following a subcutaneous injection of insulin of 10 units at 11.30 o'clock and 10 units four hours later, the blood sugar fell in five hours to 0.08 per cent.

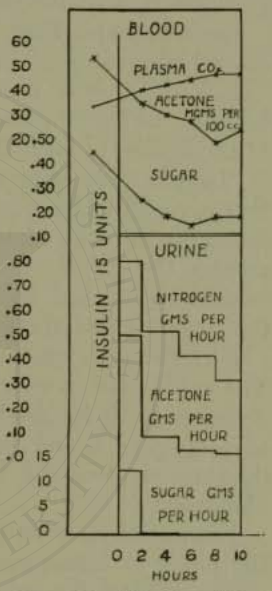


FIG. 11.—Effect on blood and urine of a single dose of insulin. (Fitz.)

Fig. 11 placed at my disposal by R. Fitz shows graphically the descent of the blood-sugar curve following a single injection of 15 units of insulin with the passing of the phenomenon and a beginning rise by the end of ten hours. Table 3 a rearrangement of a table by Fletcher and Campbell, shows the lowering in blood sugar following the administration of 20 units of insulin to a series of diabetic and non-diabetic patients and Table 4 the fall of blood sugar in two patients who were given varying amounts of insulin, as observed by its authors.

The extent to which the blood sugar drops in different individuals with the same dose of insulin varies greatly. The percentage fall

[1] Campbell and Macleod: Loc. cit., p. 61.

is less in non-diabetics than in diabetics, and the actual fall is, as is to be supposed, of far less degree. The limits of variation are so wide with the same number of units that it is not safe to predict what change a single unit will produce. In general, the greater the number of units, the greater the fall in percentage of blood sugar, but the fall is not proportionate to the amount of insulin used. Thus, with 10 units the decrease in blood sugar was 0.057 per cent, with 20 units 0.082 per cent, but with 30 units it was only 0.1 per cent. With another case 10 units lowered the blood sugar 0.037 per cent, 20 units 0.083 per cent, 30 units 0.081 per cent, but upon another day 0.118 per cent, and 50 units lowered the blood sugar even less; *i. e.*, 0.088 per cent.

Lawrence and Buckley[1] found in their experiments that 1 unit caused no greater fall in the blood sugar than $\frac{1}{2}$ unit.

It is well to bear these varying possibilities in mind in the administration of insulin, because they awaken caution and further hint at the futility of large doses of insulin.

"Insulin must cause a sort of vacuum for sugar to be set up in the tissues to fill which sugar is removed first of all from the blood and later, through the blood, from glycogen stores of the liver."[2] The greater the glycogen vacuum the more readily can insulin fill it from the blood and, therefore, the greater the glycogen vacuum, *i. e.*, the severer the diabetic state, the more powerfully can insulin act.

If the above explanation is true insulin should act best in coma. The rapid gain in weight following coma may be due to storage of glycogen with its attendant retention of water. The explanation also appears sound because in normals insulin in liberal doses does not depress the blood sugar comparably to what it does in diabetics.

Temporarily, according to Müller and Petersen,[3] the sugar in the blood is increased from 10 to 100 per cent, usually over 20 per cent, after the subcutaneous injection of insulin and the peak occurs within twenty to forty minutes. This increase does not occur if the insulin is given intracutaneously, due to the slower absorption. They attach great importance to this brief rise in the percentage of blood sugar, believing it indicates abnormal sugar metabolism and a discharge of sugar from its glycogen precursor in the liver.

The lowest percentage of blood sugar after insulin may be reached at variable periods, from one-half hour to as late as twelve hours, and the blood sugar likewise returns to normal at a variable rate.[4] The tendency of the blood sugar to fall during fasting and the

[1] Lawrence and Buckley: British Jour. Exp. Path., 1927, **8**, 58.
[2] Freise and Choremis: Monatschr. f. Kinderheilk., 1925, **31**, 1.
[3] Müller and Petersen: München med. Wchnschr., 1926, **73**, 726.
[4] Fletcher and Campbell: Loc. cit., p. 638.

variations which the blood sugar will naturally undergo when the body is or is not supplied with a moderate quantity of glycogen undoubtedly exert an influence upon the action of insulin. If the glycogen stores of the body are ill supplied or offer a vacuum, then the effect of insulin is greatly increased. The higher the blood sugar, the greater its fall, as a rule, following injections of insulin in normals as well as in diabetics.

TABLE 3.—FALL IN BLOOD SUGAR FOLLOWING THE ADMINISTRATION OF 20 UNITS OF INSULIN IN DIABETIC AND NON-DIABETIC PATIENTS. A. A. FLETCHER AND W. R. CAMPBELL.[1]

Case No.	8 A.M.	9 A.M.	10 A.M.	11 A.M.	12 noon.	1 P.M.	2 P.M.	3 P.M.	Lowest blood sugar.	Initial blood sugar minus lowest blood sugar.	Blood sugar fall in per cent of initial blood sugar.
					Non-diabetics						
1	.089	.090	.083	.120	.080	....	....	....	.080	.009	10.1
2	.094	.079	.070	.064	.075	....	....	....	.064	.030	31.9
3	.100	.083	.068	.064	.063	....	....	....	.063	.037	37.0
4	.113	.071	.091	.077	.107	....	....	....	.071	.042	37.1
6	.120	.093	.096	.088	.099	....	....	....	.088	.032	26.6
Average	.103	.083	.082	.083	.085	....	....	....	.073	.030	28.5
					Diabetics						
5	.118	....	....	.071	.071	....	....	....	.071	.037	31.3
7	.133	.099	.089	.077	.082	....	....	....	.077	.056	42.1
8	.148	.133	.125	.102	.100	....	....	....	.100	.048	31.0
9	.154	.163	.153	.089	.088	....	....	....	.088	.066	42.8
10	.160	.147	.133	.107	.077	....	....	....	.077	.083	51.8
11	.161	.172	.137	.090	.068	....	....	....	.068	.093	57.7
12	.163	.143	.122	.094	.090	....	....	....	.090	.073	44.7
13	.182	.174	.141	.100	.100	....	....	....	.100	.082	45.0
14	.200	.192	.182	.120	.097	....	....	....	.097	.103	51.5
15	.200	.178	.138	.097	.086	....	....	....	.086	.114	57.0
16	.208	.186	.175	.128	.110	....	....	....	.110	.098	47.8
17	.208	....	....	.182	.160	....	....	....	.160	.048	23.0
18	.280	....	....	.210	.170	....	....	....	.170	.110	39.2
19	.330	....	....	.182	.158	.174	.154	....	.154	.176	53.3
20	.360	....	....	.270	.217	.199	.200	.207	.199	.157	44.0
Average	.200	.150	.140	.127	.112	.187	.177	.207	.110	.089	44.1

The maximum period of influence exerted by insulin upon the percentage of blood sugar is eight hours. The highest blood sugars, therefore, should be found before breakfast, because this is usually fourteen hours removed from the last injection of insulin. It was,

[1] Fletcher and Campbell: Jour. Metab. Res., 1922, **2**, 640.

therefore, a gratifying surprise to learn that in my series of 53 diabetics who were treated for sixty-three days with insulin the average morning blood sugar had fallen from 0.24 per cent before insulin to 0.19 per cent at the end of the period despite the higher diets instituted.

TABLE 4.—FALL IN BLOOD SUGAR FOLLOWING THE ADMINISTRATION OF VARYING AMOUNTS OF INSULIN IN PATIENTS H AND D. A. A. FLETCHER AND W. R. CAMPBELL.[1]

Case.	Amount of insulin.	8 A.M.	9 A.M.	10 A.M.	11 A.M.	12 Noon	1 P.M.	2 P.M.	3 P.M.	Lowest blood sugar.	Initial B.S. minus lowest B.S.
H.	10 units	.170	.196	.166	.137	.113	....	....	....	.113	.057
	20 units	.182	.174	.141	.110	.100	....	....	....	.100	.082
	30 units	.185	.152	.085	.091	....	....	....	....	.085	.100
	Later 20 units	.118	....	....	.071	.071	....	....	....	.071	.047
D.	10 units	.172	.189	.147	.138	.135	....	....	....	.135	.037
	20 units	.160	.147	.133	.107	.077	....	....	....	.077	.083
	30 units	.182	.164	.178	.120	.101	....	....	....	.101	.081
	30 units	.200	.142	.132	.106	.082	....	....	....	.082	.118
	50 units	.152	....	....	.077	.074	.068	.072	.064	.064	.088

The lowering of the blood sugar is explained by Forrest, Smith and Winter[2] on the basis that alpha and beta glucose are transformed into gamma glucose.

(*b*) **Hypoglycemia.** — *Insulin Reaction.* — Hypoglycemia is the result of an overdose of insulin and appears to me to be the cause of a so-called insulin reaction. This state may occur in diabetics, however, quite apart from insulin administration, and on p. 214 various instances are cited. In diabetics the fall in blood sugar below normal is usually accompanied by a definite train of symptoms. These may appear when the blood sugar falls to 0.08 per cent though they are frequently not manifest until the blood sugar is 0.07 per cent. Hunger and tremor are the outstanding symptoms, but nervousness and weakness are also present, as well as pallor, flushing of the face, dilated pupils and increased pulse-rate, mask-like immobility of the face.

At 0.07 per cent to 0.05 per cent of sugar in the blood, anxiety, sweating, vertigo, and faintness appear with emotional instability; signs of cardiovascular disturbance such as tremor, subjective or obvious, hypotonia and diplopia may be manifest. These symptom are all accentuated with further lowering of the sugar in the blood. The pupils are dilated, the conjunctival reflexes sluggish, the respiration rapid and often periodic. Aphasia and delirium may occur

[1] Fletcher and Campbell: Loc. cit., p. 643.
[2] Forrest, Smith, and Winter: Jour. of Phys., 1923, **27**, 113.

and even convulsions, which, as in rabbits under similar conditions, may alternate with coma. The subject may go into a collapse with low blood-pressure and low temperature, though but comparatively few of my cases have been unconscious or even on the verge of unconsciousness. With others bradycardia has appeared and during unconsciousness a loss of control of the sphincters.[1]

Hypoglycemia appears a plausible mechanism underlying these symptoms, especially because of the observations of F. C. Mann[2] on dogs made hypoglycemic by the removal of the liver. He found that such dogs were promptly revived when they were given injections of glucose. No other sugar had the same effect as glucose, although alleviation of the symptoms has been observed after injections of maltose, mannose, dextrin, glycogen and galactose. Injections of pentose or of salt solution had no effect. Rarely, recovery was possible without injections.

Another explanation of an insulin reaction is given on p. 194 by Foshay, but this is not accepted by Trimble and Maddock.[3]

Symptoms do not invariably develop when the blood sugar falls to 0.05 per cent, and in a single instance in one of my cases symptoms of a reaction were absent when the blood sugar was as low as 0.03 per cent. With this patient, Case No. 2909, the percentage of sugar in the blood was carefully checked and the observation must be regarded as reliable.[4] John[5] has been able to collect from his series of 1000 diabetics only 10 instances in which reactions occurred when the blood sugar was above 0.08 per cent. Fletcher and Campbell report their lowest blood sugar as 0.025 per cent. This was found in their patient during the course of an influenzal bronchial pneumonia, but with glucose the patient recovered from the hypoglycemia. However, with a blood sugar at 0.035 per cent, according to the experience of Fletcher and Campbell, the patient is usually unconscious. A reaction is also more severe and more prolonged with undernourished patients, just as Macleod found it with dogs deficient in glycogen. The experience of Fletcher and Campbell, and our experience at the hospital coincides with this. Woodyatt[6] writes that another patient "received in extreme inanition but free of glycosuria, was given a large increase of diet and a calculated dose of insulin. This case developed hypoglycemic convulsions and the blood sugar was then at a level too low to read. Sugar administration restored hyperglycemia and gross glycosuria, but the patient died without regaining consciousness." Similarly,

[1] Fletcher and Campbell: Loc. cit., p. 645.
[2] Mann: Proc. Am. Physiol. Soc., December, 1920; Am. Jour. Physiol., 1920, **50**, 86; Medicine, 1927, **6**, 419.
[3] Trimble and Maddock. Personal communication.
[4] See also Stearns: Jour. Am. Med. Assn., 1925, **85**, 580.
[5] John: Arch. Int. Med., 1927, **39**, 67.
[6] Woodyatt: Jour. Metab. Res., 1922, **2** 793.

Case No. 2909 of my series, an emaciated man with diarrhea showed an insulin reaction following the injection of 1 unit. This was probably due to dehydration as Andrews and Schlegel[1] have shown that insulin injected into dehydrated animals has an intensified and prolonged effect. In edematous patients the reverse is true and this in part explains the case of Gordon, Connor and Rabinowitch.[2] Another frail woman, Case No. 5615, who entered the hospital with 10 per cent sugar became sugar-free in nine days, but showed small amounts of sugar on several days following, while having loose stools, though the diet was liberal. The carbohydrate reached 146 grams after twenty-six days, though morning blood-sugar tests on the second, eleventh, and thirtieth days after admission were 0.24 per cent or above. This patient developed a severe insulin reaction on October 28, the forty-third day, with a dose of 10 units three times in the twenty-four hours. Case No. 4277, a feeble old man developed mild delirium on a diet of carbohydrate 106 grams, protein 16 grams, fat 31 grams, after an interval of ten hours following the injection of 5 units of insulin.

Overexertion may bring on a reaction either because the available carbohydrate in the body is exhausted or because the internal secretion of the pancreas is stimulated. See p. 72.

Parnas and Wagner[3] reported the case of a girl with a tumor of the liver without being able to demonstrate any sugar in the blood.

In Millard Smith's[4] case the blood sugar was zero in the course of a reaction. The last dose of insulin given this child of four years with a history of onset of diabetes at fifteen months was 12 units at 6.30 P.M.

"When the nurse entered his room at 7.30 A.M. to dress him she noticed that he was slightly stuporous and unable to sit up. She immediately gave him 100 cc. of orange juice, after which his strength and mental activities returned. He was dressed and given breakfast at 8.00 A.M. together with his morning dose of insulin (12 units). After one hour he appeared sleepy, got onto the bed, and remained there until 11.00 A.M. when I first saw him. I suspected an insulin reaction, so attempted to rouse him. Upon waking he was drowsy but irritable, recognized individuals, but spoke only a few words. Both eyes were drawn to the left and when voluntarily directed to the front were involuntarily pulled again to the left. There was no other evidence of muscle spasm. His skin was moist and cool with a pale and somewhat cyanotic color. Pulse was 135, but fair quality. A few minutes after being awakened the

[1] Andrews and Schlegel: Arch. Int. Med., 1927, **40**, 637.
[2] Gordon, Connor and Rabinowitch: Am. Jour. Med. Sci., 1928, **175**, 22.
[3] Parnas and Wagner: Med., Klin. 1922, **18**, 137.
[4] Smith: Boston Med. and Surg. Jour., 1926, **195**, 663.

skin of his face became more pale. Finally he vomited a very large quantity of undigested material which represented his breakfast and the orange juice administered before. His color became better immediately and his stupor lessened. There seemed to be no reason for great apprehension and so another 100 cc. of orange juice was administered and then some of his dinner. After one-half hour his color again became very pale and somewhat cyanotic, followed soon by vomiting.

"Having never before reacted to insulin in this manner, the question was entertained that a gastro-intestinal upset might account for a large part of the symptoms. To make sure, a blood specimen was obtained from the arm and examined quantitatively for sugar by the method of Folin and Wu.[1] The solutions and technique conformed in every detail to the directions given by these authors. There was not the slightest reduction of the alkaline copper tartrate solution during boiling or of the phosphate molybdate reagent when added. The blood sugar was zero. The determination was later repeated with the same result.

"During the heating of the test it was seen that the blood sugar was very low and before the determination was finished the patient was given subcutaneously 0.3 cc. of adrenalin. Just after the adrenalin was given he exhibited a few twitchings of the muscles of his hands and arms. After fifteen minutes he suddenly brightened and took 100 cc. of 10 per cent glucose solution. Within another ten minutes he asked to get up and when allowed to do so appeared as strong as usual. No further hypoglycemic symptoms returned."

It appears that hypoglycemia may be accompanied by such a depression of physiological activity that glucose by mouth will not be absorbed or passed on by the stomach.

Müller and Petersen[2] point out that the hypoglycemia accompanies, but may not cause, the phenomena of an insulin shock. They explain this in an acute disturbance of the autonomous nerve system which is manifested upon almost all organs.

Laquer found that an insulin reaction in rabbits could be simulated by spinning the rabbits, indicating that insulin acts on the vestibular apparatus. Then too, it is said that the sudden drop of the blood sugar from a very high level to normal or just above may lead to a reaction. Finally a reaction is relieved by calcium and is also said to be relieved by potassium chloride.

Despite the dangers of insulin poisoning hyperglycemia without insulin has caused more deaths than hypoglycemia with insulin.

Clinically, it is important to remember (1) that the patients who are most undernourished are the ones who receive the most insulin;

[1] Folin and Wu: Jour. Biol. Chem., 1920, **41**, 367.
[2] Müller and Petersen: Klin. Wchnschr., 1926, **5**, 1025.

(2) that any diabetic has a far smaller glycogen factor of safety than a normal; (3) that in coma and fever larger doses of insulin may be required temporarily and that the need soon passes; (4) that insulin should be counterbalanced by a meal at least within an hour; (5) that oftentimes patients improve in tolerance for carbohydrate and a formerly suitable dose of insulin becomes an overdose; (6) that exercise taken in unusual amount may act like an additional dose of insulin and hasten a reaction; (7) that a low level of blood sugar which is harmless in youth may be dangerous in arteriosclerotic old age; (8) that dehydrated individuals are especially sensitive to insulin.

Symptoms.—With an overdose of insulin a reaction is apt to occur. Almost invariably this is associated with a lowering of the percentage of sugar in the blood far below normal. Occasionally one sees reports in the literature of the occurrence of a reaction although the blood sugar has fallen but little or none below normal. In our experience at the Deaconess Hospital such instances practically never occur; in fact I do not recall one, although having been on the watch for it. Perhaps it is due to the rather small doses of insulin employed. It is true, however, that patients complain of symptoms when the blood sugar is 0.20 per cent or 0.30 per cent, which have some resemblance to an insulin reaction, but closer study of the case does not justify such a diagnosis. Unless I am mistaken these patients never become unconscious, never have convulsions with these abnormally high blood sugar values, and their symptoms are not exclusively relieved with glucose.

Frequently the percentage of sugar in the blood falls as low as 0.05 per cent with scarcely a suggestion of a reaction. The child may be simply inactive or appear a bit tired out. It is impossible to relate a definite group of symptoms occurring in the course of a reaction to a given percentage of sugar in the blood, but in general the percentage of sugar in the blood falls to 0.045 per cent as the intensity of symptoms progresses to the stage of unconsciousness and convulsions.

The symptoms most commonly associated with a reaction may be restated. They begin indefinitely with hunger of unusual degree, nervousness manifested by emotional instability, such as excitement, laughter or crying simulating hysteria, aphasia, weakness, headache, faintness; then progress to a sensation of tremor and actual tremor; followed by sweating and unless the reaction is counteracted end in apathy, somnolence, unconsciousness, and convulsions. Convulsions are rare, because at the Deaconess Hospital my associates and I have seen them in but 2 cases, Nos. 2476 and 5615, in adults, in four and a half years. Occasionally the symptoms appear to come out of a clear sky. The slow mentality of the patient in an insulin

reaction, emphasized by Sansum,[1] is almost more dangerous than the unconsciousness and convulsions, because it is less obvious. This is the reason why diabetics taking insulin run risks when they drive automobiles. Frequently they are not alert enough to recognize the reaction and to take the carbohydrate which they carry.

The differential diagnosis between the unconsciousness due to the hypoglycemia of an insulin reaction and that due to acidosis, diabetic coma, is by no means always easy. Under diabetic coma this will be considered in detail, see p. 671, but here it will suffice to direct attention to the apparently causeless deep, regular respiration, rapid and regular pulse, soft eyeballs, and muscular flaccidity of diabetic coma in contrast to the normal respiration, irregular, even slow pulse with extra systoles and muscular rigidity with perhaps paralyses of ocular muscles, or rarely hemiplegia, of extreme hypoglycemia whether due to insulin or other cause.

The causes of hypoglycemic reactions cannot wholly be explained by the low percentage of blood sugar. Blood-sugar percentages as low as 0.06 are not so very rarely observed in the course of any series of blood tests. Indeed, children show these low percentages of blood sugar quite frequently. The accumulation of some toxic substance in the blood appears responsible for the effects, such an accumulation being rendered possible by variations of sugar in solution. "It may possibly be that through the lowering of blood sugar certain oxidative processes become depressed to such a degree that the brain cells are affected in much the same manner as in asphyxia." Some change in the circulation of the brain would seem not unlikely because during extreme reactions one hears of the occurrence of hemiplegia. In Case No. 2856 this lasted for several days; in a case of my colleague, Dr. F. G. Brigham, it also persisted for several days. McPhedran and Banting saw the convulsions relieved by calcium and Gigon calls attention to the convulsions in animals, even when the blood sugar is not low, which are also similarly brought to an end. Stone[2] reports an instance of monoplegia of the left arm. The ocular paralyses leading to double vision especially in children are very common.

An unusually severe reaction took place with Case No. 2476. He became so violent that neither glucose nor adrenalin could be administered. Under insulin he had gained about 100 pounds.

A diabetic doctor, Case No. 6293, aged sixty-eight years, while talking with a friend on the street fell unconscious and came to just long enough to take the sugar he carried, with prompt recovery. That morning he had had unusual exercise.

Hypoglycemic reactions have been purposely produced in some

[1] Sansum: Am. Rev. Tuberculosis, 1923, **7**, 375.
[2] Stone: Jour. Am. Med. Assn., 1926, **87**, 388.

clinics with the object of acquainting patients with their character. When one uses small quantities of insulin and changes the dose only a few units at a time, such reactions are neither common nor severe. To the author it has seemed unnecessary to subject patients to a toxic dose of insulin any more than to a toxic dose of any other drug. At the New England Deaconess Hospital hypoglycemic reactions have never been induced with design.

In an experience of nearly five years with insulin, I doubt if adrenalin has been given by me, three times, or glucose administered intravenously on account of a reaction on more than twelve occasions.

Sevringhaus[1] has ascribed various psychic reactions to hypoglycemia. These are distinguished by disorientation and amnesia. Aphasia and sleepiness have been the premonitory symptoms and in the severe reactions there has been no opportunity for the patient to secure assistance. In all of these patients the usual reaction had occurred at times, but the above symptoms resulted from prolonged hypoglycemia. One of the patients, who vomited during recovery from a reaction, aspirated some of the material into her lungs and died in three days.

Other symptoms shown by the patients were resistivity and fixity of gaze, suggesting a catatonic state. With reduction of insulin the mental depression and moroseness which the patients had sometimes shown disappeared.

False hypoglycemic reactions are not uncommon. Fear that they might be simulated in order to obtain additional carbohydrate as an antidote led us to suspect one little boy who in preinsulin days had so frequently broken his diet. He became so accustomed to blood-sugar tests upon the occasion of a reaction that in answer to the query put to the Diabetic Class—"What do you do if you have a reaction?"—invariably he would reply—"Have a blood-sugar test." He never deceived us, for his blood-sugar tests were always low. Several patients, two young men and a professor, were quite sure they were having reactions when their blood-sugar percentages were 0.29, 0.22 and 0.24, Case Nos. 1978, 2784, and 1078. The appearance of two of the young men so closely resembled patients who were having a true reaction as to mislead a nurse and an assistant of great experience. In such a dilemma the presence of sugar in the urine may solve the situation, but should glycosuria be absent a blood test alone would be conclusive. Six months after two young girls, Case Nos. 2962 and 3078, had given up insulin, because of gain in tolerance, they felt on several occasions that they were experiencing a reaction. This occurred near the time of catamenia,

[1] Sevringhaus: Am. Jour. Med. Sci., 1926, **172**, 573.

and is to be explained more probably as resulting from the nervousness accompanying this state than from a change in the blood sugar which would be far more likely to rise.

Treatment for a hypoglycemic reaction consists in the prompt administration of the antidote, which is any carbohydrate out of which glucose can be quickly formed.[1] Orange juice acts very well and is especially suitable, because while peeling the orange the patient has time to reflect and decide as to whether he is actually having a reaction due to an overdose of insulin and thus not take the carbohydrate unnecessarily and therefore harmfully. An orange is less temptation to a child than two or three pieces of sugar or even of candy. Honey or corn syrup (glucose) can be given if the patient does not swallow easily. Any solution of sugar of this type could be administered by stomach tube, by intranasal catheter, or by rectum. If the condition of the patient is critical, the glucose may be given intravenously in 5 to 20 per cent strength, the total amount given not exceeding 25 grams. Raffinose and rhamnose are types of sugar which are ineffective in insulin hypoglycemia.[2]

Protein, also, may serve as an antidote to insulin, but according to Sherrill[3] "protein ranks below preformed carbohydrate in respect to glycosuric effect and insulin requirement when the substitution is made on a basis of either equal caloric value or theoretical glucose content. Though hypoglycemia may be prevented by sufficiently large quantities of protein, this influence is surprisingly feeble and by no means in proportion to the theoretical value."

An intracardiac injection of dextrose was employed successfully to combat hypoglycemia by Imerman.[4]

Epinephrin has been employed as an antidote to insulin. Indeed, it was with the hope of standardizing epinephrin with extract of the pancreas which led Zuelzer to seek for an active pancreatic extract. It will act even more quickly than carbohydrate in overcoming an hypoglycemic reaction. The dose is 1 cc., 15 minims, of a 1 to 1000 solution. Though epinephrin is a valuable antidote with diabetics whose carbohydrate store is not utterly exhausted, it is probably useless in greatly undernourished cases, unless accompanied by the ingestion of carbohydrate. Furthermore, epinephrin increases the work of the heart and this work must be done with blood having a low sugar value flowing through the coronary arteries. Extra work under such circumstances might be dangerous. See Arterio Sclerosis and Angina Pectoris, pages 692, 707.

If a subcutaneous injection of pituitary extract is given along with

[1] Noble and Macleod: Am. Jour. Physiol., 1923, **64**, 547.
[2] Campbell and Fletcher: Jour. Am. Med. Assn., 1923, **80**, 1641.
[3] Sherrill: Jour. Metab. Res., 1923, **3**, 59.
[4] Imerman: Jour. Am. Med. Assn., 1927, **89**, 1778.

insulin the fall in blood sugar usually produced by insulin is reduced, abolished, or replaced by a rise.[1] Pituitary extract, therefore, is theoretically an antidote to insulin.

Fatal Cases.—Very few cases of death due to an overdose of insulin have been reported in the literature. No such instance has been seen by me or my associates. Three cases in which insulin was a contributing cause to death, though in 2 of these death would have occurred shortly irrespective of insulin, have been observed either by my associate, Howard F. Root, or myself. The first[2] was a woman, Case No. 5045, aged fifty-one years who had gangrene and septicemia and was seen in a hospital some distance from Boston. On account of her high morning blood sugar the insulin of this patient had been steadily increased until she received 80 units of insulin three times a day! The blood sugar taken at the time of consultation was 0.015 per cent. With an intravenous injection of 10 grams of glucose the patient recovered consciousness, but soon again became unconscious, was relieved for a second time by the glucose, but later unconsciousness returned and the patient succumbed, as she would have done undoubtedly at a later period, as a result of her gangrene. The second was Case No. 5616 in which the reaction came on during diarrhea in a patient who, it might be added, showed at necropsy a pancreatitis. The third patient was a woman with exophthalmic goiter, Case No. 5176, who entered with acidosis, slipped into coma, was brought out of it, later developed hypoglycemia which required glucose intravenously. Subsequently pulmonary symptoms developed and after five days she died and small infarcts were found. I confess that this case has only a remote connection with insulin, but if diabetic coma had not been allowed to come on requiring large doses of insulin with many blood-sugar tests to guide the course and to treat the patient, the trauma of the vein might have been avoided and so too the pulmonary infarcts. Since this case we are far more careful of the veins of our patients than ever before and frequently spare them by utilizing micro-blood sugar methods. See p. 444.

Case No. 4535 recovered from coma in November, 1926, and again in October, 1927, but ten days later broke diet and the rule to "call a doctor" when ill, took insulin every hour all night, 120 units, and died despite glucose intravenously and subpectorally administered by her physician.

Campbell and Macleod[3] report 2 deaths. "Two deaths from insulin hypoglycemia have been seen. The first, an habitual drunkard, who had been refused insulin treatment at Toronto General Hos-

[1] Burn: Jour. Phys., 1923, **57**, 318.
[2] Root: The Lancet, 1926, ii, 544.
[3] Campbell and Macleod: Medicine, 1924, **3**, 270.

pital because of this danger, received insulin from another clinic. Having been slightly inebriated, he arose in the morning with a distaste for food and omitted breakfast but injected 30 units of insulin subcutaneously. He transacted considerable business, walked considerably, hurried all morning in order to catch a train at midday. About noon he was brought as an emergency case to the Toronto General Hospital, having collapsed on the street. He was cyanosed; his heart was dilated; the heart sounds were weak; his breathing was difficult; he had edema of the lungs. Stimulants were given but he died before a needle could be boiled to administer glucose intravenously. The other case, from our own clinic, was a severe diabetic using 40 units of insulin per day, who suffered from a gastro-intestinal upset with vomiting. Without notifying his physician he took 10 units of insulin without any food. Noticing the onset of the hypoglycemia reaction he ate an orange, and later, telephoned to his physician. Feeling improved he neglected to carry out the instructions given him to rest and take more glucose. A sudden collapse occurred followed by death before assistance arrived."

Heimann-Trosien and Hirsch-Kauffmann[1] also report a death in a child who failed to recover despite the administration of adrenalin and of 107 grams glucose given by vein and by mouth. Woodyatt's[2] case died in convulsions, but was in extreme inanition before the insulin was injected. The patient of Jonas[3] succumbed eleven days after the cessation of insulin. Pemberton's[4] case was complicated by tuberculosis. Rosendahl[5] reports a fatal case who developed hypoglycemia a few days after living upon Petrén's diet and a small dose of insulin. Alkalosis together with acetonuria (!) was observed during the attack. Another case is reported by Dahl.[6]

The precipitate rigor mortis which comes on in rabbits dying after hypoglycemic convulsions is due to the absence of glycogen and the decrease in lacticidogen and not due to accumulation of lactic acid or increased acidity of the muscles.[7]

(*c*) **Renal Threshold in Insulin-treated Diabetics.**—Rabinowitch[8] reports 14 cases in which after the use of insulin for a varying period of time the renal threshold rose materially. The average blood sugar with glycosuria was 0.18 and some months later with no glycosuria it was 0.29 per cent. There was no evidence of impairment of renal function.

Insulin edema was noted in certain of these cases. It disappears

[1] Heimann-Trosien and Hirsch-Kauffmann: Klin. Wchnschr., 1926, **5**, 1655.
[2] Woodyatt: Jour. Metab. Res., 1922, **2**, 793.
[3] Jonas: Med. Clin. North America, 1924, **8**, 949.
[4] Pemberton: British Med. Jour., 1925, i, 1004.
[5] Rosendahl: Acta Med. Scand., 1927, **66**, 100.
[6] Dahl: Norsk Mag. f. Laegevidensk., 1928, **89**, 40. See also Jour. Am. Med. Assn., 1928, **90**, 1004.
[7] Hoet and Marks: Proc. Roy. Soc., 1926, B, **100**, 72.
[8] Rabinowitch: British Jour. Exp. Path., 1926, **7**, 352.

with the omission of insulin. Is it more than one sees when carbohydrate is suddenly being retained? Carbohydrate retains 3 grams water for each gram carbohydrate stored. See p. 271. Then too alkali is set free when insulin is given and these free salts accumulating in the body also lead to the retention of water. See p. 662. Van der Bergh says potassium acetate is advisable under these circumstances. In contrast to the edema of the tissues a concentration of the blood is produced by insulin.[1]

(*d*) **Glycogen Stored.**—Insulin lowers the blood sugar by facilitating its conversion into glycogen which in turn is stored in the liver and muscles. It has long been known that glucose is changed into glycogen and as such stored in the liver and it has seemed reasonable to assume that the same phenomenon took place in the muscles. Proof of this has only just been afforded by the experiments of Best, Hoet and Marks[2] which demonstrated that under the influence of insulin circulating glucose was almost quantitatively changed into glycogen. Insulin, however, is without effect upon the intravenous tolerance for levulose.[3] In another paper Best, Dale, Hoet, and Marks[4] write that the glucose which disappears from an eviscerated spinal preparation under the action of insulin is equal to the sum of the glycogen deposited in the muscles and the glucose equivalent of the oxygen absorbed.

The glycogen in the liver of the normal animal may be as low as 1 per cent, but after feeding with sugar may rise to 7 or 8 per cent and even reach 20 per cent, according to Macleod. In the depancreatized dog he has never found it over 1 per cent.

Levulose alone of all carbohydrates, according to Minkowski, is capable of storing glycogen in the livers of such animals and by feeding levulose he raised the content to between 0.72 and 8.14 per cent.

Insulin, therefore, is anabolic in action. It prepares and stores carbohydrate for burning, but does not actually burn it.[5] When the stores of glycogen are low and a vacuum exists in the liver and muscles insulin is much more effective in lowering the blood sugar. Insulin reduces the stores of glycogen only in the presence of profound hypoglycemia and probably then only as a result of (1) the convulsions of the animal and (2) adrenalin coming into play. Rabinowitch[6] also believes that glycogen formation is a necessary preliminary to oxidation of carbohydrate.

[1] Olmsted: Am. Jour. Physiol., 1924, **69**, 137; Edwards: Ibid., 1924, **70**, 273.
[2] Best, Hoet, and Marks: Proc. Roy. Soc., 1926, B, **100**, 32.
[3] Wierzuchowski: Jour. Biol. Chem., 1926, **68**, 631; Cori and Cori: Ibid., 1927, **72**, 597.
[4] Best, Dale, Hoet, and Marks: Proc. Roy. Soc., 1926, B, **100**, 55.
[5] Lawrence: Quart. Jour. Med., 1926, **20**, 69.
[6] Rabinowitch: British Jour. Exp. Path., 1927, **8**, 76.

An increase in the blood sugar is a signal for more insulin. If the signal is heeded more insulin is produced and in consequence more glucose is changed to glycogen and stored.

Exercise depends upon the oxidation of carbohydrate in the muscles. The glycogen stores are lowered. With exercise and the burning of carbohydrate the secretion of insulin apparently is augmented, and because of the small amount of glycogen in storage, it acts more effectively in lowering the blood sugar. Lawrence[1] points out that so much carbohydrate must be burned in the muscles that it is only rational to conclude that its source in part must be fat. If no carbohydrate is available, fat will be changed too rapidly and, the carbohydrate being lacking for simultaneous oxidation, ketosis results. This view of some carbohydrate being formed from fat in addition to the 10 per cent long conceded seems to be gaining ground.

Janney and Shapiro[2] believe that the seat of insulin activity is in the protein tissues and that the usual sparing of protein by carbohydrate is increased by insulin due to protein synthesis from carbohydrate metabolites. From their experiments and observations they construct a theory that diabetes may be a result of protein anabolism.

(*e*) **The Fat in the Blood Reduced and Stored.**—The migration of fat in diabetes is abnormal and it accumulates in the blood and liver. Under the influence of insulin a reduction of fat in these situations takes place. The normal quantity of fat in the liver of laboratory animals is 5 per cent. When sucrose is fed to depancreatized dogs it may rise to 20 per cent. The normal quantity of fat, total lipids, in the blood is 0.68 per cent, but in one of my diabetics, Case No. 786, it rose to 16.3 per cent, and Klemperer[3] records 26 per cent. When depancreatized dogs were fed insulin and sucrose the percentages of fat in the liver were lessened and varied between 2 and 7 per cent. When a diabetic patient of Bock, Field and Adair[4] was given insulin the total fat in the blood fell from 10.5 per cent to 4.37 per cent in forty hours.

Rabinowitch and Mills[5] have reported an éclatant case of rapid reduction of fat in the blood. They recorded simultaneously the blood sugar, blood fat, and respiratory exchange. The importance of the case merits an extended report.

Male, aged forty-three years, was admitted to the Montreal General Hospital on July 17, 1924, practically in coma. Küssmaul

[1] Lawrence: Quart. Jour. Med., 1926, **20**, 69.
[2] Janney and Shapiro: Arch. Int. Med., 1926, **38**, 96.
[3] Klemperer: Die Ther. d. Gegenwart, 1911, **52**, 447.
[4] Bock, Field, and Adair: Jour. Metab. Res., 1923, **4**, 27.
[5] Rabinowitch and Mills: Jour. Metab. Research, 1925–1926, **7–8**, 87.

respiration, marked acetone odor, eyeballs soft. Sugar and aceto-acetic acid strongly positive, blood sugar 0.385 per cent; plasma CO_2 combining power 26.2 volumes per cent; and the *blood fat 18.6 per cent.*

At 3.45 P.M. 50 units of insulin were given intravenously and blood sugar determinations were made hourly until 8.45 P.M. The results were as follows:

Time.	Blood sugar, per cent.
3:45 P.M.	0.385
4:45 P.M.	0.400
5:45 P.M.	0.370
6:45 P.M.	0.244
7:45 P.M.	0.227
8:45 P.M.	0.222

At 10 P.M. 20 units of insulin were given. The following morning the patient appeared to be well out of coma, blood sugar 0.185 per cent and no acetone odor to the breath.

The blood fat was 9.4 per cent. Assuming the subject had 5 liters of blood, approximately 460 grams of fat had disappeared from the circulation. This could obviously not be accounted for by oxidation, since it would represent a heat production of over 4000 calories in less than eighteen hours. The subject was at rest in bed during the interval, and the acidosis had disappeared.

Since a marked degree of lipemia was still present, an attempt was made to correlate the changes in the sugar and fat content of the blood, and the respiratory exchange following glucose and insulin. For this purpose, the determinations were made simultaneously. Blood sugar, blood fat, and respiratory exchange determinations were first made. One hundred grams of glucose, and 100 units of insulin were then injected intravenously.

TABLE 5.—SIMULTANEOUS OBSERVATIONS IN A DIABETIC UPON BLOOD SUGAR, BLOOD, FAT, AND METABOLISM. RABINOWITCH AND MILLS.

Time.	Blood sugar, per cent.	CO_2 liters per hr.	O_2 liters per hr.	R. Q.	Calories per hr.	Urine.		Blood fat, per cent.	Remarks.
						N, gm. per hr.	Glucose, gm. per hr.		
2:25 P.M.	0.285	9.870	14.016	0.704	65.6	....	....	9.5	100 gm. glucose
3:30 "	0.500	12.438	16.560	0.750	78.4	3.75	25.0	7.4	and 100 units
4:30 "	0.344	10.596	14.772	0.717	69.8	2.80	28.8	6.8	insulin given
5:30 "	0.238	11.934	15.948	0.748	75.1	0.49	8.1	3.6	at 2:30 P.M.
6:30 "	0.166	9.522	12.918	0.737	60.8	0.55	6.3	2.1	

Following the administration of the glucose and insulin, there was an initial rise in the degree of hyperglycemia, followed by a fall.

In four hours the blood fat had decreased from 9.5 to 2.1 per cent. Applying the same assumptions as previously, 370 grams of fat left the circulation, accounting for over 3000 calories. The respiratory exchange data show that less than 30 grams of fat were oxidized, accounting for less than 300 calories.

During the period of observation (four hours) 64 grams of glucose were excreted in the urine. The calculations of both sugar and fat oxidized must, of necessity, be approximate. The nitrogen data can hardly be accepted as representing the protein metabolism. With the introduction of 1 liter of fluid directly into the circulation much of the nitrogen excretion may be attributed to a "washing out" of accumulated nitrogen. Professor Lusk, when shown the data, interpreted them on this basis. It will be noted that the nitrogen excreted could otherwise account for the total metabolism of the period of observation.

The disappearance of the fat from the blood stream is more difficult to explain. It is quite obvious from the above data, that the greater part of the fat which left the circulation was stored. It would appear that not only glucose but fat also must exist in a certain chemical or physical state for proper distribution prior to oxidation. Professor Bloor suggested that the phenomenon might have been due to changes in the permeability of the tissues to fat. The hypothesis of change of permeability by insulin for sugar, he stated, is still more reasonable for fat, since the fat molecule, as compared with that of glucose is a very stable one and not likely to undergo molecular change readily. This hypothesis also fits in better with Allen's conception of the cause of lipemia in diabetes—a general cachetic condition of the whole organism which would affect all the cellular functions including permeability.

(*f*) **Ketone Bodies.**—*Acidosis.*—A decrease in acidosis registered by a fall in the ketone bodies can be anticipated from the changes which have been shown to take place in the sugar and fat of the blood. When the sugar is burned, the fat is burned, and the ketone bodies must decrease. This, in fact, takes place. The fall in ketone bodies is strikingly shown in a chart which Reginald Fitz constructed from studies upon the blood chemistry of one of his cases of diabetic coma and by his courtesy is inserted herewith. Fig. 12 also exhibits the accompanying changes in blood sugar and blood CO_2.

During sixteen hours there was a precipitous descent of ketone bodies from 140 to 60 mg., and the percentage of blood sugar from 0.6 to 0.14 per cent along with the administration of 65 units of insulin. In passing it should be noticed that the rise in carbon dioxide in the blood was not commensurate with the fall in ketone bodies. This discrepancy between acetone bodies and CO_2 was

also observed by Banting, Campbell and Fletcher, and by others. The curves also demonstrate that the percentage of sugar in the blood falls more rapidly than the decrease in percentage of ketones and that ketones both disappear later from the urine and return earlier than glycosuria as observed first in Toronto. Later investigations in Toronto and at Petrén's[1] clinic would indicate that the blood sugar and β-oxybutyric acid fell in a parallel manner.

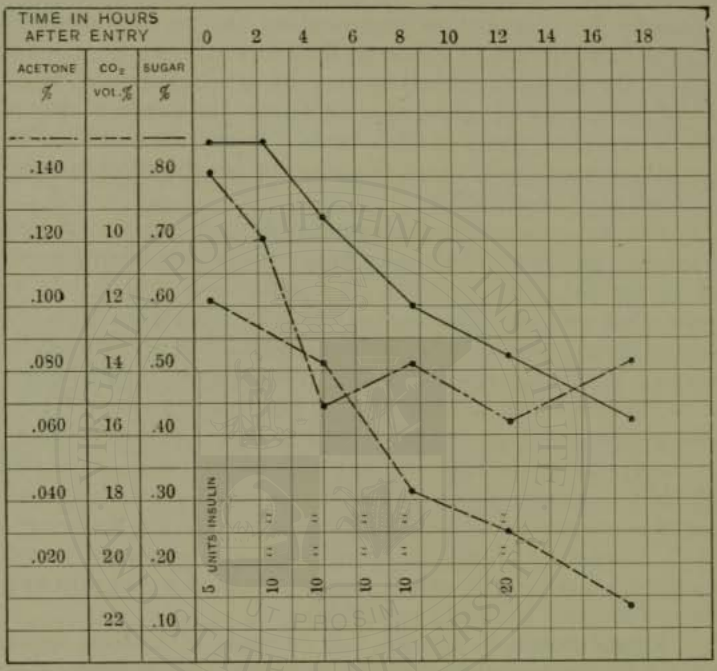


FIG. 12.—The effect of insulin on the blood chemistry of a case of diabetic coma. (Reginald Fitz.)

Banting, Campbell and Fletcher[2] also have published an excellent table showing the two-hourly output of sugar and ketones in the urine for a twelve-hour period following injection of insulin. Table 6.

The influence of insulin upon the carbohydrate and nitrogenous metabolism of a diabetic patient and incidentally upon the acidosis is beautifully exhibited in Table 7 furnished me by R. Fitz. His moderately severe diabetic was given a ten-hour "Insulin Fast Day" and analyses of the blood and urine made at two-hourly intervals. The urine excreted at entrance to the hospital before

[1] Petrén: Nordwestdeutschen Gesellschaft für inn. Med. in Greifswald, June 1925.

[2] Banting, Campbell, and Fletcher: Jour. Metab. Res., 1922, **2**, 547.

insulin was given contained 5 per cent sugar, the ferric chloride reaction ++, and the acetone as total acetone bodies was 0.26 per cent. The blood sugar was 0.47 per cent, blood acetone 55 mg. per 100 cc., and the carbon dioxide in volumes per cent 35.2. Fifteen units of insulin were then given. Within six hours the blood sugar was 0.17 per cent and the glycosuria had disappeared. During ten hours the nitrogen excretion fell from 0.82 gram per hour to 0.33 gram per hour and the total acetone excretion from 0.52 gram per hour to 0.03 gram per hour. It is true that fasting alone would lower the hyperglycemia, nitrogen excretion, and acidosis, but no one could expect such marked reductions in so short a period as ten hours.

TABLE 6.—VARIATIONS IN SUGAR AND KETONES IN URINE AND BLOOD AFTER INSULIN. BANTING, CAMPBELL AND FLETCHER.

Time.	Volume, cc.	Sugar.		Ketones.	
		Per cent.	Grams.	Mg. per liter.	Mg. per 2 hrs
7– 9	40	0.75	0.3	1737	70
9–11	250	0	0	262	66
11– 1	520	0	0	0	0
1– 3	460	0	0	0	0
3– 5	470	0	0	213	100
4– 7	240	0.43	1.16	491	115

TABLE 7.—INFLUENCE OF INSULIN UPON CARBOHYDRATE AND NITROGENOUS METABOLISM OF A DIABETIC. REGINALD FITZ.

Time, hours.	Nitrogen excretion per hour, grams.	Urine.		Blood.			Insulin, units.
		Sugar excretion per hour, grams.	Total acetone excretion per hour, grams.	Sugar, per cent.	Acetone mg. per 100 cc.	CO_2 vol., per cent.	
Entry.	Urine excreted at entry before insulin was injected had 5 per cent sugar and a ++ ferric chloride reaction. The acetone was 0.26 per cent.			0.47	55.0	35.2	15
0.2	0.82	13.00	0.52				
2	...	.....	...	0.27	36.9	42.6	
4	...	.....	...	0.20	31.8	44.5	
2.5	0.53	Trace	0.10				
6	...	.....	...	0.17	29.0	46.5	
5.8	0.43	None	0.04				
8	...	.....	...	0.20	20.0	48.4	
8.10	0.33	None	0.03				
10	...	.....	...	0.20	26.4	48.4	

The influence of insulin upon carbohydrate metabolism has been sufficiently discussed elsewhere, but it is appropriate here to mention its effect upon protein metabolism. That this is reduced the table of Fitz would indicate, but the subject is by no means simple. In this special instance we have: (1) The influence of fasting, which in itself would lower protein metabolism, not only on account of the temporary absence of food, but because of the permanent effect of fasting; (2) the sparing action of the combustion of carbohydrate which saves calories otherwise required from protein and fat; (3) the saving of calories indirectly, because of better utilizability of fat. In observations of longer duration in which nitrogenous metabolism has been observed to change from a minus to a plus basis all these factors come into play, and also another factor which in long continued observations is of greater importance, namely, the extra amount of food which the patient is given and, because of its utilization, is able to retain and use for the formation of new tissue. The change in nitrogen metabolism is therefore an indirect rather than a direct result of insulin.

The influence of insulin upon acidosis can easily be predicted from its effect upon the metabolism of carbohydrate. When carbohydrate burns freely, acidosis disappears. Even a fasting diabetic with little store of carbohydrate in the body is shown by insulin to have enough carbohydrate available for combustion, when properly burned, to allow the complete combustion of fat. Insulin shows that the diabetic has more depots of carbohydrate at his disposal than have been credited to him. That insulin plus carbohydrate should dispel acidosis could be anticipated, but that insulin plus carbohydrate already existing in the body should so quickly dispel acidosis is another of the marvelous properties of this extract. From where does the carbohydrate come which is burned? To a considerable extent from the blood, as shown by the falling blood sugar, though perhaps not more than (4000 cc. blood x 0.0047) 12 grams in this way, but an additional quantity may come from sugar in solution in the tissues, for we must not forget the body is about 60 per cent water, and hence presumably the balance from the oxidation of carbohydrate derived from the protein metabolized $-(0.82$ gram nitrogen per hour x 2) + (0.53 gram x 3) + (0.43 gram x 2) = 13 grams. This experiment with insulin shows how little total glucose is required to lessen acidosis, providing it is oxidized. Fat may also be a source of carbohydrate.

The real test of the action of insulin upon acidosis is the result of the treatment of diabetic coma since its discovery. Six of the 1138 patients seen by me during the twelve months ending July 1, 1926, died of coma and none of the 1241 cases traced during the following year. Results of the treatment of diabetic coma are described

on p. 643 and the cases treated on my service at the Deaconess Hospital are summarized in tables 1 and 2 on pages 1284 and 1285 *Med. Clin. N. Amer.*, 1927, 10, No. 5.

(*g*) **Metabolism.**—The immediate and direct effect of insulin upon the metabolism is negligible, but the remote and indirect effect is profound. Insulin allows the patient to tolerate more carbohydrate and thus more food. In consequence of the extra food the metabolism rises, but not in consequence of the insulin *per se*. Likewise the respiratory quotient is affected not directly, but indirectly, when under the influence of insulin carbohydrate is changed into a state which allows oxidation and when this oxidation of carbohydrate takes place an elevation of the quotient occurs. Thus, according to Holten,[1] who has studied with extreme care 18 diabetics, "the diabetic respiratory quotient usually rises after insulin. The rise relative to the standard quotient is greater two hours than four hours after insulin (the mean is + 0.04 two hours after insulin and + 0.016 four hours after). Two hours after insulin a rough parallelism can be demonstrated between the blood sugar fall and the quotient rise, while four hours after insulin there is a connection between the quotient rise and the standard quotient, the rise being greatest with low standard quotients and least with standard quotients of about 0.80. With very high standard quotients (0.90 and over) a fall in the quotient after insulin was demonstrated.

"The explanation of these facts, as far as I can judge, must be that the insulin stimulates the combustion of carbohydrate. This combustion has fallen in intensity four hours after insulin. It is demonstrated that the blood sugar fall also diminishes in rapidity three to four hours after insulin. The fall in the quotient with high standard quotients is explained by the cessation of the production of fat from carbohydrate in consequence of the administration of insulin.

"In depancreatized animals the respiratory quotient does not find its final low level, of about 0.65, of combustion of food devoid of carbohydrate for some days. Is this not to be explained by the presence of insulin in the other tissues of the animal, existing there before and remaining there temporarily after the operation and, therefore, enabling the last remnant of glycogen in the body to be burned?

"The mean heat production two hours after insulin is 1.4 per cent lower, and four hours after insulin 1.5 per cent higher than before. For reasons discussed it must be taken for granted that in reality the insulin causes a fall in the heat production in diabetics. This is explained, at any rate partly, by the quotient rise in analogy with the fact demonstrated by Krogh and Lindhard that the total metab-

[1] Holten: Jour. Metab. Res., 1924, **6**, 1.

olism is higher with very low and very high quotients than with medium values. Probably insulin occasions a still greater decrease than can be explained by the quotient rise, as it endows the diabetic organism with the power of greater economy in combustion processes.

"The ventilation rises on an average 6.9 and 10 per cent, two and four hours after insulin, respectively. The discrepancy is partly explained by the difference in the total metabolism at these two times. The observed ventilation rise is about 3.5 per cent greater than would be expected from the quotient rise. This difference is presumably real and must be due to a slight diminution in the alveolar carbonic acid tension."

The remote gain in basal metabolism in the first few months of the use of insulin when only a few units were available is shown by the case of Bonnie P., Case No. 866. His metabolism at the beginning of treatment was the lowest in the series. His diabetes was of eight and a half years' duration. His weight had fallen to 50 per cent below normal standard. On October 14 and 16 his basal metabolism was 854 and 749 calories, respectively; in other words, −33 and −43 per cent by the Harris and Benedict standard. These values were well supported by values for the ensuing three weeks. Ten weeks later the metabolism showed a material gain, but he still was 26 per cent below the normal level. In March, 1923, this most faithful patient contracted erysipelas and died. Upon an average of 12 units insulin daily he had gained 10 pounds in weight. This accidental infection, which so far as is known was unconnected with the administration of insulin, prevented what might have been essentially a complete restoration to health. His gradual improvement seemed so wonderful to us all in those early insulin days that we were content to allow it to proceed slowly and gradually. Despite the gain in metabolism it will be observed the percentage of blood sugar rose from 0.13 to 0.27 per cent even though he remained essentially sugar free.

Few today know what patients formerly endured in order to live.

The metabolism of Case No. 2801 rose between October 7 and January 15 from −20 per cent to −5 per cent, the computed calories from 1128 to 1338 for the twenty-four hours. In Russell, Bowen, and Pucher's[1] case the metabolism rose from −38 per cent to −27 per cent with a gain in weight of 11 pounds.

The statements made above conform to the results of Wilder and Boothby.[2] Davies and his coworkers[3] give another explanation of the failure of the respiratory quotient to rise after insulin as

[1] Russell, Bowen, and Pucher: Bull. of Buffalo Gen. Hosp., 1923, **1**, 41.
[2] Wilder and Boothby: Jour. Metab. Res., 1922, **2**, 720.
[3] Davies, Lambie, Lyon, Meakins, and Robson: British Med. Jour., 1923, **1**, 847.

TABLE 8.—CASE NO. 866, BONNIE P. AGE AT ONSET IN APRIL, 1914, THIRTY-ONE YEARS. LOW BASAL METABOLISM.

Date.	Weight, net kg.	Urine.		Blood sugar, per cent.	Diet in grams.				Basal metabolism before and after treatment with insulin.[1]				
		Diac. acid.	Sugar, per cent.		C.	P.	F.	Cals.	Oxygen consumed per minute, cc.	Carbon dioxide eliminated per minute, cc.	R. Q.	Computed calories per 24 hours, cals.	* Variation from standard H. and B., per cent.
1915													
May 22	54.1	0	4.0	....	..	..	..	....					
June	52.7	0	0	....	33	91	158	1918					
1918													
Jan. 29	50.9	0	0	0.24	40	105	144	1876					
1922													
Oct. 13	....	0	0	0.12	31	74	75	1095					
Oct. 14	39.9	0	0	....	31	74	75	1095	124	99	0.79	854	−33
Oct. 16	42.1	0	0	....	31	74	75	1095	108	87	0.81	749	−43
Oct. 23	42.9	0	0	0.13	31	74	75	1095	124	100	0.80	857	−35
Oct. 25	41.6	0	0	....	37	80	81	1197	122	97	0.78	840	−36
Oct. 30	41.8	0	0	0.14	32	104	65	1059	124	102	0.83	864	−34
Nov. 6	41.5	0	0	0.19	51	93	94	1422	125	105	0.84	873	−33
Nov. 10	41.8	0	0.1	0.23	51	73	105	1441	130	106	0.81	901	−31
Nov. 24	42.5	0	0	....	51	73	105	1441	135	111	0.82	938	−29
Dec. 12	42.6	0	0	0.27	52	74	109	1485	139	111	0.80	961	−27
Dec. 15	42.8	0	0.2	0.22	52	74	121	1593	148	116	0.79	1021	−22
1923													
Jan. 23	43.0	0	0	0.17	52	74	121	1593	141	114	0.81	977	−26
Feb. 5	45.9	0	0										
Mar. 10		Erysipelas and Death											

Treatment with insulin began November 11, 1922. (See page 62.)

high as the fall in blood sugar would lead one to expect. They suggest that the liberation of the alkali consequent upon the removal of the acetone bodies might result in a compensatory retention of carbon dioxide.

TABLE 9.—CONDITION OF AUTHOR'S FIRST 83 PATIENTS TREATED WITH INSULIN, WITH CAUSES OF DEATH.

A. Fatal Cases.

Case No.	Age at onset years.	Total duration years.	Date.	Cause of Death.
705	52.0	14.0	Nov. 22	Angina pectoris.
866	31.0	8.9	Mar. 23	Erysipelas.
1305	10.5	5.5	Oct. 22	Coma.
1443	36.7	12.2	June 25	Diabetes.
1618	30.8	6.8	Jan. 24	Coma.
1794	25.2	8.0	June 25	Coronary thrombosis.
1889	13.4	8.4	Feb. 27	Coma.
1970	42.3	11.8	Feb. 25	Cardiac.
2046	37.2	1.9	Oct. 22	Staphylococcus, septicemia.
2148	40.7	12.9	Oct. 22	Cirrhosis of liver, tuberculosis.
2192	27.8	2.8	April 23	Coma
2201	41.3	24.6	Sept. 24	Angina pectoris.
2271	12.8	5.1	June 26	Furunculosis.
2290	55.3	6.9	Dec. 25	Pulmonary hemorrhage.
2302	69.4	11.2	Sept. 25	Cardiac, arteriosclerosis.
2304	47.3	4.1	Mar. 23	Cardio-renal.
2422	35.9	7.3	Mar. 26	Bronchopneumonia, coma.
2446	35.8	1.1	Dec. 22	Lobar pneumonia, coma.
2626	61.0	8.7	Mar. 24	Pneumonia.
2662	12.8	1.5	Sept. 23	Coma.
2668	12.6	7.3	June 25	Coma.
2716	62.6	5.3	Jan. 26	Coma.
2725	16.3	4.3	May 23	Coma.
2729	21.3	1.7	Nov. 23	Coma.
2801	14.9	1.2	Aug. 23	Coma.
2853	34.6	13.0	Feb. 25	Cancer of breast.
2908	62.7	12.2	Sept. 25	Hemiplegia.
2909	33.6	7.0	Sept. 25	Coma.
2946	44.4	2.1	June 24	Automobile accident.
2960	55.0	8.0	May 23	Prostate operation, apoplexy, hypoglycemia.
2972	65.8	5.3	May 26	Automobile accident.
2980	56.0	8.0	April 24	Cardiac.

Average age at onset of 32 fatal cases, 37.4.
Average duration of diabetes of 32 fatal cases, 7.4 years.
Average age at death of 32 fatal cases, 45.0.
Number of deaths in 1922, 5; 1923, 8; 1924, 5; 1925, 9; 1926, 4; 1927, 1.

(*h*) **Causes of Death of Diabetic Patients Treated with Insulin.**—In the *Journal of Metabolic Research*, 1925, **2**, Nos. 5–6. there were reported the first 83 cases treated with insulin from the writer's

series of diabetics. In Table 9 the fatal cases, numbering 32, of this group up to July 1, 1926, are recorded. There are no cases untraced. The remaining 51 patients are alive. The duration of the diabetes in the living cases has already exceeded that of the fatal, despite the living cases averaging fifteen years younger than the fatal at onset.

B. Living Cases.

Case No.	Age at onset years.	Total duration years.[1]	Case No.	Age at onset years.	Total duration years.[1]
632	30.0	15.0	2508	4.5	6.0
1245	44.6	15.5	2551	28.4	9.8
1446	33.6	16.3	2560	5.9	6.1
1469	10.7	9.6	2640	50.9	11.2
1500	41.5	12.4	2687	23.8	5.6
1542	37.1	9.9	2702	28.3	7.9
1544	48.8	11.8	2704	51.3	8.1
1616	5.5	7.9	2746	5.4	6.7
1750	36.3	10.9	2776	8.3	6.4
1895	14.8	6.9	2783	36.6	6.3
1930	26.8	7.3	2784	15.2	6.5
1931	42.3	11.0	2802	14.4	5.4
1949	7.1	7.2	2815	2.8	4.8
1997	10.8	7.8	2876	58.3	9.5
2024	10.8	6.8	2877	6.9	5.6
2063	14.3	8.7	2895	55.2	15.1
2174	44.1	6.3	2905	30.0	14.1
2256	14.6	8.4	2919	3.3	5.5
2296	29.8	14.5	2931	5.9	4.7
2366	14.2	6.7	2943	30.9	8.9
2383	35.8	5.8	2948	27.7	5.1
2397	42.8	5.9	2962	12.3	4.6
2406	34.0	9.2	2970	23.0	7.2
2419	14.4	7.3	2975	6.9	6.9
2448	17.9	5.6	2978	1.6	5.5
			2979	2.8	4.9

Average age at onset of 51 living cases, 23.6 years.
Average duration of diabetes of 51 living cases, 8.3 years.

A second and much larger group of insulin patients comprises the 1535 patients who received insulin between August 7, 1922, and July 1, 1926. These cases have been traced to the latter date. The results of the compilation of the fatal cases show them to number 253. The influence of insulin can be determined largely by the percentage of the deaths from coma and this was found to be 21 per cent. In Table 10 the deaths are classified by disease.

The third method of testing the effect of insulin is to inspect the causes of death of all patients who have died in the Banting Epoch which I call August 7, 1922—July 1, 1926, so far as my own cases are concerned. *The data are shown in Table 161, p. 375.*

[1] Duration to July 1, 1927.

TABLE 10.—DIABETIC PATIENTS WHO HAVE TAKEN INSULIN, EITHER REGULARLY OR INTERMITTENTLY. TOTAL FATALITIES AND FATALITIES DUE TO COMA.

Fatal insulin cases, arranged according to disease.	Banting, Era Aug. 1922 to July 1926.
Total deaths	258
A. Coma present	68
(Coma incidental to other disease)	16
B. Coma absent	
1. Cardiorenal	72
Cardiac	41
Nephritis	9
Apoplexy	14
Arteriosclerosis	8
2. Infections	67
Pneumonia	16
Influenza	2
Erysipelas	2
Pertussis	1
Meningitis	1
Acute abdominal	1
Appendicitis	2
Carbuncle	2
Gangrene, sepsis	37
Gas bacillus	1
Multiple infections	1
Pancreatitis	1
3. Tuberculosis	14
Pulmonary tuberculosis	14
4. Cancer	11
Tongue	1
Larynx	1
Stomach	1
Liver	2
Pancreas	5
Transverse colon	1
5. Inanition	3
6. Miscellaneous	19
Duodenal ulcer	1
Cirrhosis	2
Enlarged prostate	3
Suicide	3
Accidental	4
Old age	1
Hyperthyroidism	1
Insulin reaction	1
Diabetes	3

C. INSULIN IN THE TREATMENT OF DIABETES.

1. Introduction and Summary.—The use of insulin in the treatment of my series of diabetic cases was begun August 7, 1922, and since that date has been employed with more than 1500 patients of whom 293 were treated in the first twelve months. Seven of the first 100 diabetics coming for treatment received it, but with succeeding hundreds the number treated with insulin had risen progressively so that in May it had changed to 64 in 100 and by September, 1923, to 77 in the last 100 hospital admissions. Table 11 shows the number and percentage of all the true diabetics, irrespective of their entrance to hospitals, who have employed it. It is cheerful to note that 40 patients in the first 1000 of my series lived long enough to take insulin. Succeeding thousands show a steady increase of patients receiving insulin up to the fourth thousand. From then on the percentage remains constant and approximately two-thirds of the true diabetics are now using the drug.[1]

[1] All the insulin used in the treatment of the patients and in the investigations here recorded came originally through the instigation of the Insulin Committee of Toronto and upon their recommendation to the Eli Lilly Company. For the privilege of using insulin and its prompt and generous supply I am profoundly grateful. Whenever the word insulin is used in the text in connection with my patients, it means "Iletin," the trade name of the insulin manufactured by the Eli Lilly Company.

I have no prejudice against the insulin of any manufacturer, but when my diabetic children came back to life in 1922, they sent Mr. John K. Lilly a Round Robin Christmas letter and subsequently christened their dolls with his name.

TABLE 11.—DIABETIC PATIENTS WHO HAVE TAKEN INSULIN, EITHER REGULARLY OR INTERMITTENTLY. TOTAL FATALITIES AND FATALITIES DUE TO COMA, JULY 1, 1926.

Series.	True diabetics in the series.	Total insulin cases.		Fatalities among insulin cases.		Fatalities from coma.	
		Number.	Per cent.	Number.	Per cent.	Number.	Per cent.
1–1000	906	40	4	12	30	1	8
1001–2000	865	76	9	13	17	0	0
2001–3000	839	199	24	44	21	20	45
4001–4000	843	530	63	123	23	40	33
5001–5000	809	513	63	54	11	6	11
3001–5350	284	177	62	8	5	1	13
Total	4546	1535	34	254	17	68*	27

2. Justification for giving insulin:

(*a*) **The Abolition of Coma.**—The abolition of coma as a cause of death from diabetes in hospital and largely in the home has followed the introduction of insulin. Last year 43 of the 1241 patients seen, died, but there was no death of diabetic coma or in individuals under the age of fifteen years. Formerly two-thirds of my patients succumbed to coma. Table 11 also shows the decreasing percentage of deaths among the insulin treated patients as one progresses from the older to the more recently treated cases, namely from 30 per cent to 5 per cent, but it also shows the small number of deaths from coma even though these patients were scattered all over the United States.

(*b*) **The Prolongation of Life of Diabetic Children.**—A second justification for the use of insulin is the prolongation of the life of children which has occurred since its discovery. It is true that formerly the occasional diabetic child lived a decade and I have had 12 such, 3 dead and 9 now living, but the average duration was 2.4 years up to 1922. Today there are 51 living diabetic children who have had the disease 7.3 years and my 238 living diabetic children on the average have had diabetes 4.1 years. After making all allowances for fatal cases 23 months of life were added on the average to each of my diabetic children during the 2 years ending July 1, 1927.

(*c*) **Good Health.**—Good health, not tolerable health, is the right of the diabetic today and this is the real justification for the use of insulin. Physicians have hardly become accustomed to the change which insulin has wrought and even yet do not expect to see happy vigorous diabetics in their offices or quite understand that they

* Of the 68 cases shown death was due to other causes in 16 instances, although coma was present. The causes of death in these 16 cases were as follows: cardiac 2; infections 10; pulmonary tuberculosis 1; carcinoma of breast 1; inanition 1; hyperthyroidism 1.

should be in good health and entering into active life. When I think of what the diabetics were in the days of treatment with undernutrition and what they are now with insulin, I am reminded of the words of the Prophet Ezekiel thousands of years ago. No better description of the transformation which has taken place can be found than in the account of his vision. (See Ezekiel 37, 1 to 10).

3. Who Should Take Insulin.—Any diabetic who cannot keep the urine free from sugar and the sugar in the blood normal and himself in good health with the diet allowed should take insulin. Furthermore, insulin is desirable temporarily for those who do not need it, simply as a matter of education and insurance. An infection makes a diabetic worse and any diabetic may acquire an infection and, therefore, be faced suddenly with the necessity of using insulin. If he has been educated in its use, insulin represents so much accident insurance which is immediately available.

Insulin is also given by me to save the patient time and money and the hospital beds for diabetics in coma or with surgical or other emergencies. Thirty cents' worth of insulin will offset a patient-hospital-day, because with it the patient can be made sugar-free so much more rapidly. Perhaps a fifth or a fourth of my patients give up insulin upon leaving the hospital. I seldom urge insulin upon a patient save, of course, in coma or in infections or in a surgical or other emergency such as hyperthyroidism. It is possible to treat the individual by undernutrition and to bring him back to a fair condition of health by methods which were employed for nearly a quarter of a century. But such treatment never lasts and seldom the week goes by before the patient begs for insulin. Patients of this sort are often the best patients in the end, because they have character and can be trusted to use insulin intelligently.

The types of patients treated with insulin have ranged in severity from the severest to the mildest; in age from an infant of ten months to an old man of eighty-seven years; and in duration of the diabetes from a few days to more than a quarter of a century.

The policy adopted in the treatment of diabetes with insulin has been to utilize along with it all those measures which have proved of the greatest value in the treatment of diabetes without insulin. These are: adherence to a diet which will keep the urine sugar-free, avoidance of overnutrition or extreme undernutrition, and a method of life compatible with the strength such a diet affords, particularly utilizing exercise because of its action in lowering the percentage of sugar in the blood.

Insulin does not cure diabetes.[1] Insulin does not allow a diabetic

[1] Certain sentences and paragraphs in what follows appeared in articles by the author in the Jour. Am. Med Assn., 1923, **80**, 1581, and Jour. Metab. Res. 1923, **2**, 651.

to eat anything he desires. It is a potent preparation alike for evil and for good. Thomas D., Case No. 1305, omitted insulin for five days, continued his relatively high diet, developed a mild infection, and entered the hospital to die seven and a half hours later of coma. That was in October, 1922, when we had little insulin and still less experience with its use. A patient having diarrhea but with a tolerance for 114 grams carbohydrate took 1 unit and the blood sugar fell to 0.03 per cent, and another patient, Case No. 5615, with a tolerance for 140 grams carbohydrate, though also having diarrhea developed so severe a reaction that glucose intravenously was required to revive her. Her blood sugar fell to 0.04 per cent. Conversely, Miss M., Case No. 1542, our first case and the severest diabetic on our list, who had gone down to the street from her apartment but once in nine months, felt able after six weeks of treatment to walk with ease four miles daily, has gained 60 pounds in four and a half years, and is active in her occupation as head nurse. In California a doctor's secretary made equally as spectacular a recovery even with the handicap of advanced pulmonary tuberculosis. Mrs. M., Case No. 2980, with rapidly ascending gangrene, fever, 5 per cent sugar, and marked acidosis, was first seen on a Sunday, brought to the hospital the same evening, given insulin, and the thigh amputated at 10 o'clock the next morning by R. C. Cochrane. After eight days the 30-unit daily dose of insulin was omitted; ten days later she became sugar-free and remained so for months, ultimately dying in 1924 of heart failure.

Insulin is a remedy primarily for the wise and not for the foolish, be they patients or doctors. Everyone knows it requires brains to live long with diabetes, but to use insulin successfully requires more brains. Two ignorant patients, who were helped by insulin and needed it, went home without it, and their physicians, though living nearby, did not take the trouble to come to the hospital either to see the patients or learn about insulin. In contrast was the case of an alert little girl of fifteen years, Case No. 2802. After two weeks of our best efforts with dietetic treatment alone she seldom could keep sugar-free, yet she was wise and with insulin has gained 39 pounds in 3.5 years, 56.5 per cent of her body weight. Her elderly, overworked country doctor traveled nearly 200 miles to see for himself this new form of treatment and to take her home. She is now 19.4 years of age, 60 inches tall, happy and active. We have had no coöperation in doctor and patient greater than this.

Insulin is less dangerous than morphine, and it has these advantages; whereas an excess of morphine leads directly to sleep, coma, and death, an overdose of insulin causes a warning train of symptoms beginning with nervousness and extreme hunger as the blood

sugar drops below 0.07 per cent, progressing to tremor and sweating, subconscious or evident, and ending with unconsciousness and convulsions as the blood sugar reaches 0.03 per cent. Death is possible. Again, unlike morphine poisoning, recovery follows the simplest of measures, the juice of an orange or 1 to 3 teaspoonfuls of sugar, and takes place promptly, often within five or ten minutes.

Insulin has revolutionized diabetic treatment in more ways that one: (1) It can give more food, strength, and weight, but (2) to do this it demands not only a knowledge and respect for the diabetic diet on the part of the doctor and patient, but adherence to the same if the diabetic wishes to get his money's worth for the insulin he injects, and (3) it promotes coöperation in effort to combat the disease between doctor and patient.

The first cases of diabetes treated beginning in August, 1922, were those who were the most severe. Thirty were selected for this reason from among about 1000 diabetic patients living at that time. Later cases of milder degree were added to the list, including several representing surgical emergencies. Still later others were added to the list who were distinctly less severe in type, yet quite unable to maintain weight and do their daily tasks. A certain number of children with acute onset were also chosen for treatment. The results of treatment in these first 83 cases are shown in Table 9. Among the group treated were many so-called (to use Woodyatt's term) "pedigreed" diabetics in that they had already found their way into medical literature. These were Cases No. 632, 866, 1305, 1542, 1794, 2174, 2560. See Case Index at end of volume.

TABLE 12.—EFFECT OF INCREASE IN DIET AFTER LONG-CONTINUED UNDERNUTRITION—NO INSULIN. CASE NO. 866.

Date.	Diacetic acid.	Sugar in urine, gm.	Average daily diet.				Blood sugar.	
			C.	P.	F.	Cals.	Date.	Per cent.
October:								
14–24 inc. . .	0	0	31	74	75	1095	Oct. 22	0.13
25–31 inc. . .	0	0	36	84	79	1191	Oct. 30	0.14
31–Nov. 5 inc.	0	0	43	86	86	1290	Nov. 6	0 19

The increase in the well-being of the patients not only in weight and strength, but also in spirit, was remarkable soon after the beginning of treatment. Since many of these patients were of the severest type of undernourished diabetics and were given far more food than they had had for months or years, the question arose as

to whether diet or insulin was responsible for the improvement. Consequently. Mr. P., Case No. 866, who had had diabetes for eight years, whose original weight was halved, whose metabolism was the lowest of any reported diabetic in the world, was asked to return to the Clinic and undergo an increase of diet exactly like that of our first case, Miss M., Case No. 1542. The results obtained with Mr. P., are summarized in Table 12. This table shows that on a diet of 1095 calories the fasting blood sugar was 0.13 per cent and the urine sugar-free. When this diet was increased by 100 calories or 10 per cent, the urine remained sugar-free as before, but the blood sugar rose to 0.14 per cent. Again the diet was increased by 100 calories, making a total increase of 20 per cent from the original diet. The urine still remained sugar-free, an index of the long years of faithful following of dietetic rules by this patient, but the blood sugar at the end of the period had risen to 0.19 per cent. Sugar soon appeared in the urine. With insulin this patient tolerated an increase in diet perfectly well and gained 10 pounds in weight, but I am very sorry to say that on March 10, 1923, he succumbed to erysipelas, though in no wise connected with his treatment with insulin. See pages 62, 63, and Table 12.

Sexual maturity has taken place in a large number of children. Menstruation has returned in 2 of the severest cases after an absence of six years and six and a half years respectively. Prior to treatment with insulin I recollect but 1 diabetic female whose catamenia, having once ceased, returned.

4. **Dosage.**—The quantity of insulin which a diabetic patient requires to keep sugar-free and the blood sugar normal varies primarily with the severity of the disease and intercurrent complications, and secondarily with the diet and amount of exercise.

The severe diabetic manufactures or has available less endogenous insulin than the mild diabetic and consequently more exogenous insulin must be administered to make up for his deficiency. First among the complications are infections. These invariably make the diabetes more severe and, therefore, increase the demand for insulin. So does coma, even though it supervenes when the disease is mild. A diabetic with an incompetent heart or a damaged kidney requires extra insulin and patients with a high blood-pressure as a rule need more than those whose blood-pressure is low. But beware! (See p. 692.)

Conversely, the thin, frail, feeble patient whether young or old is best treated with a small dose and even then may surprise his attendants with a terrifying reaction. If a patient fails to digest a meal, and it matters little whether it is vomited or retained in the stomach, his need for insulin suddenly drops and a reaction

may ensue akin to that of the cachectic patient. Likewise in the presence of diarrhea a very little insulin, even a single unit, may lead to unconsciousness.

Secondarily the diet regulates the dose of insulin required. First of all it is the carbohydrate in the diet, but closely concerned are the total calories, as well as the protein and fat. Perhaps it is not so much the available glucose-forming material in the latter as it is the fatty acids which tend to turn the patient toward acidosis which in and of itself increases the need for insulin. Here in America we reckon 58 per cent of glucose-forming material from protein and 10 per cent from fat. In Germany the glucose from protein is reckoned at 80 per cent and that from fat disregarded. Hence with this confusion one had best cling to carbohydrate and total calories in planning diets and glucose equivalents of a unit of insulin.

Exercise exerts a marked effect on insulin needs. Case No. 632 says a game of golf is worth 5 units. Days without golf he takes 20 units in the morning and 5 units at night, but on days with golf he omits the night dose. Even before the discovery of exogenous insulin we knew this and recognized that the milder diabetic who could burn some carbohydrate could burn far more with exercise and that the severe diabetic who could burn little carbohydrate was made worse when an extra quantity of endogenous food, caused by exercise, was thrust upon him. Perhaps we did not quite realize that exercise increased the production of insulin in the mild diabetic, but was unable to do so in the severe, or if it did not increase the production of insulin enabled it in some way to make ready for oxidation the additional carbohydrate which exercise set free. Exercise in truth in the diabetic must always be thought of in terms of food. Apparently it is only the severest of the severe diabetics who fails to react to exercise with a lowering of blood sugar, *i. e.*, with increased secretion of insulin. Before insulin I had in mind only one case and I recall none since. Just as with normal individuals, such as those who take part in a Marathon run, exercise lowers the blood sugar and in the case of extreme exercise such as that cited to 0.045 per cent, so exercise lowers the blood sugar in diabetics. Under its influence carbohydrate utilization rises and unless insulin is decreased or carbohydrate in the diet increased the patient experiences a reaction.

Infections and exercise both increase the metabolism, but in the former case the increase involves pathological processes and the insulin may be secreted[1] less freely or be less potent. Exercise is normal and, unless excessive and in an exceptionally severe diabetic, does good.

The disease and its complications, the diet and exercise are the

[1] Sweeney: Arch. Int. Med., 1928, **41**, 420.

four variables with which one must reckon in prescribing insulin. But there is a fifth variable which must not be overlooked, namely the patient, because all depends on his reliability, regularity of life and intelligence. These five variables explain in large measure why in some clinics little insulin is used and in others more.

Small doses of insulin from the start have characterized my method of treatment for several reasons. First the glucose equivalent is relatively much larger per unit of insulin with small rather than with large doses of insulin. Thus a depancreatized dog fed 600 grams of meat and 100 grams sucrose was given 20 units of insulin and on two different days[1] metabolized 5.8 grams glucose per unit, but when fed the same diet and given 40 units, he metabolized 3.0, 3.3, 3.1, and 3.0 grams glucose per unit. Incidentally it should be mentioned that the larger amount of carbohydrate given the more per unit insulin was utilized. With carbohydrate dosage increasing from 50 to 100 to 150 grams the glucose equivalent per unit rose from 3.7 grams to 5.8 grams to 7.6 grams per unit insulin. The glucose equivalent of insulin, when all conditions of diet and kind of insulin were the same, varied within a relatively narrow range. This last conclusion is contrary to the experience of John.[2] Second, with one patient, Case No. 1194, whose carbohydrate tolerance was 114 grams the injection of 1 unit lowered the blood sugar to 0.03 per cent. Allen[3] has reported a similar result with 0.5 unit. The possibility that this might occur with other patients whose tolerance was far less, indicated the necessity for the use of small doses in the routine treatment of large numbers of cases remaining in the hospital for short periods or by physicians in general practice, and it is especially for the latter group that my system of diabetic treatment is planned. Furthermore, to save time and to educate the patient in the use of insulin and diet it is my practice to begin insulin in most cases before the first meal following entrance to the hospital. At this time the tolerance of the patient is unknown but a moderately restricted diet is prescribed for the ensuing twenty-four hours usually containing carbohydrate 60 to 100 grams, protein a little under 1 gram per kilogram body weight, and sufficient fat to make a total intake of about 20 calories per kilogram. Within one day the diet is readjusted and enlarged. For these reasons it has been my custom to begin with small doses.

The first dose of insulin is usually 5 units before each meal, as often less as more, and is maintained, decreased, or increased on subsequent days as glycosuria and calories require. Usually as

[1] Allan: Am. Jour. Physiol., 1924, **67**, 275; *see also* Jordan: Am. Jour. Physiol., 1927, **80**, 441.

[2] John: Arch. Int. Med., 1927, **39**, 67.

[3] Allen: Jour. Metab. Res., 1922, **2**, 866.

time goes on the noon dose is omitted and the dose before breakfast made somewhat larger than the dose before the evening meal.

A third reason for small dosage was the sad experience with a boy, Thomas D., my second case, who during the absence of his local physician and with other serious illness in his home, gave up insulin for five days, failed to restrict his diet, developed a slight infection, and went into coma from which he died. Unquestionably large doses of insulin will allow patients to take more food and thus gain weight very rapidly, but with large doses of insulin the patient is walking on longer insulin stilts and his equilibrium is therefore correspondingly endangered. With small doses progress is more gradual, but quite as sure and certainly safer. A fourth reason for using small doses was the fear, not entirely groundless, that as time went on the dosage of insulin might need to be increased, and indeed this is true, but not so much due to a diminution in the power of insulin as to an increase in the diet. Fifth, the treatment of diabetes with insulin should follow the best lines of treatment of diabetes without insulin. In other words, overfeeding should be discountenanced, and overfeeding is apt to result when large doses of insulin are given.

The cost of insulin is the sixth reason which deters from large doses. Most patients with diabetes are in moderate circumstances. It is unfair to treat patients in the hospital with large doses of insulin without cost and then to send the same patients home expecting them to pay for that dosage of insulin indefinitely. The sale of insulin is a boon rather than a detriment to insulin therapy in general, but the expense should be kept low. When a patient pays for insulin, he is far more likely to use it wisely. Patients become very keen and learn with surprising readiness at which meals following insulin the carbohydrate can be increased or decreased, often adjusting the dose far more skilfully than can their physicians, who are seldom as familiar with all their conditions of life. Success with diabetic patients depends largely upon their willingness to make sacrifices for hospital board, treatment, and now insulin. The diabetic dependent upon charity seldom does well, just as it is hard for a rich diabetic to conform to rules, though he is far more apt to attempt it today than formerly.

In general it is safer to work from low units up than from high units down. The doses of insulin which my patients at the present time are receiving can be illustrated in three ways: (1) With a group of 30 successive hospital patients; (2) with a similar group of former patients reporting at the office for a single visit; (3) with five groups of patients, 10 in each group, whose ages vary from childhood to sixty-nine years, who have been under treatment with insulin for four or five years.

TABLE 13.—INSULIN IN THE TREATMENT OF 10 DIABETIC PATIENTS BETWEEN THE AGES OF FIFTEEN TO TWENTY-NINE YEARS INCLUSIVE. 1923 TO 1926.

Year.	Number.	Age at onset, average years.	Duration, average years.	Weight, average pounds.	Insulin dose, average.	Diet.		
						Carbohydrate, average gm.	Protein, average gm.	Fat, average gm.
1923	10	22	3.3	110	34	74	59	132
1924	10	22	4.3	117[1]	22[4]	70[7]	61[10]	135
1925	10	22	5.3	132[2]	45[5]	66[8]	64[11]	125
1926	10	22	6.3	137[3]	47[6]	76[9]	68[12]	128

[1] Average of 9.
[2] Average of 8.
[3] Average of 7.
[4] Average of 9.
[5] Average of 8.
[6] Average of 8.
[7] Average of 9.
[8] Average of 7.
[9] Average of 6.
[10] Average of 9.
[11] Average of 7.
[12] Average of 6.

TABLE 14.—INSULIN IN THE TREATMENT OF 10 DIABETIC PATIENTS WITH AGE OF ONSET BETWEEN THIRTY AND THIRTY-NINE YEARS INCLUSIVE. 1923 TO 1926.

Year.	Number.	Age at onset, average years.	Duration, average years.	Weight, average pounds.	Insulin dose, average.	Diet.		
						Carbohydrate, average gm.	Protein, average gm.	Fat, average gm.
1923	10	34	3.2	113	18	63	61	130
1924	10	34	4.2	117[1]	28[3]	65[5]	61[8]	121[11]
1925	10	34	5.2	119[2]	29[4]	57[6]	62[9]	126[12]
1926	10	34	6.2	130	33	67[7]	63[10]	132[13]

[1] Average of 8.
[2] Average of 9.
[3] Average of 8.
[4] Average of 9.
[5] Average of 8.
[6] Average of 8.
[7] Average of 8.
[8] Average of 8.
[9] Average of 8.
[10] Average of 8.
[11] Average of 8.
[12] Average of 8.
[13] Average of 8.

My present dosage of insulin is greater than five years ago, but not much greater. At that time the average daily dosage for the first 127 patients for an average period of one hundred and seven days was 11 units daily. Twenty-nine diabetic patients in the hospital on August 22, 1923, were receiving an average of 18 units. With 31 children at that early period the average dosage was 10 units during an average period of one hundred and twenty-two days, but with 13 children under the age of fifteen years, the average dosage was 4 units for an average period of eighty-nine days. The largest quantity of insulin taken by one of my patients in 1923, excepting in coma, was 63 units, Case No. 2256; she is now taking 56 units. Case No. 2801 then took 45 units; she died in coma

August 18, 1923. Miss M. (Case No. 1542) at times received 35 units, and now receives 45 units. The first cases treated erred in receiving toolittle, and undoubtedly if I had given insulin more freely to Mr. P., Case No. 866, he would have gained more than 10 pounds in thirteen weeks and would have resisted erysipelas better.

TABLE 15.—LIVING INSULIN CASES BETWEEN THE AGES OF FORTY TO FIFTY-FOUR YEARS.

Year.	Number.	Age at onset, average years.	Duration, average years.	Weight, average pounds.	Insulin dose.	Diet.		
						Carbohydrate, average gm.	Protein, average gm.	Fat, average gm.
1923	10	45	6	114	11	64	63	109
1924	10	45	7	125	17	75	68	130
1925	10	45	8	128	23	79	56	94
1926	10	45	9	132	27	99	69	115

A few patients formerly under my care but now living in different parts of the country report the use of large doses. Thus Case No. 1782, with onset of diabetes at age of 20.7 in September, 1919, is now employing 136 units, 40—40—40—16, with a diet of carbohydrate 226 grams; protein 55 grams; fat 134 grams. The lowest weight he reached during his diabetes was $92\frac{3}{4}$ pounds in June, 1922, and now his weight is 172 pounds. Now and then he has an insulin reaction. I saw him last in November, 1921.

TABLE 16.—TREATMENT OF 10 DIABETIC PATIENTS WITH AGE OF ONSET BETWEEN FIFTY-FIVE TO SIXTY-NINE YEARS.
1923 TO 1926.

Year.	Number.	Age at onset, average years.	Duration, average years.	Weight, average pounds.	Insulin, dose.	Diet.		
						Carbohydrate, average gm.	Protein, average gm.	Fat, average gm.
1923	10	60	3.7	126.0	13	75	59	121
1924	10	60	4.7	112.6	14	64	74	111
1925	10	60	5.7	128.0	20	83	61	130
1926	10	60	6.7	128.0	16	82	63	108

Case No. 2476 did not even measure his insulin, ate liberally, took insulin freely and gained 100 pounds in weight. He returned because of the dreadfully alarming reactions which drove his family to distraction. We reduced his insulin to 60 units, limited his

carbohydrate to 36 grams for two meals, and one of these reactions developed. As four of us doctors could not get near him to give carbohydrate or adrenalin, it was possible to observe the maniacal actions of a patient under insulin during hypoglycemia. By the end of two hours he quieted down, with glucose intravenously and orally he gradually improved, and his exhaustion was over in twenty-four hours. I suppose the advocates of high insulin dosage will retort—see how strong big doses of insulin make a patient and how much weight can be put on!

TABLE 17.—COMPILATION OF GROUPS 1, 2, 3, 4 AND 5. SHOWING COMPARISON OF AGE AT ONSET, DURATION, WEIGHT, INSULIN, AND DIET. 1923 TO 1926.

Group (age).	Number.	Age at onset, average years.	Duration, average years.	Weight, average increase (lbs.).	Insulin, average increase (units).	Diet.		
						Carbohydrate, average increase (gm.).	Protein, average increase (gm.).	Fat, average increase (gm.).
1. 1 to 14 . .	10	9.5	6.2	32	9	37	17	−4
2. 15 to 29 . .	10	22.0	6.3	27	13	2	9	−4
3. 30 to 39 . .	10	34.0	6.2	17	15	4	2	2
4. 40 to 54 . .	10	45.0	9.0	18	16	35	6	6
5. 55 to 69 . .	10	60.0	6.7	2	3	7	4	−13

One other of my cases I know has taken 100 units. I had not seen him for four years. He was too fat! Why should a diabetic deliberately ape the state of the majority of diabetics before they contract the disease?

The quantity of insulin required varies with the severity of the diabetes, with infections, with acidosis, with food, exercise, and weight. Allen says the minimum insulin requirement of children is lower than that of adults but the requirement per kilogram of weight is considerably higher. This may be due to growth and more food. The difference in dosage between that necessary for maintenance of weight and that demanded for growth is all important.

The minimum insulin requirement compatible with sugar-freedom can be crudely estimated in depancreatized animals and in patients with maximally severe diabetes in a state of extreme inanition. This requirement may apparently be as low as 4 units per day in a young child, but is probably 12 units or more for an adult. Any diet sufficient for maintenance of life even on the lowest plan of nutrition probably requires a doubling of these figures. The need for insulin is related quantitatively to the body mass as well as to the quantity of food to be metabolized (Allen).

Dosage has not increased as much in our series after the patient has gained weight and is maintaining it, as it has increased while the weight has been advancing. This statement is made as an impression, but is supported by some facts. Addition of diet, however, has caused an increase in the amount of insulin required even though the tolerance appeared to be improving. Miss M., Case No. 1542, when weighing 30 kilograms and receiving 1200 calories, required in the neighborhood of 30 units of insulin daily. With her weight at 40 kilograms on the same diet, or 30 calories per kilogram body weight, she required 10 units. When the diet was then increased 5 per cent, it was necessary to increase the insulin as well. When her weight has risen to 46 kilograms and the calories to 1310 or 29 per kilogram, the insulin needed was much more. Now in 1927 she weighs 136½ pounds naked, takes approximately carbohydrate, 58 grams; protein, 56 grams; fat, 110 grams, and 45 units of insulin. In this instance and in some others the quantity required appeared to depend chiefly upon the amount the diet was in excess of actual body requirements. For gain in weight more insulin was required than for maintenance of weight. It is the surplus diet and the gaining weight, therefore, which demand increasing units of insulin rather than the weight already added.

A very one-sided view of the dosage of insulin would be obtained if reference was not made to the methods of other physicians whose treatment of diabetes is known to yield good results. Perhaps the largest doses are given by Sansum in California and Geyelin in New York City. In the discussion of the High Carbohydrate Diet detailed consideration will be given to their views. Those whose diets more nearly approach the theoretical ketogenic-antiketogenic ratios prescribe less insulin because they contain the least quantity of carbohydrate which it is safe to give. Should one so desire one could calculate the standard basal metabolism for the patient, add 20 per cent or more for activity, and estimate by Woodyatt's, Shaffer's, Wilder's or some other ratio the distribution of carbohydrate, protein, and fat. Then with allowance for excretion of sugar the dose of insulin could be calculated on the basis of 1 unit for 1 gram, or 1½ grams, or 2 grams of glucose according to each one's idea of the glucose equivalent of 1 unit of insulin. How variable the glucose equivalent of insulin is, even in the same patient, Priesel and Wagner[1] have shown. Holm[2] even figures from his experiments and calculations that the carbohydrate equivalent of 1 unit was 8.75 grams glucose.

Theoretical calculations as to the amount of insulin a patient requires are unsafe, because in the first twenty-four hours of treat-

[1] Priesel and Wagner: Klin. Wchnschr., 1927, **6**, 65.
[2] Holm: Arch. f. exp. Path. u. Pharm., 1927, **121**' 368.

ment the patient improves so rapidly, and delays as well as danger are caused if one waits to determine the tolerance. In these theoretical estimations of the amount of insulin needed I have never seen allowance made for the well-known fact that the first 10 units of insulin are more effective than the second 10 units, which in turn are more effective than the third. However, theoretical dosage must have proved its value or well-known clinicians would not employ it.

5. **Frequency of Administration of Insulin.**—The frequency of injection depends first of all upon the severity of the disease. The severe diabetic requires insulin three times a day, because the action of insulin is largely over in eight hours. A few patients require insulin four times a day to keep sugar-free throughout the twenty-four hours. Temporarily in coma and in the presence of infections insulin must be given still oftener, due I suspect to its early destruction in the body fully as much as to any loss of potency. It would be interesting and valuable to know whether 10 units given every ten minutes in diabetic coma would do more good than 60 units of insulin given once an hour. (See p. 661.) In general it is recognized that 30 units of insulin divided into three doses in the day are more effective than when given in a single dose. The mild diabetic gets along very well on a single dose of insulin, because he is sugar-free when without food in contrast to the severe diabetic who secretes sugar in the urine constantly though more after meals. I was struck at Bertnard Smith's clinic to see how few patients took their insulin more than twice in twenty-four hours and yet the doses were moderate. When one sees patients who are taking very large doses it is not uncommon to find that they take insulin but twice a day. I suspect that the early and earnest advocates of a single dose of insulin daily have changed their ideas, because one hears little said in favor of this plan today. Bliss[1] working with a depancreatized dog found that hypoglycemic collapse occurred if the insulin was given at one dose, even if all the food for the day was crowded into five hours.

Fletcher and Campbell[2] and the Toronto group call attention to the development of acidosis in the later hours of the day if insulin is given but once in the twenty-four hours. It is my impression that in giving insulin twice a day I am simply following the example of the Toronto workers in this, as in many other respects. It is sometimes desirable to give insulin late in the evening so that the patient will wake up a mild diabetic because of the glycogen thereby stored in his liver. I know that by so doing less insulin will be needed in the next twenty-four hours.

[1] Bliss: Jour. Metab. Res., 1922, **2**, 385.
[2] Fletcher and Campbell: Jour. Metab. Res., 1922, **2**, 637.

With children who have devoted mothers it is often possible to omit an occasional evening dose, and with Billy B., Case No. 2560, this is often done for several days at a time. I question, however, the advisability of endeavoring to see with how few units a patient can get along. If the urine of the patient is kept sugar-free constantly throughout the twenty-four hours, such an attempt is quite justifiable, but otherwise not.

The number of doses in the second place depends upon or regulates the distribution of carbohydrate between the three meals. At the Deaconess Hospital the nurses have dietary schedules for a given quantity of carbohydrate, protein, and fat and these are divided between the meals according to the number of doses of insulin.

The four period urinary testing of urine is of great advantage in deciding about the proper dose of insulin as well as about the diet. If the morning urine, after breakfast to just before lunch, contains sugar too much food, carbohydrate, or calories were given at breakfast or not enough insulin before it; if the afternoon urine, from after lunch to before an evening dinner, contains sugar the same rule applies; and likewise this holds for the evening urine, that after dinner until and including on retiring, as well as to the night urine, which is that for the remainder of the twenty-four hours.

The time of administration of insulin is usually before a meal because the object of the dose is to bring the blood sugar to a normal level. As insulin reaches its peak of action in about an hour it is usual to give it one-half hour before a meal, because the blood sugar tends to reach its height at about one-half hour after a meal and thus the best effect of insulin counterbalances the worst effect of the diet. Occasionally the blood sugar is so high that it is advisable to give the insulin a full hour before a meal. At other times at night the blood sugar before dinner may be relatively low and one obtains better results if the insulin is given after eating. Particularly is this the case in hospitals because the three meals, breakfast, dinner, and supper come so near together.

How many variables must be considered in the administration of insulin! How thankful all will be when insulin or something as good as insulin can be given in such a form (1) that its action will be for twelve hours or more instead of eight hours, and (2) that no sharp peak effect of insulin will occur due to rapid absorption but that slow absorption will be the rule. Attempts on our part to produce this latter effect by injecting insulin into the fat tissue of the body so as to prolong the period of absorption have not met with notable results.

A sugar-free urine is just as necessary in my opinion with diabetic patients treated with insulin as diabetic cases treated without

insulin. I believe that unless the urine is kept sugar-free during the additional length of life these patients will enjoy, complications due to hyperglycemia and glycosuria will ensue. Hitherto there has been comparatively little opportunity to determine what the effects of hyperglycemia for long periods would be, but with the avoidance of death from coma the lives of these patients will be so much prolonged that the effects of hyperglycemia will be manifest. Until proof accumulates that hyperglycemia is not accompanied by distressing complications such as cataract and arteriosclerosis, it appears wiser to maintain urine and blood as nearly normal as possible.

The status of the patient is known with difficulty if glycosuria is present. The presence of more than a trace of sugar involves innumerable quantitative analyses. The whole virtue in modern treatment has been the abolishment of quantitative analyses and elaborate methods. To bring these all back into practice will retard the advance we have laboriously attained without insulin. One cannot have frequent quantitative analyses of sugar in the urine year in and out and so one loses control of the utilization of the diet.

Glycosuria is not only tolerated but encouraged by several clinicians highly skilled in the treatment of diabetes. Even 20 grams of glucose in the urine are allowed with design. To this plan of treatment I am emphatically opposed. Diabetics for years have been taught to keep the urine sugar-free and it has been the general opinion among the best men treating diabetes hitherto that the danger attending diabetics with urines free from sugar is less than when the urine does contain sugar. If one faces about, allows or encourages the presence of sugar in the urine today, one breaks the patient's morale. If it is immaterial to success in the treatment of diabetes whether the urine is free or not free from sugar the patient will see no reason why he should not deliberately take food sufficient to allow the presence of sugar in the urine. Success in the treatment of diabetic children lies in keeping their urine sugar-free. If sugar appears, a penalty follows. Take away the necessity to keep the urine sugar-free and the control of that diabetic child is gone forever.

Directions for Patients Taking Insulin.—1. Insulin is prepared in solutions of different strengths. Learn your dose in units (not in cubic centimeters) and how to measure the amount of solution to give that number of units. One strength has 10 units in 1 cc. and is called U-10, another has 20 units in 1 cc. and is called U-20, another 40 units and another 80 units, termed U-40 and U-80 respectively. No matter how the syringes are marked $\frac{1}{10}$ of a

cubic centimeter would contain $\frac{1}{10}$ of the units of the quantity in a whole cubic centimeter of the special preparation used.

2. An insulin reaction usually occurs two to four hours, but may occur earlier or later depending upon the diet and even as late as fourteen hours after an injection, and can be recognized by the sudden onset of hunger, tremor, sweating, unconsciousness. Other symptoms are pallor, faintness, nervousness, dilated pupils. The urine is sugar-free unless it has not been voided for some time.

3. A reaction should be treated by eating an orange, or by taking other carbohydrate such as 2 or 3 lumps of sugar or 2 or 3 teaspoonfuls of corn syrup.

4. At present it is not prudent to use insulin without daily examinations of the urine.

5. If your usual exercise is not obtained, on that day reduce your diet.

6. Arrange for a supply of insulin for two weeks in advance.

7. If your supply of insulin fails:

(*a*) Notify your doctor by telephone or telegraph, and

(*b*) Omit one-third of your diet.

8. If you have symptoms such as nausea, vomiting or pain, which prevent taking food, do not omit your insulin unless the urine is sugar-free. Call your doctor. Vomiting is an evil omen in diabetes.

For the instruction of patients who receive insulin, the following directions have been prepared.

INSTRUCTIONS FOR GIVING INSULIN SUBCUTANEOUSLY.—*A. Sterilizing.*—Wash the hands thoroughly with soap and water. Wrap the cylinder and the piston of the syringe separately in a piece of cloth and cover them and the wired needle with cold water in a dish, heat to boiling, and let boil for three minutes. Pour off the water, being careful not to touch anything in the dish, and allow to cool by standing. Paint the top of the insulin bottle with medicated alcohol.

B. Loading.—Draw out the piston so that the syringe contains a little more air than the amount of insulin needed.

Push the needle cautiously but firmly through the rubber cap until the point is just seen, invert the bottle; force the air from the syringe into the bottle and then withdraw as much insulin as is desired. By holding the syringe and needle-point upward air is easily expelled from the syringe before withdrawing it from the bottle.

C. *Injecting.*—The desirable site for injecting insulin is one where the skin is loose. It is well to change the place with every dose. For example, the left thigh on Monday, the right thigh on Tuesday, the left arm on Wednesday, the right arm on Thursday, the left leg on Friday, the right leg on Saturday, and so forth.

Having decided on the site for injection, rub gently with alcohol an area as large as a walnut.

Pick up a fold of the skin between the thumb and forefinger of the left hand, and with the syringe held parallel to the skin, push the needle quickly and firmly into the fold nearly up to the butt. The tip of the needle should then feel loose in the soft tissue between the skin and the muscle.

Then change hands so that the butt of the needle and the end of the syringe are held in the thumb and the first two fingers of the left, and the piston is held by the right hand.

Force the insulin gradually out of the syringe, while withdrawing the needle slowly, so that the insulin may not all be left in one spot.

If the insulin has been given too close to the upper layers of the skin a white blister-like elevation will appear.

Touch the spot lightly with clean cotton until the insulin has been absorbed.

D. Cleaning Up.—Rinse the syringe and needle with cold water immediately. Dry the syringe and needle with a cloth and blow air through the needle repeatedly with the syringe. Rub off any irregularities of the point on a fine stone such as a razor hone. A fine wire should always be kept in the needle.

E. Needles.—The needle found at the New England Deaconess Hospital most satisfactory for the administration of insulin has been one of 25-gauge and $\frac{7}{8}$ inch long. A shorter needle, $\frac{5}{8}$ inch, is advisable for beginners, because it requires less skill to use, and is less apt to break, but the longer penetrates to the deeper subcutaneous tissue. Some of the patients have used at home a gold needle with success, and this may prove to be especially adapted for continuous treatment. So far platinum needles have been only moderately satisfactory. Needles of "rustless steel" have been useful.

Site of Injection, Insulin Maps.—The site of injection of insulin is not an indifferent matter. If it is injected into the upper layers of the skin it acts more powerfully, but the pain and the so-called "insulin burns" make this undesirable. Conversely I have tried giving it before the evening meal deeply into the lower fat layers to delay absorption, but only with indifferent success. It is best injected subcutaneously, distributing the solution so as not to injure any one special area of skin. But most important of all is to vary the site of injection. For this purpose my nurses have made insulin maps especially for the little children. By this I mean the body forms printed with dots for each dose of insulin during the month so that no two doses will be in the same place, and thus avoid injuring the skin. All my diabetics learn to give insulin on the right side of the body in the morning and the left

side at night, and in four longitudinal and parallel lines down the extremities. The Sunday dose begins at the upper end of the line and the Saturday dose is at the lower end. Never give insulin many times in one place. Necrosis of tissue occurs, an abscess may form, failure of absorption is bound to ensue, the dosage in consequence is increased and if by chance the same quantity is given in another part of the body a reaction follows.

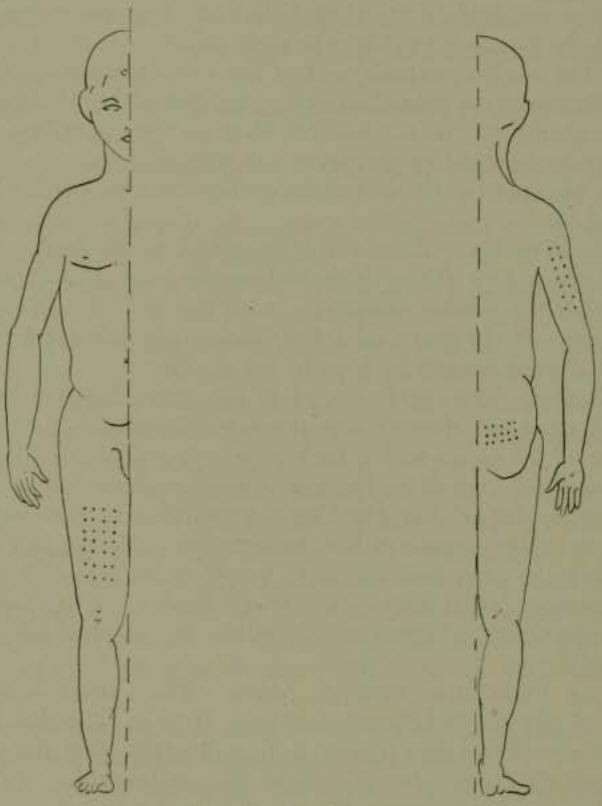


FIG. 13.—Insulin maps.

METHODS OF ADMINISTRATION OF INSULIN.—Insulin injected intravenously acts more promptly than by any other route of administration, but the effect is soon over. It leaves the blood in two to four minutes.[1] When injected subcutaneously absorption takes place more slowly and the action is prolonged. The intradermal method gives more striking results still, the most powerful

[1] Kepinow and Dutaillis: Compt. Rend, de la Soc. Biol., 1927, **96**, 371; Heymans and Heymans: Ibid., p. 719.

in fact, and the most lasting of all (Müller and Corbitt[1]), but wheals and insulin burns may be produced, and it is the most painful route. If the insulin is inserted into the muscles, they are injured, necrosis takes place and scar tissue is formed. This was observed with Case No. 2801 who preferred to inject her insulin in the same place and with good reason because the destroyed tissue did not react with pain. Local lipodystrophy has been described (see p. 727).

Various investigations have been carried out with the idea of securing the effects of insulin by routes not requiring the use of a needle. All, other than those outlined above, have proved to be either valueless or impractical. Harrison[2] has recently clinically shown that insulin by inunction is a failure.

When injected intracutaneously Müller, Wiener, and Wiener[3] believe the deposit of insulin acts by a nerve stimulation which increases the glycogen-forming function of the liver, which effect is active as long as the insulin deposit exists as such. "It is particularly strong if the insulin deposit is made in the skin because of its close relationship to the autonomic nervous system. The nerve effect is weaker after deposition of the insulin in organs in which absorption takes place rapidly, for instance, the subdermal tissues, and is lacking after intravenous administration. The hormone effect in the circulation and in the body tissues is relative to the dose, but the neural effect of insulin does not depend on the dosage. Simultaneously with the beginning of the absorption from the insulin deposit and with the consequent entrance of insulin into the circulation the direct hormone effect is manifested. The nerve effect decreases simultaneously with diminution of the insulin deposit outside of the circulation and disappears as the last part of the insulin deposit is absorbed."

6. **Insulin in Diabetes of Varying Duration.**—The shorter the duration of diabetes, the more amenable it is to insulin just as it is to diet. The rapid response of early detected cases is due to the benign character of the disease at this stage rather than to any specific therapy. Therefore, always try a new remedy upon a diabetic of long duration to secure reliable information and discount a favorable report when based upon a case with recent onset. One should add another qualification; namely, that the severity of the diabetic in question be known before beginning any important test. A diabetic may be old and a case of months,' perhaps even years' duration, lose considerable weight, excrete as much as 9 per cent sugar, and yet yield as promptly to treatment as a child with an

[1] Müller and Corbitt: Jour. of Lab. and Clin. Med., 1924, **9**, 608.
[2] Harrison: Quart. Jour. Med., 1927, **20**, 187.
[3] Müller, Wiener, and Wiener: Arch. Int. Med., 1926, **37**, 512.

onset of a few days' or weeks' duration, providing the old long-standing diabetic has never been exposed to a low-carbohydrate, high-fat diet. In illustration I would cite Case No. 6288, with onset of diabetes in 1911 at the age of forty-two years, who entered the New England Deaconess Hospital on September 12, 1927, with 7 per cent sugar and four days later, upon a diet of carbohydrate, 135 grams; protein, 62 grams; fat, 113 grams; excreted 2 grams of sugar in the urine in twenty-four hours while taking 15 units of insulin; also Case No. 6299 with onset of diabetes in 1902 at the age of forty-six years, who entered the New England Deaconess Hospital in September, 1927, with 3 per cent sugar and five days later on a diet of carbohydrate 108 grams, protein 67 grams, fat 117 grams, excreted 5 grams of sugar in twenty-four hours while taking 10 units of insulin.

In the early days of insulin I did not appreciate the significance of the preceding paragraph as I do now.

An endeavor was made to determine the effect of insulin upon patients who had developed diabetes most recently. The case of shortest duration was Olive H., Case No. 2962. With this girl of twelve years, diabetes developed suddenly December 10, 1922, and she was brought for treatment on January 11, 1923, showing 9 per cent sugar in the urine. She was placed upon the routine test diets, became sugar-free in four days, beginning insulin on the third day, and eventually developed a tolerance for 155 grams carbohydrate and 41 calories per kilogram body weight. Olive's case is of especial interest because some weeks later while taking 4 units twice a day she developed a reaction, scarcely recognized the first forenoon, but definite the next, and between February 9 and December, 1923, insulin was omitted. This I should not do today. Cases of short duration often make remarkable gains in tolerance, but seldom if ever has the gain in tolerance for carbohydrate and for calories as well, been as great. Insulin was used, beginning with 1 unit on the second day of treatment, and continued up to the last day in the hospital, January 31, 1923, the doses being increased to 4 units twice a day, therefrom 3 units twice a day until February 9, when it was discontinued and was resumed in December, 1923.

Another early case was a little Finnish child, aged three years, Aune N., Case No. 2979. The symptoms of diabetes also began suddenly on October 4, 1922, and sugar was discovered December 3, 1922. Attention is called to the similar type of onset of these two cases and also to the more favorable initial course of the preceding case, due presumably to the earlier beginning of treatment. The patient entered the hospital upon December 18, with 4.5 per cent of sugar and +++ acidosis. This did not immediately decrease, and five days later at midnight there were warning symptoms of

coma. Insulin had not been started when she entered the hospital, but was then begun and three doses of 2, 4, and 4 units were administered during the remainder of the night and continued in similarly small quantities from then on. Thirty-six hours later the child had so far recovered that she sat up in bed, played at the window, and threw a kiss to the doctor on his leaving the room. Twelve units of insulin were then being given daily. The diet was steadily increased, and on January 15, 1923, the carbohydrate was 76 grams, protein 37 grams, fat 46 grams, calories 866. Insulin was omitted occasionally before supper, and in consequence a trace of sugar appeared in the urine, promptly to disappear the next day when insulin was resumed. On March 31, the little girl returned for a morning visit, was sugar-free, and indeed had been constantly sugar-free, and was continuing her original diet, which had been arranged with design to be of extraordinary simplicity. It consisted of oatmeal 60 grams, orange 200 grams, eggs 3, 20 per cent cream 120 cc., 5 per cent vegetables 360 grams. Her subsequent career has been cheerful and as usual for a diabetic child she stands high at school. Table 18 shows her progress.

My most favorable case of the application of a high-carbohydrate and low-fat diet treated with small doses of insulin is described on page 591 and illustrates what I consider the best type of treatment of the modern early diagnosed diabetic.

TABLE 18.—DIABETES IN A CHILD, AUNE, CASE NO. 2979. AGE AT ONSET 2.9 YEARS IN OCTOBER, 1922.

Date.	Urine sugar, per cent.	Diet in grams.				Naked weight, lbs.	Height, inches.	Insulin (units).
		C.	P.	F.	Cals.			
1922, Dec. 18	4.4	..	..	..	....	32	...	0
Dec. 18–19	4.5	57	10	1	277	32	...	0
Dec. 28–29	0.3	30	28	37	565	31	...	16
1923, Jan. 6– 7	0	56	33	44	752	31½	...	8
Jan. 23–24	tr.	76	37	46	866	32¼	...	3
Mar. 31	0	76	37	46	866	33¼	38¾	3
June 2	1.8	76	37	46	866	32	...	3
June 14–15	0.2	59	39	63	959	32¾	39½	10
1924, April 26	0	59	38	64	964	34	41	16
1925, Nov. 21	0.1	59	39	64	968	35	41	9
1926, July 10	0.2	63	47	80	1160	38[1]	42½	20
1927, July 16	0.6	75	52	71	1134	49[1]	45	16
Oct. 29[2]	tr.	80	52	76	1212	51[1]	...	20

An early patient, Case No. 2801, which surprised us then, but would not now because (1) of our better knowledge of goiter, (2)

[1] Dressed weight.
[2] Attended 10th Diabetic Anniversary Party of Eleanor.

through faulty administration of insulin resulting from repeated injections in one site only, and finally (3) through errors in diet. This young girl with her enlarged adolescent thyroid gland responded unsatisfactorily. Diabetes had developed acutely on June 27, 1922, was recognized on July 26, and on July 28, the patient came for treatment showing 6 per cent of sugar and ++++ acidosis. The metabolism was +17 per cent when compared with the Girl Scout group of the Nutrition Laboratory series, but was —20 per cent on the DuBois scale. Various methods of dieting were unsuccessful, but with insulin, begun on August 19, 1922, the patient had gained from a weight of 82 pounds to 95 pounds in the course of two hundred and fifty-four days. However, 35 units were required daily to enable this patient to utilize carbohydrate 49 grams, protein 63 grams, fat 144 grams, calories 1744. This patient is cited elsewhere as an example of the danger of the withdrawal of insulin and her death in coma is reported on page 75.

Another early juvenile case, stubborn without insulin, hopeful with, was Alice S., Case No. 2802, aged fifteen years. She had resisted treatment by undernutrition during two weeks, and the outlook appeared very grave. Insulin was started, and at once improvement began. Upon admission August 11, 1922, which was five months after onset of diabetes, her weight was 67.5 pounds. When insulin was begun the weight was 66.3 pounds, height $59\frac{3}{4}$ inches. She left the hospital on November 2, 1922, weighing 69.3 pounds and at present weighs 106.5 pounds naked, and her height is 5 feet. She regulated her own diet of carbohydrate 37 grams, protein 48 grams, fat 85 grams, she took 23 units of insulin and carried out her own treatment with the help of her mother. In 1928 her diet was carbohydrate 34 grams and insulin 24 units.[1]

Overweight as a result of insulin was plainly manifested by the appearance of Alice S., and suggested a possible danger of insulin to which Allen called attention. One very noticeable early effect of insulin treatment is a filling out of the face which may become noticeable within a day or two or even within a few hours after the first dose of insulin. This fullness of the face persists, and certainly in the early stage and possibly also in later stages of the treatment it is out of proportion to the general gain of weight. The skin is noticeably clear. The patients seem to tend readily to become obese, and it is questionable if there is not an undue proportion of fat deposited on the trunk in comparison with the limbs. The general appearance of patients who have thus been unduly fattened with insulin is more or less suggestive of the so-called dystrophia adiposo-genitalis. An attempt was made to correct this gain in weight and with some success.

[1] I have not seen this patient in five years. I suspect the diet to be wrong and writing this book has disclosed it.

TABLE 19.—DIABETES IN A CHILD, ALICE S., CASE NO. 2802. AGE AT ONSET, 14.5 YEARS IN FEBRUARY, 1922.

Date.	Urine sugar, per cent.	Diet in grams.				Naked weight, lbs.	Height, inches.	Insulin (units).
		C.	P.	F.	Cals.			
1922, Aug. 11	4.0	..	..	..	....	67	60	0
Aug. 11–12	1.7	61	16	1	317	....	..	0
Aug. 24–25	0.6	7	19	48	536	71¼	..	0
Sept. 18–19	0.5	26	41	97	1141	67¾	..	0
Sept. 20–21	0.1	26	41	97	1141	66¾	..	6
Nov. 1– 2	0	28	43	86	1058	69¼	..	9
Dec. 11–12	0.2	30	52	98	1210	76½	60	9
1923, Jan. 1	tr.	24	52	95	1159	82	..	14
July 17–18	0	28	51	91	1135	92[1]	60	24
1924, May	0	..	..	..	....	100	..	24
Nov.	0	..	..	..	....	106¾	..	24
1926, Feb. 18	0	37	48	85	1105	106½	60	24
1928, Jan. 28	0	34	53	98	1230	111¾	61½	24

7. **Insulin in the Home.**—The million members of the Diabetic Club of America occasionally spend a few days in their various hospital clubhouses, but for the greater part of the time, like most club members, they live at home. If insulin is to be of permanent help in diabetes it must be usable by diabetics in their own dwellings. Constantly reference has been made to the improvement which patients have obtained after leaving the hospital. In most cases the improvement has been fully as great and in many instances greater than before they were discharged. Our attitude toward the treatment of diabetic patients in general has governed us in this regard and dosage with insulin has been kept low and calories in the diet have been kept low as well, in order that the home treatment of insulin might be safe. In the second month of treatment Thomas D., a little boy, died in coma, apparently as a result of having omitted insulin in his home. He felt so much better, had so much confidence in the good that he had received from insulin that he probably believed, as did his family, that the omission of it for a few days would be of little consequence. We have not forgotten the lesson which his case teaches. If insulin is to be used in the home, the patients must not only be educated in dietetic treatment but they must be educated in treatment with insulin. For this reason our efforts to teach patients the fundamentals of diabetes have been trebled. The increased attention given to education and the increased cost of treatment due to insulin have been offset by decreased cost of medical attendance and the shortening of hospital stay.

[1] Dressed weight.

But patients must realize that they should remain under medical supervision and no matter how well they feel consult a physician every three months. I never talk to a diabetic audience without proposing the query—"What should a diabetic do if he feels sick"—and if all present do not answer I repeat the question until each one responds—"Call the Doctor." Constantly in this book deaths will be found recorded because this rule was not observed.

One of the best examples of improvement of treatment in the home is Miss Pauline C., Case No. 2422, a school teacher who had become much discouraged with her diet and returned to the hospital for treatment with insulin on November 22, 1922. She then weighed 81 pounds and was 47 per cent under standard weight. During thirty days of hospital stay with dietetic treatment, supported by an average daily dose of 10 units of insulin, glycosuria and acidosis disappeared and she gained 5 pounds. On December 16, 1922, the carbohydrate of this patient was 54 grams, when levulose was added to it in 5-gram doses three times daily. This she tolerated and along with the levulose extra calories were given in the form of fat. Upon discharge from the hospital she continued to take levulose made by Mr. Bean in Prof. Folin's laboratory. Improvement continued at home and she returned a month later with a further gain of 2 pounds and without glycosuria. She answered the query ofttimes raised as to whether insulin is worth the cost, by resuming her work as a school teacher which had been abandoned for four and a half months.

Sequel.—Her improvement in her own eyes was so considerable and satisfactory that she returned for investigation at rare intervals, the *last* in November 17, 1923, when it was found that her diet was carbohydrate 41 grams, protein 49 grams, fat 122 grams, calories, 1458. Then it was discovered her tolerance must have risen and at once the diet was increased to carbohydrate 50, protein 38, fat 122, calories 1450; she remained sugar-free and the blood sugar was 0.20 per cent after a meal. She died of bronchopneumonia and coma on March 20, 1926.

Many other such cases of patients returning to work or working with far more efficiency than before the advent of insulin are available. There is no question but that accidents due to insulin will occur in the future and they must be expected, but the advantages gained by home treatment with the resumption of work more than offset prolonged periods of hospital stay. Each insulin diabetically trained patient sent home to his physician I consider the best sort of diabetic missionary. These patients are taught to coöperate with their doctors at home and to help in the details of treatment which doctors, seeing few cases, have little time to learn. If I felt the only good accomplished in the treatment of diabetes was

in the treatment of my few cases under supervision the reward would seem slight, but if these patients help their physicians in the treatment of other cases then painstaking teaching is worth while. The law in Massachusetts also favors coöperation in treatment with insulin between the patients, the doctor and the hospital physician. The law declares that patients using insulin must have insulin permits in order to possess syringes and these permits must be signed by physicians in duplicate, the one copy being retained by the patient, the other recorded at the Massachusetts State Board of Health.

It is alluring to see patients gain weight, but it is our belief that it is safer to increase the diet so moderately and to give insulin in such conservative doses that dangers from its omission or from complications as a result of diet or the disease will be lessened.

8. **Omission of Insulin.**—The chief danger in insulin lies in its omission rather than in an overdose. Over and over again in this book examples of this will come to the fore (see pp. 74, 88, 645). The reason for the danger is obvious. Upon the basis of insulin the quantity of protein and fat which a diabetic can utilize with his scant power of burning carbohydrate is increased; without the support of insulin the protein and especially the fat are no longer adequately oxidized and acidosis results which in turn may lead to death. Ignorantly patients omit insulin when they vomit, because they have been taught to follow insulin with a meal. They should be made to understand that they eat their own bodies, when not otherwise supplied with food, and unless they have proof by a sugar-free urine that they are assimilating all of this body food they should continue to take insulin, though the doses are lessened in quantity while at the same time taken in greater frequency, because the consumption of one's own body in place of food is continuous and not as breakfast, dinner, and supper. When the metabolism is increased as in fever or in hyperthyroidism the danger of omitting insulin proportionately mounts higher.

9. **Pain from Injection, Abscesses; Oral Administration.**—The pain of an insulin injection is slight. Otherwise children would not so readily give it to themselves. Their little fingers are so delicate that often they can administer it with less discomfort than their elders, and this they soon recognize. With injections of insulin at the hospital no accident has occurred and but one abscess resulted. Indeed, of all of the patients who have received insulin in our series we have heard of but 4 instances of an abscess, either in or outside the hospital, and all of these promptly healed. One of these was in a girl, Case No. 3008, who clandestinely broke her diet, took up Christian Science and developed multiple abscesses and yet recovered. Later she improved greatly, although in May, 1927,

she was having slight insulin reactions. Another which occurred in the hospital was in a negro whose skin was most sensitive to insulin. "Insulin burns" due to the injection of insulin into the superficial layers of the skin were caused in a few instances. Presumably these were due to the tricresol used as a preservative rather than to the insulin. They were not of importance. Case No. 2448, however, had so much annoyance from the insulin which he was receiving in dilute form that he gave it up and brought himself near death's door despite our previous warnings. So soon as a stronger preparation, 20 units in 1 cc., was given him his troubles disappeared. This patient was a severe case and had his diet been greater in quantity, due to larger doses of insulin, it is questionable whether recovery would have taken place. As it was, the change for the better was so great in forty-eight hours that in astonishment his uncle fainted on entering the room. On two other occasions he nearly went into coma by breaking diet or giving up insulin or both combined. He was alive in July, 1927.

Other avenues for the administration of insulin have been sought to replace the subcutaneous method. In coma it is desirable to give the first dose of insulin intravenously, because it acts more promptly, but otherwise there is universal agreement that the subcutaneous injection is the one to be employed. Even in coma we are apt to follow the intravenous dose with a subcutaneous dose very soon. Repeated trials have been made with preparations of insulin furnished by the Eli Lilly Company and two other investigators for administration by mouth. All of these tests have been unsuccessful, though at first hope was entertained that insulin so administered was yielding good results because the glycosuria was so low for one, two, or three days after the subcutaneous method of injection had been omitted and the oral adopted. By the fifth day with all patients and in two days with one of the severest cases the futility of the oral method was manifest. In the last trial 450 units by mouth failed to replace 10 units insulin subcutaneously. Deprived of their insulin, the patients wilted. Already attention has been called with design on several occasions to the distressing result which transpired when the little boy, Thomas D., gave up insulin for five days. Invariably when insulin is left off, the diet should be reduced at least one-third and the patient watched with closest care. More hopeful experiments have been made by Murlin and Hawley.[1]

Examples of the substitution of the oral for the subcutaneous method of administration of insulin follow:

Miss M., Case No. 1542, our first case, was free from glycosuria on a diet containing carbohydrate 14 grams, protein 32 grams, fat

[1] Murlin and Hawley: Am. Jour. Phys., 1927, **83**, 147.

98 grams. She was receiving 8 units of insulin twice daily. This was omitted and a special preparation, furnished us through the courtesy of the Eli Lilly Company, was substituted by mouth. The first day she received 24 units, the second day 60 units, the third day 84 units, the fourth day 96 units, and upon the last day 396 units. The results are shown in Table 20. During this period the diet remained unchanged. It will be seen that at once sugar appeared in the urine, that it did not increase materially for the first day, but eventually rose to 49 grams. Along with the sugar there was development of slight acidosis. At the end of the period insulin subcutaneously was resumed, and in four days the patient had regained her former tolerance. The change in the appearance of the patient during these few days was definite. The habitus of a severe diabetic returned—the dry skin, the drawn look, the bright flush in the face, and the decreased brightness of the eye. (See Fig. 5.)

TABLE 20.—OMISSION OF INSULIN SUBCUTANEOUSLY AND ITS ADMINISTRATION BY MOUTH. MISS M., CASE 1542.

Date.	Di-acetic acid.	Sugar in urine, gms.	Diet.					Glucose balance, gms.	Blood sugar, per cent.	Insulin.	
			C.	P.	F.	Cals.	Total glucose.			Subcutaneously, units.	By mouth, units.
October											
23	0	0	14	32	98	1066	43	+43	0.23	16	...
24	0	0	14	32	98	1066	43	+43	....	16	...
25	0	0	14	32	98	1066	43	+43	....	8	24
26	0	12	14	32	98	1066	43	+31	....	0	60
27	0	34	14	32	98	1066	43	+ 9	....	0	84
28	0	36	14	32	98	1066	43	+ 7	....	0	96
29	0	29	14	32	98	1066	43	+14	....	0	96
30	0	33	14	32	98	1066	43	+10	0.29	0	192
31	+	49	14	32	98	1066	43	+ 6	0.25	0	396
November											
1	0	11	14	32	98	1066	43	+32	0.26	16	...
2	0	8	14	32	98	1066	43	+35	....	16	...
3	0	5	14	32	98	1066	43	+38	....	20	...
4	0	0	14	32	98	1066	43	+43	....	20	...

Insulin has also been given intranasally, intratracheally, and rubbed on the tongue; by duodenal tube, by rectum, and by vagina. Telfer[1] is the only author who claims any degree of success by other than oral methods and he employed inunctions.

Recently Miller[2] found some action by oral administration of insulin when the insulin was given dissolved in absolute alcohol or 95 per cent alcohol within keratinized capsules.

The experience with the cases just cited, who have omitted insulin

[1] Telfer: British Med. Jour., 1923, i, 715.
[2] Miller: Arch. Int. Med., 1926, **38**, 779.

is a definite warning of the danger of this omission by any patient whose diet has been increased with its help. Too much emphasis cannot be laid upon the danger of continuing the high diet when insulin is discarded. The foundations for the increased diet are certainly removed when insulin is omitted. All patients upon discharge from the hospital should be thoroughly instructed to reduce the diet if for any reason they do not obtain insulin or if for any reason they suspect the insulin has deteriorated in strength. They should be warned that the danger creeps on slowly and gains in intensity from day to day. With increased diets due to insulin they are walking on insulin stilts. The longer the stilts, the greater the danger of a fall when they are taken away. In this diabetic game one is treating patients for years and the closer one keeps to the ground, the better.

With gastro-intestinal upsets, especially when accompanied by vomiting and diarrhea, when less food is taken, insulin should be reduced, but not omitted, but here from a different danger, namely hypoglycemia. Yet these upsets may be complicated by acidosis, so that it requires a clear head to detect what is going on. Bed, nursing, liquids, a little carbohydrate in the form of orange juice or a cracker or two (5 grams carbohydrate) and expectant treatment, will enable one usually to weather the squall.

Usually I advise dividing each dose of insulin in half and doubling the number of doses. Then if two urinary specimens remain sugar-free the next dose of insulin may be omitted, but not more than two doses of insulin in succession should be omitted even if the urine does remain free from sugar.

The correct balancing of carbohydrate given, and insulin injected is a nice problem. Precautions have been taken to have glucose accessible for an emergency. Whereas it is advisable that the glucose solution should be fresh and sterilized, Allen states that this is not an absolute prerequisite and a filtered glucose solution can be substituted. The percentage of glucose commonly employed is 5 per cent and the quantity given 500 cc., but one can employ 20 per cent solution of glucose and give a correspondingly smaller quantity.

Insulin can, however, be discontinued fairly abruptly in at least three types of patients: Those recovering (1) from surgical emergencies; (2) from acute infections; and (3) from severe acidosis in mild diabetes. In severe acidosis, by common consent, it should be diminished very gradually. Rapid changes in insulin dosage may be made under close observation in the hospital, but only gradual changes should be attempted in the home.

Cases of long standing in elderly people react to insulin slowly just as they react to dietetic treatment slowly and patience is necessary to await results. Particularly is this true with arteriosclerotic

patients. With these cases the comparatively large doses of insulin may fail to render the urine sugar-free for weeks, but persistence in diet and treatment evolves success out of an apparently hopeless condition. Such an instance is that of Mr. S., Case No. 2626, who was reported in my article in the *Journal of Metabolic Research* as refractory, but he later did well taking 115 grams of carbohydrate, sugar-free, with 10 units of insulin. He died of pneumonia in March, 1924.

TABLE 21.—DEATH FROM ANGINA PECTORIS IN A DIABETIC, AGED SIXTY-SIX YEARS, WEIGHT 80.4 KILOGRAMS.

Date.	Urine, vol.	Diacetic acid.	Sugar.		Diet.				Blood sugar.	Insulin units.
			Per cent.	Gms.	C.	P.	F.	Cals.		
1922										
Nov. 16	s. s.	0	2.2	24						
17	2400	0	0.5	12	65	28	26	606	0.18	2
18	1300	0	0.4	5	35	33	56	776	....	4
19	1900	0	0.3	6	35	33	56	776	....	4
20	2200	0	0.2	7	40	49	78	1058	....	6
21	1000	0	0.2	2	40	57	83	1135	....	6
22	....	..	...	..	44	65	99	1327	....	6

Insulin can be omitted gradually in certain cases of recent onset, even in children, and with increasing frequency in elderly patients. Time enough has not elapsed to show whether it is for a temporary or a prolonged period. Case No. 2962 and Case No. 3078 represent the former type (see pages 50 and 86) and Case No. 3310 the latter.

The total number of omissions of insulin among those treated is considerable, because insulin is used to shorten hospital stay and later is found unnecessary in order to maintain weight and strength and a carbohydrate intake of 100 or more grams.

10. **Protein Reactions.**—Reactions due to the injection of insulin other than those caused by a lowering of the blood sugar were reported with the use of the first preparations employed. Such reactions have developed at most with but 4 of our patients. With Case No. 2802 urticarial wheals occurred with pruritus, and these were relieved by bathing with sodium bicarbonate and a whitewash. Severer reactions, however, have been noted by others, though with very rare exceptions. Wilder and Boothby[1] obtained these in but 3 of their patients, and likewise their experience was confined to the early days of the production of insulin. They described such a reaction as follows:

[1] Wilder, Boothby, Barborka, Kitchen and Adams: Jour. Metab. Research, 1922, **2**, 701.

"The patient in Case 2, had been without insulin for five days, and received, December 2, 1922, at 8.10 A.M., 30 units of Iletin 722845, followed by a light breakfast. At 8.15 A.M. he was nauseated, his face flushed, and he vomited. Severe pain developed in the epigastrium followed by diarrhea and profuse sweating. The pulse, at first full and bounding, became weak and slow, 50 each minute. At 8.50 A.M. he was drowsy, the epigastrium pain was less severe, but persisted as a dull ache. One hundred grams of orange juice were given by mouth. At 9.00 A.M. he was more alert and by 9.10 A.M. all the symptoms had disappeared and the pulse was strong, with a rate of 86 each minute. This reaction was believed to be due to hypoglycemia, particularly because the symptoms abated so promptly after the orange juice was given. We were disillusioned, however, as soon as the report of the blood sugar reached us. Blood drawn at 8.45 A.M. contained 270 mg. of sugar for each 100 cc. At 10.00 A.M. a moderate urticarial rash developed around the arm, and to some extent, on the face supporting the evidence that the reaction was not due to hypoglycemia, but was a protein effect."

A severe protein reaction was also obtained in one patient treated by Williams.[1]

"Case 1524 for several months was given the extract prepared by the University of Toronto from the pancreas of beef animals. Later, when the preparation of the Lilly Company was substituted, which is made from pancreas of the pig, the patient experienced promptly most severe anaphylactic reactions which apparently could not be overcome. All attempts to use highly purified and practically protein-free extract have proved futile and have had to be abandoned. The following is a description of the phenomenon observed after an injection of the pork material September 23, 1922. Patient apparently normal, no pruritus, urticaria or edema evident. Five cubic centimeters insulin injected intramuscularly. Three minutes later patient stated that upper lip felt stiff and swollen, followed rapidly by dry mouth. In ten minutes lips became greatly swollen. Small wheals then appeared on all parts of the body. The reaction increased in violence for two hours, during which time the wheals became larger and coalesced. No nausea or vomiting occurred. Patient very weak and prostrated. Heart sounds rapid, regular, clear. Lungs normal. Adrenalin, 15 minims subcutaneously and atropine sulphate $\frac{1}{100}$-grain by mouth were given, affording slight relief. Twenty-four hours later patient had recovered from the reaction, but was very weak. The weakness and prostration persisted for four days. During

[1] Williams: Jour. Metab. Research, 1922, 2, 729.

this time much skin exfoliated from various parts of the body. It is interesting to note that this patient has been having beef extract since May 17, 1922, to February 1, 1923. . . The patient has exhibited no evidence of sensitivity against beef material, which dispels the fear one time entertained that he might become sensitive to this and other proteins and make the administration of the extract a difficult problem." I have been informed recently that this patient is in excellent condition and is now taking the insulin ordinarily supplied to patients by the Lilly Company.

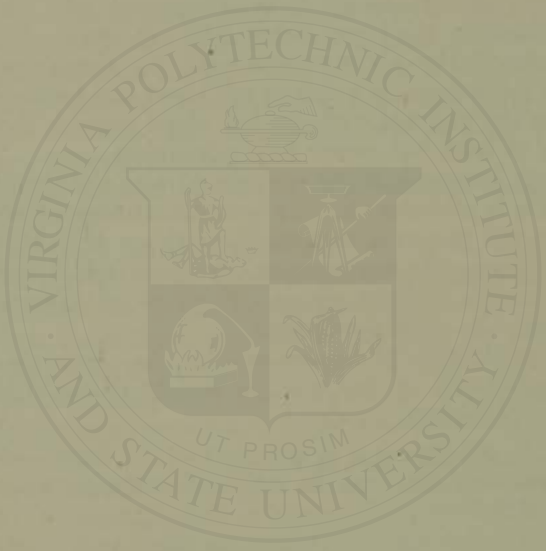
11. **Hyperinsulinism.**—Seale Harris[1] reports several non-diabetic patients who had symptoms of an insulin reaction, manifested by weakness, nervousness, hunger, faintness, quivering, cold extremities. These symptoms were invariably relieved by taking carbohydrate. Twelve patients in all were discovered who showed percentages of sugar in the blood below 0.07 per cent. At least 9 of these presented the above symptoms. In starvation one does not get low percentages of sugar in the blood and he therefore concludes that in the patients with the low blood sugar it was not their low supply of food, but rather hyperinsulinism.

Now that we are becoming better acquainted with the symptoms of hypoglycemia it is probable that the symptomatology of various diseases or states will receive a new interpretation. Hypothyroidism, Addison's disease, the nervousness, weakness and trembling of nursing mothers fall into this group. Bowcock of Atlanta has drawn my attention to these possibilities.

The artificial production of hyperinsulinism has been used to increase the appetite and in this way the weight of non-diabetic patients by Falta[2] in Vienna.

[1] Harris: Jour. Am. Med. Assn., 1924, **83**, 729.

[2] Falta: Wien. klin. Wchnschr., 1925, **38**, 757; Sonderbeilage der Wien. klin. Wchnschr., 1926, **59**, Heft 13.



SECTION III.

THEORY, INCIDENCE, ETIOLOGY, AND CURABILITY.

A. DEFINITION OF DIABETES MELLITUS AND GLYCOSURIA.

1. DIABETES is a disease characterized by an increase of sugar in the blood and the excretion of sugar in the urine; it is dependent upon disease of the pancreas, particularly of the islands of Langerhans, whose secretion, insulin, not only promotes the conversion of glucose into glycogen and the deposition of the latter in the liver and muscles, but also exerts an influence upon the conversion of protein and fat into sugar.

My rule in the treatment of diabetes is to consider any patient who has sugar in the urine demonstrable by any of the common tests to have diabetes mellitus and to treat him as a diabetic until the contrary is proved. This method of procedure is safer for the patient than to make use of the term glycosuria, which begets indifference and may lead to disaster. It is convenient to classify patients with glycosuria or with a history of glycosuria into four groups: true diabetics, potential diabetics, renal glycosurics, and unclassified diabetics. Under true diabetics are placed patients whose blood sugar on an unrestricted diet is 0.14 per cent or more fasting or 0.17 per cent or more after a meal with simultaneous glycosuria which is plainly related to diet. Potential diabetics are those with glycosuria closely related to the diet who easily become sugar-free with slight restrictions, but whose blood sugar is below 0.14 per cent fasting and never reaches 0.17 per cent after a meal. Renal glycosurics are individuals who have shown a constant glycosuria, irrespective of diet, for years, are symptomless, and have a blood sugar which is invariably normal. "Unclassified" diabetics by my nomenclature include the remaining cases of glycosuria, especially those associated with organic disease: for example, that of the gall-bladder, kidney, occasionally of the thyroid, cancer of the pancreas, and often pregnancy. These cases form a dangerous group. One never rests easy with an "unclassified" diabetic. Such a diagnosis worries the doctor, annoys the patient, and exasperates insurance agents.

The drug glycosurias and those of traumatic and emotional origin are almost invariably of a temporary nature, so that doubt concerning the diagnosis of diabetes mellitus vanishes when sugar is constantly found in the urine. To this there is one exception, renal glycosuria, for a discussion of which and of glycosuria in pregnancy, which is somewhat related to it, see pages 861 and 899.

B. NAUNYN'S CONCEPTION OF DIABETES MELLITUS.

Naunyn[1] thoroughly believed in the unity of diabetes, notwithstanding the manifold causes which appeared to lead up to it. It must have been a great satisfaction to this Nestor of the disease to find his theory proved correct by Banting and Best. He sees in heredity the common bond which unites the different forms, or as he says, "to speak more exactly, the heredity of the diabetic tendency." Variety in the etiology of diabetes becomes understandable if one sees in the disease the development of an individual tendency. Almost any illness or injury, no matter how slight it may be, may serve as a cause. Furthermore, the experience that an individual, who at one time has been diabetic or even has had a suspicious glycosuria which has passed for years as cured and has even dropped out of memory, perhaps for decades, may again become diabetic under favoring influences, is in conformity with this view.

This diabetic tendency is generally congenital—indeed, in many cases hereditary, and this heredity is demonstrable in 20 per cent of the cases. The cases in which heredity is demonstrated differ in nowise from those in which heredity is not demonstrated. (See page 145.)

According to the manner in which the development of the diabetes stands to the diabetic disposition, Naunyn distinguishes three forms of the disease:

1. The diabetes of young people, chiefly between thirty and forty years of age: Naunyn's "true[2] diabetes." In this group the congenital weakness of the sugar metabolism, of itself or often in conjunction with some accompanying circumstance (illness, accident, exertion, excesses), may lead to an insufficiency of the metabolism of sugar even without the addition of the disease of a diabetic organ. In this type one must conceive of an especially severe tendency to the disease and this accounts partly for the especial severity of its form, but only in part, for this severity depends in high degree upon the great demand which youth makes on metabolism.

2. The diabetes, usually mild, of elderly people. In this type,

[1] Naunyn: Der Diabetes Mellitus, Wien., 1906, p. 37.
[2] Pure.

the tendency is less severe. The disease comes late to development, and for this it requires a lowering of the vitality which comes with age. The age of a man depends on the condition of his arteries. So here, too, arteriosclerosis comes into play, and with the arteriosclerosis come to the front all those conditions which favor the development of diabetes—overnutrition, luxurious living, and, especially, excesses in alcohol. Syphilis, which is so important according to many authors in the cases of arteriosclerosis, strange enough to say, appears to play no great rôle here. Yet diabetes can also appear even without the presence of arteriosclerosis merely as a result of old age with its coincident lowering of vitality

3. The rôle which the tendency plays in the different cases of this group varies. In general the tendency is present, although it need not be strong and can be wanting. To the organic type of diabetes belong those cases in which the disease of the diabetic organs appears as the cause of the diabetes. Thus, diseases of the liver, of the nervous system, whether organic, functional, or traumatic, diseases of the thyroid gland and of the pancreas are here found, and the pancreas, according to experiment and autopsy, holds the first place. In these organic diseases arterioclerosis is important, and in this way arteriosclerosis may be the cause of diabetes.

C. MODERN DIABETIC THEORIES.

With health in the bank a man can face the world and so can a diabetic with glycogen in his liver. Glycogen in the liver implies the possession of insulin, because insulin alone can deposit it.

Without glycogen in the liver the healthy and the diabetic are in want. The normal child goes into acidosis, the diabetic into coma, because of the want of glycogen, because the liver glycogen account is overdrawn. Make a fresh deposit of glycogen to the child's account by food or to the diabetic's account by food endorsed by insulin and the stringency in the glycogen market is relieved. In the human organism finances are on a glycogen rather than on a gold basis—on a glycogen rather than on a glucose basis, because there are 300 to 400 grams of glycogen in the body for 70 to 80 grams of glucose. We should talk of a glycogen deficit or vacuum rather than of a glucose deficit or vacuum.

But there is another banking system in the body which receives deposits of glycogen, and that is the muscular system. When insulin and sugar are injected into a muscle the equivalent of one-half of the sugar is spent in oxidation and the balance is deposited as glycogen. So accurate are the experiments that 90 per cent of the sugar absorbed by the body can be traced. It looks today as if the success of an athlete might be directly dependent on the

capacity of his muscular system to store glycogen, and physical training may simply mean an increased power of the muscles to store glycogen. Muscles depend solely on glycogen for their activity, because from it they derive sugar. The food of a muscle in health or disease is glycogen. A muscle never ceases to use carbohydrate until it is dead. Glycogen is the sole component of a muscle diminished by muscular contraction, and the most vital muscle of all, the heart, is the most tenacious of it and the most susceptible to its loss. If there is much glycogen stored, the muscles can accomplish much, but if there is little stored, protein and fat must be converted into glycogen, and that takes time. The 25-mile Marathon run shows how muscular action uses up glycogen. Toward the end even the blood sugar falls below normal, because glycogen cannot be supplied fast enough for the runner's supreme effort. In diabetes wise clinicians take advantage of this power of exercise to burn nascent sugar formed from glycogen, and the progressive doctor makes his patient exercise whether in or out of bed. The muscular contractions of convulsions are the despairing gesture of the muscles for glycogen to burn, and being a signal for help may be life saving to the individual with a low blood sugar. Can the excess of lactic acid formed in exercise be converted into glycogen? Do liver glycogen and muscle glycogen play distinctive roles in the body? These are still mooted questions.

Another function of insulin, some think, is to prevent excessive transformation of protein and fat into glucose. This goes on in the liver, and in this factory alone is the machinery set up to convert the raw materials, protein and fat, into the finished product, glycogen. There is only a hint that this may go on unaided by insulin in the muscles. When insulin is deficient, as in diabetes, many believe the conversion of fat and protein to sugar goes on unchecked. This might not be so harmful of itself, although it does lead to hyperglycemia and glycosuria, but that is not the whole story. As a result of the breakdown of protein and fat come other derivatives—the ketone bodies and the liberation of an excess of these leads to acidosis and diabetic coma. Insulin prevents this excessive liberation, because by the storage as glycogen of the sugar formed from protein and fat, it makes available enough harmless food to supply the body's needs and the remaining products of protein and fat destruction take their normal course.

Glycogen is the carbohydrate capital which the normal and the diabetic, too, can use in exchange. The diabetic is in trouble because his carbohydrate as it reaches and leaves the blood is in the form of glucose, no matter whether ingested as food or formed from protein and fat in the liver. To be utilizable glucose must be

transformed or dissociated (Woodyatt), whether for oxidation or polymerization, into glycogen.

Formerly some thought, Benedict and I did not, that the diabetic organism had lost its power to burn sugar. Today we know that the diabetic can burn sugar if the sugar first can be transformed into glycogen. During extreme exercise the respiratory quotient of the calculated added metabolism in normals rises to unity—1—because the muscles live on carbohydrate; without a liver Mann's dogs had a respiratory quotient approaching 1, because they burned carbohydrate predominantly. With the liver gone protein and fat cannot be transformed into carbohydrate even with the help of epinephrin. Remove the liver from a depancreatized dog and his respiratory quotient is also 1. In other words, a dog without a liver, whether normal or depancreatized, in order to live must depend upon carbohydrate.

A high-fat diet is inimical to the diabetic just as it is to normals. A high-fat diet in the modern treatment of epilepsy causes hyperglycemia and acidosis, symptoms which are tolerated because less harmful than epileptic convulsions. A high-fat diet will be tolerated a long while by old dogs, but will produce hyperglycemia and finally kill normal puppies with symptoms of coma. Depancreatize a fat dog and his diabetes is worse than that of a thin dog. With an excess of fat in the body diabetes begins, with an excess of fat in the diet diabetics grow worse and insulin acts less well. From the products of an excess of fat, the ketone bodies, diabetics died until insulin came to their rescue. Should a high-fat and low-carbohydrate diet be continued, I suspect in the future they would also die despite insulin, because of arteriosclerosis. A high-fat diet does not stimulate the production of insulin; fattened depancreatized dogs are liable to coma. Therefore, why fatten diabetics with excessive doses of insulin and any kind of food? My fat adolescent diabetic girls, save for acidotics, are my only diabetics with a high blood fat and the ones who require the most insulin and from it obtain relatively the least returns.

The corollary of the above gives us the modern diet for diabetics. Do not make the fat too high or the carbohydrate too low. Strike a balance. Do not try to treat the diabetic like an epileptic on the one hand or like a normal individual on the other. As for protein, use discretion.

Is sugar formed out of fat except from its glycerol moiety? Opinion is divided and not wholly on continental lines. European opinion favors it; American opinion has been against it, and fortunately has been made utilitarian through the fundamental work of Woodyatt in his assignment of glucose values to all foods.

The idea of the formation of sugar from fats "must still be classified as a theory or hypothesis open to criticism and . . . is in no sense in the nature of an established fact."

Woodyatt believes the glucose must be dissociated before it can enter into chemical reactions and suppress the breakdown of protein and fat. Insulin is *sine qua non* for oxidation, storage or reduction to glucose. Without insulin glucose acts in the body like lactose or salt. Without insulin it participates in no chemical reactions.

Woodyatt still thinks that the anomaly of the metabolism which characterizes diabetes mellitus is primarily an anomaly of the glucose metabolism pure and simple, and that in handling diabetic cases and in adjusting doses of insulin it is expedient and practical to focus the attention on glucose (or the equivalents of glucose). This need not imply ignoring calories, infections, emotions, exercise, exophthalmic goitre, etc., which are also capable of affecting the tolerance. Until he published his paper on Objects and Method of Diet Adjustment in Diabetes there was not a satisfactory method of estimating the probable effects of two different diets containing different quantities of carbohydrate, protein, and fat on a given diabetic patient. Labbé stated that there was no way of knowing from one diet what another would do.

The formation of a large amount of sugar out of fat has common sense together with a certain amount of new experimental evidence to support it against the dextrose-nitrogen theory. It is contrary to all our conceptions of factors of safety in the body to believe that one's life is protected by only 300 or 400 grams of glycogen and exactly 58 per cent of its most vital tissue protein. I cannot feel that the D:N ratio resembles Newton's law. It is also reasonable to assume that if plants can convert carbohydrate to fat and fat to carbohydrate animals should do the same, but the theory of reversible action has not been proved to be universal. It is difficult to explain first how an athlete can perform prolonged work on calories derived from glycogen alone, and second to explain the high respiratory quotient of exercise without carbohydrate somehow having been made available. But a respiratory quotient is a resultant of forces—the oxidation of fat which lowers it and the combustion of carbohydrate which raises it. From the respiratory quotient alone, therefore, it is not safe to assess the actual quantity of carbohydrate, protein, and fat which has entered into metabolism. These considerations make one slow to vote upon the question notwithstanding the fact that the dehepatized as well as the dehepatized and depancreatized dog show quotients approaching unity. That the glycogen exhausted liver of the fat-fed dog, perfused with defibrinated blood, yields glucose out of proportion to any remaining traces of glycogen which it may retain, and quite independently of lactic acid or of protein metabolized, speaks for

fat-carbohydrate conversion, but such a preparation, like the eviscerated animal, is very artificial.

I am not very consistent. I use the Woodyatt theory, though not pushing it to extremes, in the treatment of my cases, but common sense tells me that more than 10 per cent of fat is available for the glycogen which both my diabetic patients and I need. At any rate, these new experiments and old and new theories are unlocking some hitherto closed doors of intermediary metabolism.

Loewi's[1] glycemin is perhaps one of these new doors. Manufactured in the liver it resembles a hormone and, according to Loewi, it prevents the attachment of glucose to the cell and is thus antagonistic to insulin which favors the connection. Confirmation is awaited.

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D. TENDENCIES TO LOSS AND GAIN IN TOLERANCE.[2,3]

Most of the older writers believed that the tendency of the diabetic glycosuria, particularly if untreated, was to increase. There are numerous exceptions to the rule if the diabetes has been treated, but I know of none where the disease has been allowed to take its course without medical intervention. Since A. A. Hornor and I paid especial attention to the group of diabetics of fifteen and twenty-five or more years' duration, a good many cases have come to light in which the disease has shown little if any progress. All of these patients, however, have been treated to a certain extent and though the treatment may have been very slight, strictly speaking, it has been enough to take them out of the class of

[1] Loewi: Klin. Wchnschr., 1927, **6**, 2169.
[2] Ska Rabinowitch: Quar- Jour. Med., 1928, **82**, 211.
[3] See Harrison: Loc. cit., p. 186.

untreated cases. If treatment has been thorough the question changes, but even then I must acknowledge, with my methods of treatment without insulin, I was unable to guarantee to the patient that the severity of his disease would remain unaltered. Even with my most conscientiously treated cases the diabetes almost invariably became more severe. In 1923 I felt the majority of diabetics lost tolerance as the duration of their disease progressed; today I feel that the evidence points the other way. There were a few exceptions among the milder group of diabetics, as Case No. 899, p. 602, and occasionally a case of moderate severity became milder. Such improvement very likely would be explained today by loss of weight, removal of the source of infections, an environment leading to better use of the muscular system, a more favorable diet, or some other factor rather than to an actual alteration in the force of the original diabetic tendency. But there is another element which may be more important than all the others: namely, the element of time which allows an opportunity for the pancreas to regenerate. Hitherto the disease has run its course in so brief a period that regeneration did not have time to occur. Now the tenure of the disease is adequate for this purpose.

The following cases illustrate losses and gains in tolerance, and, though several are in non-insulin days, they are reported because of their long duration or other exceptional attributes.

Case No. 8 shows this tendency of the glycosuria to increase. The case dates back many years and, of course, strictly modern methods were not followed, yet the patient was carefully treated. The description of the case is as follows:

A woman showed the first symptom of diabetes in the spring of 1899, at the age of sixty years, and 5 per cent of sugar was found in June. She had gradually lost 20 pounds during the preceding fifteen years and weighed 165 pounds when the diagnosis was made. Under rigid diet the urine promptly became sugar-free; the tolerance rose to 130 grams and, save for very transitory intervals, remained so for nine years, until 1908. During 1908, and until the autumn of 1909, it returned, but except at one analysis was less than 1 per cent. In October, 1909, the sugar amounted to 4.6 per cent, and a carbuncle appeared. With prompt surgical care, vaccines, the restriction of carbohydrates, and the temporary utilization of the oatmeal diet, the sugar disappeared, and the carbuncle healed promptly. But the urine did not remain permanently sugar-free, although only about 30 grams of sugar were excreted daily. In the spring of 1911, the sugar again rose at the time of an attack of lobar pneumonia, but as recovery took place and restricted diet was instituted, the sugar disappeared. Evidently the patient could be freed from sugar, but upon a diet

containing only about 30 grams of carbohydate. This seemed too narrow (compare treatment in 1912 and now) for the patient after thirteen years of dieting, so that it was practically impossible to keep the urine free from sugar continually. Residence in a hospital for a few days in September, 1912, in order to have several teeth removed, lowered the sugar to 0.8 per cent.

Except for the brief periods of illness due to the carbuncle and pneumonia, the patient remained well during all these years, and was unusually strong and vigorous for a woman of seventy-three years, although the palpable signs of arteriosclerosis with intermittent claudication and high blood-pressure suggested the outcome. She finally succumbed to a lingering illness subsequent to a hemiplegia, death being due to a terminal pneumonia in 1913.

The diabetic and the diabetic tendency have been more sinned against than sinning in this question of losing tolerance. When we have proof that patients such as Cases Nos. 632, 1895, 3550 exist with gains of tolerance for carbohydrate amounting to 100 grams during the last four years, is it fair to say that the diabetic tendency in other cases less favorably situated decreased? Might it not have been that these other cases grew worse because of the unfavorable diets and other external conditions to which they were exposed rather than to the inherent diabetic tendency? Three positive cases such as those above cited, who are known to have been carefully treated, are worth 300 cases under indifferent care. Insulin is the agent which protects these patients. Insulin is allowing us to find out what sort of a diet and what conditions of life are best for the diabetic. It is not at all inconceivable that eventually the application of this knowledge will yield such large returns as to make insulin itself unnecessary.

The exceptional careless of diet and lucky diabetic, who escapes being caught in the traps of the disease, coma and arteriosclerosis, and who lives for ten years, never proves to be so severe with our modern methods of investigation as he may appear or as we might expect. One boy, Case No. 1609, (see p. 112), seldom kept sugar-free and was my despair ten years ago when his diabetes began at ten years of age. He never permitted himself to be sinned against for long with a low-carbohydrate high-fat diet or even a low-protein diet. His diabetic tendency has not increased.

Doubt certainly arises as to the progressive character of the disease when one sees cases of diabetes, untreated for years, able to become sugar-free with restricted diet and apparently able to acquire a considerable tolerance for carbohydrates. If the disease were actually progressive, then such a patient should ultimately, barring death from accidental causes, lose all tolerance for carbohydrate, but a case with complete loss of tolerance has not yet come to my

observation. These long-standing, neglected cases are, apparently, easily amenable to modern treatment. Case No. 436 (see p. 144) who has not kept sugar-free and Case No. 632 (see p. 111) who has been sugar-free since insulin, were examples of very slow progression of diabetes, but the latter has now increased his tolerance by 100 grams of carbohydrate. Case No. 2201 had diabetes for twenty-four years and then showed a carbohydrate tolerance for 100 grams for weeks at a time with 10 units of insulin, though when she first came under my observation in 1921 she was excreting 7 per cent sugar with a fasting blood sugar of 0.53 per cent. This fell to 0.15 per cent fasting and 0.22 per cent one hour after food under diet and the 10 units of insulin. Despite her high tolerance for carbohydrate, she took insulin hoping to prevent further disease of the retina, but she succumbed to angina pectoris in 1924.

Further evidence of value would be afforded by a study of very mild cases of diabetes discovered by routine or insurance examinations. If such cases, often very little treated, remained stationary for years, it would be evidence against a progressive tendency. The group of potential diabetics is also of value in this connection. Among the 189 so classified this diagnosis has thus far been changed to true diabetes in 3 instances in the course of one year. This special group is not available for study, but it can be said that cases of diabetes discovered by insurance examinations live an unusual length of time. Then, too, my group of 161 cases of diabetes of twenty or more years' duration also offer some information. One hundred and five of these patients are now living and in many of them the disease appears to be stationary.

A low percentage of blood sugar in cases of long duration is also evidence against a progressive tendency. Thus, in 14 cases of twenty or more years' duration, of the analyses of blood sugar which have been made, 10 were 0.2 per cent or below, 3 were between 0.21 and 0.25 per cent, and 1 between 0.26 and 0.49 per cent.

It is a credit to Sherrill,[1] then working in Allen's clinic, and to Newburgh and Marsh,[2] that years ago they recognized this capacity of diabetics to hold their own against the disease.

In my opinion cases of diabetes carefully treated do infinitely better than those cases which are neglected. In each group exceptional examples of the disease can be found in which there is little tendency to progression, but careful investigation usually shows that an advancing tendency existed which now should be halted.

One must not forget that wide fluctuations in severity occur in one and the same diabetic largely owing to treatment or its neglect. A case untreated today may simulate severity, and if carefully

[1] Sherrill: Jour. Metab. Res., 1922, **1**, 667.
[2] Newburgh and Marsh: Arch. Int. Med., 1923, **31**, 455.

treated for the subsequent three years may appear no worse, but was the original estimation of severity correct? Case No. 983 appeared severe in 1916, but a few weeks sufficed to prove the disease mild which her condition in 1923 and 1926 substantiated. It is quite another matter to demonstrate that it remains as mild as when first seen. My cases ought to furnish more evidence upon this interesting question of loss or gain of tolerance in the course of years, and I shall seek it.

The tendency of the diabetic patient to gain in tolerance for carbohydrates when the urine becomes sugar-free is the fundamental principle upon which all treatment has been and is rightly based, and that by which the value of all therapeutic measures is determined. This proposition is a reverse of the preceding, and it would appear to hold, so far as evidence is available, both experimentally and clinically, yet here again the evidence should be far more carefully weighed than heretofore. Among the older cases, Case No. 194 is an excellent illustration of this gain in carbohydrate tolerance in a child and its later loss when the treatment was interrupted.

TABLE 22.—VARIATIONS IN CARBOHYDRATE TOLERANCE. CASE NO. 194.

Date.	Volume, c.c.	Diacetic acid.	β-oxybutyric acid, gm.	Nitrogen, gm.	Ammonia, total gm.	Sugar in urine.		Carbohydrate in diet, gm.	Carbohydrate balance, gm.	$NaHCO_3$, gm.	Naked weight of patient, kilos
						Reduction, gm.	Rotation, gm.				
1908											
April 18–19	1800	+	..	..	..	..	50	90	+40	8	
19–20	2610	−	..	..	1.9	..	78	90	+10	8	49.2
20–21	1710	++	..	..	..	..	44	64	+20	8	49.2
21–22	1890	++	..	..	..	..	60	60	..	8	49.2
22–23	1600	+	..	20.1	1.9	..	42	60	+20	8	49.4
23–24	1650	+	..	..	..	..	20	40	+20	8	49.5
24–25	1650	+	..	..	..	..	17	20	+5	8	49.6
25–26	1590	+	..	..	..	..	16	15	−	8	50.2
26–27	2970	+	..	..	1.5	0	12	10	−	8	50.4
27–28	1650	0	..	..	..	0	−	12	+10	8	50.0
May 1– 2	1830	0	..	13.0	..	0	−	16	+15	0	50.2
Nov. 11–12	1500	0	..	..	..	0	..	50±	+50	0	53.6
1909											
Feb. 1– 2	1520	0	..	..	..	0	..	90±	+90	0	
May 10–11	....	0	..	..	..	0	..	90±	+90	0	55.9
July 27–28	....	..	..	..	..	0	..	90±	+90	0	55.9
Sept. 18–19	2820	−	..	13.6	0.5	17	11	15	−	20	53.0
22–23	3280	+++	13.0	11.2	0.6	42	24	15	−25	20	52.9
23–24	2577	+++	14.3	8.0	0.5	50	43	165	+115	20	52.3
24–25	2410	+++	14.1	10.0	..	19	−	15	−5	20	52.6
1910											
Oct. 25–26	2300	+++	..	15.9	2.4	80	64	−	−	−	53.6
Nov. 29–30	2000	+++	..	..	..	+	64	−	−	−	52.6
Dec. 10	Death in coma.										

Female, born August 16, 1893, single, no occupation, onset of diabetes at age of fourteen years in February, 1908; sugar in the urine March, 1908; came under observation April 18, 1908; died in coma December 10, 1910. There was no history of diabetes in the family. Father died of pneumonia, mother and brother well. The past history included scarlet fever, dysentery at three years of age, measles, mumps, whooping-cough, chicken-pox, enuresis nocturna which ceased at the age of four years. (I have repeatedly observed this symptom in the early history of diabetic children). Always a voracious appetite, sometimes eating six potatoes at a meal; ate much candy. During the year preceding the onset of the disease the patient developed rapidly both in height and weight. In February, 1908, she showed weariness. Early in March polydipsia, polyuria and polyphagia were present, and sugar was demonstrated in the urine. In the previous year the urine was normal.

During the whole period of illness the patient remained in good condition and attended school with comfort. *The diet was rigidly adhered to and not relaxed except when the diagnosis was at one time doubted by the local physician. Catamenia was established for the first time in March, 1909.* The patient died in coma on December 10, 1910. The harmfulness of doubting a diagnosis is well illustrated by this patient's career. She was an ideal case for faithful treatment and even without insulin with present day treatment this patient should have lived at least four years longer. Remembering her tragic end I am always very slow to tell a patient he does not have diabetes if any doctor has ever found sugar present in the urine or thought it present. I tell such patients to have their urine examined each month for a year and thereafter at least every six months for life, even though I find no proof of diabetes.

Case No. 564 (see p. 520) shows a remarkable gain in tolerance from a minus carbohydrate balance of 70 grams to a positive balance of 50 grams, lasting for years. Case No. 203 (see p. 188) also illustrates a gain in tolerance, for now, August, 1927, this boy is able to take a free diet without the appearance of sugar. Case No. 653 showed 5.8 per cent and 174 grams sugar on a free diet in September, 1913, but now, thirteen and a half years later, at the age of sixty-six years, eats between 200 and 300 grams carbohydrate and is free from sugar. This patient, like several others, takes comparatively little fat. The remarkable case of Geyelin and DuBois,[1] who progressed from a minus carbohydrate balance of 75 grams to a positive balance of 160 grams, is another striking illustration of gain in tolerance. Case No. 30 showed sugar for eighteen years, and yet now, in 1927, twenty-five years after onset of diabetes, is

[1] Geyelin and DuBois: Loc. cit., p. 209.

sugar-and albumin-free on a diet of approximately 120 grams of carbohydrate made up of starch rather than of actual sugar. No matter whether a true diabetic or a potential diabetic, as I have now classified him, his case is instructive. Case No. 321, with onset in 1905 at the age of fifty-one years, came for treatment with 5.4 per cent of sugar in 1910. He soon developed a tolerance for 90 grams carbohydrate. Later this rose to carbohydrate 181 grams, protein 57 grams, and fat 102 grams. He died in 1924 of angina pectoris. Case No. 632 (see p. 108) had difficulty in becoming sugar-free in July, 1913, at the age of thirty-one years, upon carbohydrate 15 grams, but in 1917 maintained an active life, played golf better than ever, and reached a position of eminence in his country in his military vocation, yet he kept sugar-free upon a diet of carbohydrate 29 grams, protein 85 grams, and fat 150 grams. This tolerance again fell by 1922 and he was forced to give up exercise. His diet was carbohydrate 15 grams, protein 69 grams, fat 103 grams. With 8 units of insulin daily it was raised to carbohydrate 43 grams, protein 76 grams, fat 150 grams and in the six months ending in May, 1923, he had gained 14¼ pounds and been able to take up golf and work. Tolerance has continued to advance and in December, 1927, after fifteen years of diabetes it has risen from its low level of carbohydrate, 15 grams without insulin to 133 grams with 24 units of insulin. I recall no other patient who lived as accurately by the scales for six years on so low a carbohydrate diet, and no patient with onset of diabetes at thirty years who has been rewarded with a greater increase in tolerance.

The best writers are all most emphatic in their approval of the endeavor to promote tolerance for sugar by rendering the patient sugar-free. Naunyn says, "From my experience I consider it highly probable that among the early, strictly treated cases which passed in the beginning as severe, but later took a favorable course, there is many a one for which one must thank this early strict treatment; moreover, on the other hand, there can be no doubt that the cases which run ultimately a severe course have undergone little, if any, energetic care." And again he urges not to be "content to maintain the patient for a time in just an endurable condition, but rather to strive to improve the diseased function, or at least to check further inroads on the same." So universal are the two principles that there is an increase in severity the longer the disease lasts and that the progress of the disease is checked by making the patient sugar-free, that it makes any glycosuria, no matter how inconsiderable, worthy of energetic treatment.

Today many writers not only insist that the urine should be maintained free from glycosuria, but that the blood sugar should always be at a normal level. Rabinowitch is still more progressive and would demand a normal blood fat as well.

A normal blood sugar is desirable, but I am not convinced that it is a necessity for improvement in the state of the diabetes. The diabetes of Case No. 1609 began when he was 10.7 years old. It was severe in type, his weight fell from 90 to 71½ pounds during the first two years. He broke his diet continuously and it seemed a miracle that he escaped death from coma. Even with insulin he was seldom sugar-free, but on February, 1927, he appeared in my office as an attractive, healthy looking young man of twenty years, weighing 135 pounds, 5 feet 7¾ inches tall. His urine contained no sugar, the blood sugar eight hours after a meal was 0.21 per cent, his diet contained by his estimation 35 grams carbohydrate, but I suspect considerably more, and he was taking 10 units of insulin in the morning, 10 at noon and 16 at night. He was working hard, carrying on his own small farm. Similarly Case No. 428 after nineteen years of marked glycosuria became sugar-free and remains so with 19 units of insulin upon a diet of about 86 grams carbohydrate. His improvement, like that of the boy just cited, was in the face of years of glycosuria and hyperglycemia.

A sugar-free urine is more important than a normal blood sugar. It is never normal to show glycosuria, but variations in the blood sugar rising as high as 0.16 per cent after a meal are normal phenomena. It is an open question if what is normal for some hours a day must be considered deleterious if it persists a few hours longer. I consider a normal blood sugar desirable in every case of diabetes provided it can be attained with reasonable restrictions of diet and with moderate dosage of insulin, but I do not believe it to be a necessity for improvement. A similar viewpoint is held by R. D. Lawrence,[1] based on other grounds.

Concerning the necessity for a normal or nearly normal percentage of the blood fat before improvement can take place, less can be said because our data are still inadequate. In general a high blood fat signifies a more serious condition than a high blood sugar. I suspect, but I cannot prove the statement, that the patients who have survived diabetes for many years with success despite hyperglycemia have done so without a chronic acidosis or hyperlipemia. In other words, at the expense of hyperglycemia they have utilized enough carbohydrate to avoid such phenomena.

[1] Lawrence: Quart. Jour. Med., 1926, **20**, 69.

E. INCIDENCE.

1. **Increase in the Incidence of Diabetes Mellitus Is Now Checked** —The incidence of diabetes in the registration area of the United States more than trebled in the closing twenty years of the last century, but has less than doubled in the similar opening period of the present. Between the years 1915 and 1925 the rate per 100,000 has remained nearly constant averaging 16.2 for the first half of the decade and 17.3 for the latter half and was actually less for the year 1925 than for the year 1915.

Such a rapid rate of increase as took place between 1880 and 1915 is evidence in itself that a fallacy exists somewhere in the statistics or their collection. Convincing proof that this is the case is furnished by a comparison of the statistics for the registration area of the United States during the years 1910, 1911, 1912 and 1913, because during these years the death-rate for diabetes was nearly stationary. Such a sudden halt in the progressive frequency of the disease could not have been brought about without some obviously remarkable improvement in treatment, preventive or otherwise. This we know did not take place in 1910. This striking interruption in the advancing incidence of the disease is also indicated by the statistics of New York and Boston. Thus, in Boston during 1912 and 1913, the death-rate from diabetes was less than during 1910 and 1911. But since 1913, a remarkable advance is registered throughout the country, and in New York and Boston as well. This rapid rise in mortality in 1914, 1915 and 1916, I believe attributable to the increased attention devoted to this disease by the medical profession and by the newspapers following the announcement of the undernutrition method of treatment by F. M. Allen.

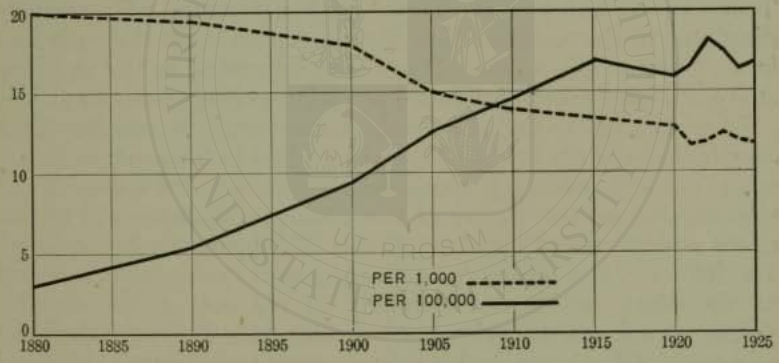


FIG. 14.—The falling total death-rate per 1000 and the rising diabetic death-rate per 100,000 between the years 1880 and 1925 in the registration area of the United States.

In Fig. 14 and Table 23 are displayed the falling rate of deaths from all causes per 1000, the rising rate of deaths from diabetes per

100,000, and the per cent of diabetic deaths to total deaths during the last forty-five years in the registration area of the United States.

The decrease in the diabetic death-rate, beginning with 1915, may be explained first, by the general tendency to eat less food during the war, and second, by the less accurate observation of the civilian population due possibly to the withdrawal of physicians from general practice and their entrance into the army. It is, therefore, not surprising that in 1920, the rate began to rise because these two factors had ceased to be operative. The discovery of insulin in 1921 augmented the rise because it focussed attention upon the disease to a remarkable degree and brought many new cases to light. This artificial statistical increase has been more than offset by the actual improvement in treatment which insulin has afforded.

Correlations between the death rate from diabetes and other demographic factors have recently been made by Jordan.[1] It is noteworthy that whereas crude and adjusted rates for age and sex were nearly alike in 1900, being 11 and 10.4 respectively, in 1920 the difference was notable, being 20.6 for the crude and 18.7 for the adjusted rate. The adjusted rate in 1920 varied from 6.5 in Tennessee to 2.15 in New York. Such differences will gradually disappear in the course of time if they depend upon the variations in accuracy of diagnoses. The reader interested in the technical study of diabetic statistics should not fail to consult Jordan's article.

Instability of the diabetic death-rate is certain to continue until examinations of the urines of each individual in the community are made, not only with each illness, but also once or twice yearly. In this way the actual number of latent cases of diabetes will be disclosed and the morbidity of the disease will apparently be increased. The influence of a second factor is the report of deaths as recorded on the death certificate. Formerly 65 per cent of the diabetic deaths were due to diabetic coma. Today coma is largely abolished as a cause of death and during the two years ending July 1, 1926 and 1927 was reduced to 10 per cent and zero respectively of my total diabetic mortality. In the place of coma arteriosclerosis in appearing. Whereas diabetic coma was recorded on the death certificate as a primary cause of death and was classified with diabetes, the manifestations of arteriosclerosis in the brains, heart, kidneys, and in the lower extremities as gangrene relegate diabetes to a secondary cause and it thus escapes mention in mortality data. For this reason private collections of deaths in diabetes in the future will assume an added value, because such will show the actual number of diabetic fatalities as well as their true causation.

Man's increasing longevity, the relatively greater increase in incidence of the diabetic mortality in females, the growing pre-

[1] Jordan: Am. Jour. Hygiene, 1928, **8**, 55.

ponderance of deaths from diabetes at over fifty years of age instead of under fifty years of age, and the remarkable reduction of diabetic mortality in children will all claim attention in any study of the total diabetic mortality.

TABLE 23.—TOTAL AND DIABETIC MORTALITY IN THE REGISTRATION AREA OF THE UNITED STATES.

Year.	Population in registration area, per cent.	Deaths from all causes.		Deaths from diabetes.		Diabetic deaths to total deaths per cent.
		Number.	Rate per 1000 population.	Number.	Rate per 100,000 population.	
Census year:						
1880	17.0	169,453	19.8	237	2.8	0.14
1890	31.4	386,212	19.6	1,089	5.5	0.28
1900	37.9	512,669	17.8	2,693	9.3	0.53
Calendar year:						
1900	..	539,939	17.6	2,996	9.7	0.55
1901	..	518,207	16.5	3,212	10.3	
1902	..	508,640	15.9	3,312	10.4	
1903	..	524,415	16.0	3,681	11.3	
1904	..	551,354	16.5	4,259	12.9	
1905	..	545,533	16.0	4,397	13.0	0.81
1906	..	658,105	15.7	5,331	13.0	
1907	..	687,034	16.0	5,801	13.9	
1908	..	691,574	14.8	6,274	13.9	
1909	..	732,538	14.4	7,024	14.4	
1910	58.3	805,412	15.0	8,040	14.9	0.91
1911	..	839,284	14.2	8,805	14.9	
1912	..	838,251	13.9	9,045	15.0	
1913	..	890,848	14.1	9,660	15.3	
1914	..	898,059	13.6	10,666	16.2	
1915	..	909,155	13.6	11,775	17.5	1.31
1916	..	1,001,921	14.0	12,199	17.1	
1917	..	1,068,932	14.3	12,750	17.0	
1918	..	1,471,367	18.1	12,927	15.9	
1919	..	1,096,436	12.9	12,683	14.9	
1920	82.2	1,142,558	13.1	14,062	16.1	1.22
1921	..	1,032,009	11.6	14,933	16.8	1.40
1922	85.3[1]	1,101,863	11.8	17,182	18.4	1.56
1923	87.6	1,193,017	12.3	17,357	17.9	1.45
1924	..	1,173,990	11.9	16,453	16.6	1.40
1925	..	1,219,019	11.8	17,385	16.9	1.43

The lengthening of human life in retrospect and prospect is entertainingly discussed by Irving Fisher.[2] He quotes Dublin's statement made in 1922 that ten years can still be added to human life by applying existing knowledge alone and adds data which suggest that this increase will be reached by 1940 and that the average life time "by the year 2000 would reach the highly respectable figure of eighty-two years."

[1] Exclusive of Hawaii.
[2] Fisher: Am. Jour. Pub. Health, 1927, **17**, 1.

The percentage of diabetic deaths to total deaths has risen even more rapidly than the diabetic death-rate. Between 1880 and 1925 it rose ten-fold to 1.43 per cent. This is partly accounted for by the fall in deaths from all causes throughout the United States. Like the diabetic death-rate, however, it has risen little since 1915. In 1900 diabetes ranked twenty-seventh as a cause of death in the registration area of the United States, but in 1920 it was twelfth. In Massachusetts for the same years its place changed from twenty-first to eleventh, and in New York City during 1923 it ranked tenth.[1]

TABLE 24.—DEATHS PER 100,000 OF POPULATION FROM THE CHIEF CAUSES OF DEATH IN THE REGISTRATION AREA OF THE UNITED STATES, 1920.[2] EMERSON AND LARIMORE.

Organic diseases of heart	141.9
Pneumonia and bronchopneumonia	137.3
Tuberculosis, all forms	114.2
Bright's disease and nephritis	89.4
External causes (violent deaths including suicide and homicide)	88.8
Cancer	83.4
Cerebral hemorrhage	80.9
Influenza	71.0
Congenital debility and malformations	69.9
Diseases of arteries	22.8
Puerperal state	19.2
Diabetes	16.1

"The increase in the incidence and death-rate from diabetes in the United States, and in New York City in particular, has been more rapid than that of any other disease for which we have records in the last fifty years."[3] Here is justification for the added attention devoted to the study of diabetes in the last few years. Practitioners today have far more cases of diabetes to treat than their fathers, not because there are twice the number of cases, but because they live nearly twice as long.

All age groups have been about equally represented in the statistical increase in diabetes. This is shown by a study of Table 25, in which the relative proportion of the population of the United States in the registration area at different groups is given for the years 1890 and 1920, along with the corresponding percentage of deaths from diabetes. In this table the decreasing percentages of population under twenty years of age in 1920, compared with 1890 is manifest. This is due in part to the marked prolongation of life (see Table 45) and, doubtless, in part to a falling birth-rate. The feature of the table which caused its insertion into the text is, however, the right-hand column. This shows that the diabetic

[1] Emerson and Larimore: Arch. Int. Med., 1924, **34**, 585.
[2] U. S. Census Bureau Mortality Rates, 1910–1920.
[3] Emerson and Larimore: Loc. cit., p. 44.

mortality per 100,000 in 1920 per decade, as compared with 1890, has about doubled. Closer inspection of the table shows that this approximate doubling of mortality holds for each age period. It is true that for the period forty-five and over the mortality has nearly trebled, rising from 20.6 to 57.3, but this can be accounted for by the decrease in mortality for unknown age groups from 13.75 in 1890 to 3.36 in 1920.

TABLE 25.—RELATIVE PROPORTION OF THE POPULATION OF THE UNITED STATES IN THE REGISTRATION AREA AT DIFFERENT AGE GROUPS IN 1890 AND IN 1920 WITH CORRESPONDING PERCENTAGE MORTALITY FROM DIABETES.

Age group, years.	Population.	Per cent of total.	Percentage mortality per 100,000.	
			Total.	Diabetic
1890.				
Under 5	2,392,447	12.2	5591.70	0.96
5– 9	2,373,440	12.0	589.86	0.85
10–14	2,204,293	11.2	318.60	2.22
15–19	2,055,305	10.5	562.40	1.90
20–44	7,244,021	36.9	1196.00	3.63
45 and over	3,339,050	17.1	3927.50	20.60
Unknown	50,884	0.003	4180.00	13.75
Total	19,659,440	99.9		
1920.				
Under 5	9,239,058	10.75	2688.80	2.03
5– 9	9,014,012	10.37	300.10	2.83
10–14	8,409,709	9.68	234.20	4.32
15–19	7,527,480	8.65	411.20	4.65
20–44	33,876,531	38.98	718.70	6.46
45 and over	18,711,942	21.52	3005.30	57.30
Unknown	119,047	0.001	1349.00	3.36
Total	86,897,779	99.95		

A more accurate conception of trends in diabetic mortality, I believe, is afforded by the statistics of the State of Massachusetts than by those now available for the country as a whole, particularly as relate to sex and age.

The diabetic death-rate and the ratio of diabetic deaths to total deaths are quite uniformly higher in Massachusetts than in the Registration Area. In 1922 the per cent of diabetic deaths to total deaths reached its peak, 1.85 per cent, or 1 diabetic death for 54 total deaths.

The abrupt fall in the diabetic death-rate for individuals under twenty years of age and for those between twenty and forty-nine years is strikingly exhibited in Fig. 15 prepared by Miss Angeline Hamblen of the Massachusetts State Board of Health. The mortality for diabetes in persons under twenty years of age and between twenty and forty-nine years of age has been cut in half and that for diabetes in persons over fifty years of age has doubled. The actual

TABLE 26.—TOTAL AND DIABETIC MORTALITY IN MASSACHUSETTS.

Year.	Deaths from all causes.		Deaths from diabetes.		Diabetic deaths to total deaths, per cent.
	Number.	Rate per 1000 population.	Number.	Rate per 100,000 population.	
1880	35,292	19.8	83	4.7	0.24
1890	43,528	19.4	188	8.4	0.43
1900	51,156	18.2	330	11.8	0.64
1910	54,407	16.1	575	17.0	1.06
1915	53,131	14.4	673	18.2	1.26
1916	56,366	15.1	783	21.0	1.39
1917	56,628	15.0	776	20.6	1.37
1918	78,842	20.7	680	17.9	0.86
1919	52,345	13.7	633	16.5	1.21
1920	53,632	13.9	796	20.6	1.48
1921	47,780	12.2	777	19.9	1.63
1922	51,115	13.0	948	24.1	1.85
1923	52,380	13.2	852	21.4	1.63
1924	49,466	12.4	772	19.3	1.56
1925	51,890	12.5	806	20.0	1.56
1926	52,888	12.6	835	19.8	1.58

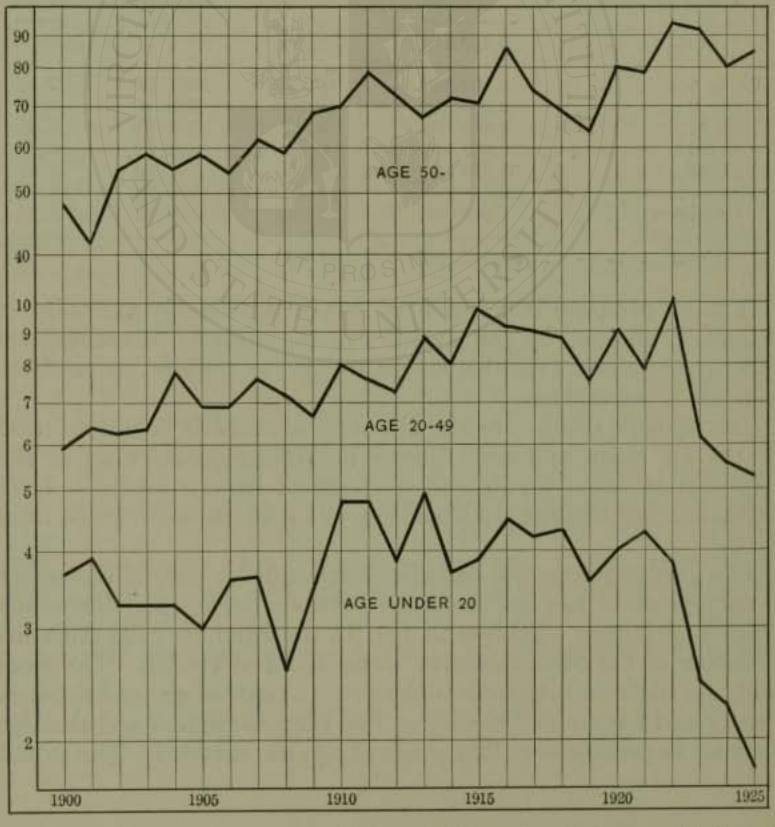


FIG. 15.—Average death-rates from diabetes in Massachusetts by age. Death-rate per 100,000 population.

death-rate for these age groups is shown in Table 27 and the per cent of total deaths from diabetes in each group in Table 28. Between 1921–1925, 86 per cent of all diabetic deaths in Massachusetts took place at or above the age of fifty years.

TABLE 27.—AVERAGE DEATH-RATES FROM DIABETES IN MASSACHUSETTS BY AGE. DEATH-RATE PER 100,000 POPULATION.

Years.	Age group. Under 20.	20 to 49.	50 plus.
1901 to 1905	3.4	6.8	54
1906 to 1910	3.6	7.3	63
1911 to 1915	4.3	8.3	73
1916 to 1920	4.1	8.7	77
1921 to 1925	2.9	7.0	86

TABLE 28.—PER CENT OF TOTAL DEATHS FROM DIABETES IN AGE GROUPS.

Year.	Per cent in age group. Under 20.	20 to 49.	50 plus.
1900	11	24	65
1910	10	23	67
1920	7	21	72
1925	3	13	84

The death-rate for the age group 50 plus has risen with slight variations since 1900. The rate for the age group 20 to 49 was also rising between 1900 and 1922 but since then it has shown a decided decline. The rate for the age group under 20 has been falling since 1910 but has had a much more rapid decline since 1922.

TABLE 29.—SEX AND THE DIABETIC DEATH-RATE IN MASSACHUSETTS.

Year.	Male.	Female.
1900	12.8	10.8
1901	9.5	12.7
1902	11.0	14.9
1903	12.3	15.1
1904	12.5	15.2
1905	11.7	15.9
1906	11.7	15.0
1907	12.5	17.3
1908	11.8	15.8
1909	12.4	18.4
1910	14.4	19.5
1911	16.9	19.9
1912	14.2	19.4
1913	15.7	19.4
1914	15.3	19.8
1915	16.2	20.8
1916	17.7	24.7
1917	18.3	23.2
1918	16.4	19.6
1919	14.3	18.7
1920	17.3	23.6
1921	15.1	24.4
1922	18.2	29.2
1923	15.8	26.3
1924	13.9	23.8
1925	15.5	23.4

The influence of sex upon the diabetic death-rate in Massachusetts is shown in Table 29 and Fig. 16. Whereas diabetes has increased among males in the last twenty-five years 20 per cent, it has risen among females 117 per cent. The reasons for so great a discrepancy will be discussed later. Suffice it to say here that these figures prove that the increase in diabetes has been chiefly due to its extraordinarily growing prevalence among females.

The combined influence of age periods and sex are shown in Fig. 17. The lessening advance in diabetic mortality in males and the remarkable decline in diabetic mortality in persons under fifty years of age and especially under twenty years give grounds for hope that the worst days of diabetes are over.

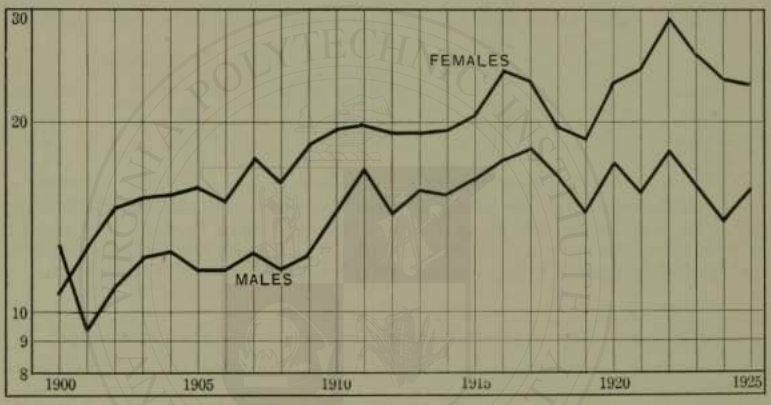


FIG. 16.—Sex and the diabetic death-rate in Massachusetts.

Confirmation for the Massachusetts tables has been afforded through the courtesy of Dr. Augustus Knight, Medical Director, and Dr. Louis I. Dublin, Statistician of the Metropolitan Life Insurance Company. The experience of this insurance company which insures about one-sixth of the total population of the United States is exhibited in Table 30 and Fig. 18. The remarkable increase in colored females is the most outstanding feature and is akin to the increase which took place among whites in the last years of the last century.

New York City's total mortality per 100 population has been more than halved in the last forty-five years, but the diabetic death-rate per 100,000 population has increased six-fold, and the percentage of diabetic to total deaths has increased thirteen-fold. The data are given in Table 31.

Boston shows a higher mortality from diabetes than that of any city which has come to my attention, but New York has the highest

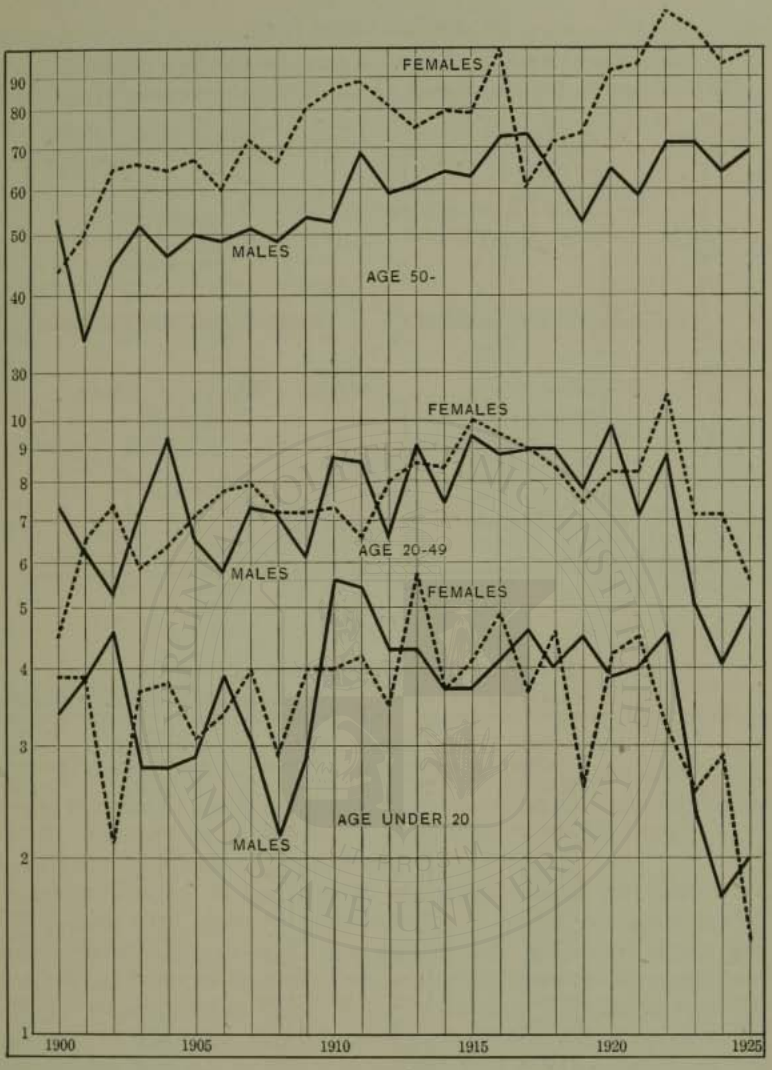


FIG. 17.—Sex and the diabetic death-rate in Massachusetts.

TABLE 30.—AVERAGE AGE OF DEATH FOR THOSE DEATHS OCCURRING FROM DIABETES. 1926–1920, 1916–1911.[1]

(Experience of Metropolitan Life Insurance Company. Industrial Department Premium Paying Business.)

Color and sex.	1926.	1925.	1924.	1923.	1922.	1921.	1920.	1916.	1915.	1914.	1913.	1912.	1911.
Total . . .	54.4	54.7	54.0	53.5	51.9	51.1	51.2	52.9	52.1	52.4	51.0	52.4	51.5
White males .	50.7	50.6	50.5	49.0	47.1	45.4	46.9	49.2	48.6	48.5	46.0	48.3	46.5
White females .	56.5	57.0	56.0	55.8	54.0	53.9	53.4	55.0	53.8	54.4	54.0	54.6	54.7
Colored males .	47.9	48.4	50.9	50.8	48.9	48.5	47.5	49.1	48.9	47.8	47.9	48.6	49.2
Colored females	51.5	51.2	50.3	50.9	51.8	49.8	51.7	51.2	51.6	53.1	48.2	52.2	48.3

[1] Data for 1919, 1918 and 1917 not available.

DIABETES MELLITUS.

DEATH-RATE BY AGE PERIOD. WHITE AND COLORED PERSONS.
Metropolitan Life Insurance Company. Industrial Department 1911 to 1926.

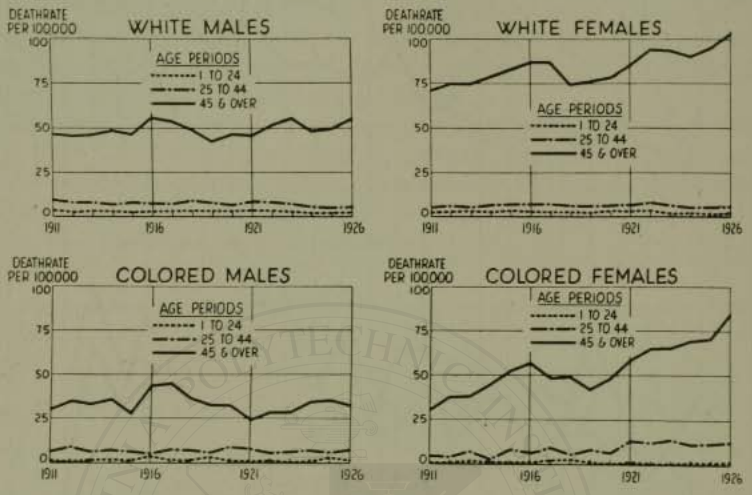


FIG. 18

TABLE 31.—TOTAL AND DIABETIC MORTALITY IN NEW YORK CITY.

Year.	Deaths from all causes. Number.	Deaths from all causes. Rate per 1000 population.	Deaths from diabetes.. Number.	Deaths from diabetes.. Rate per 100,000 population.	Diabetic deaths to total deaths, per cent.
1880	31,937	26.4[1]	44	3.6[1]	0.14
1890	40,103	24.6[1]	130	8.0[1]	0.32
1900	70,872	20.6	357	10.4	0.50
1910	76,742	16.0	768	16.0	1.00
1915	76,193	14.6	1109	20.2	1.45
1916	77,801	14.7	1118	20.0	1.44
1917	78,575	14.6	1153	21.0	1.47
1918	96,989	17.9	1011	18.0	1.04
1919	74,131	13.4	955	17.0	1.29
1920	73,393	12.9	1075	19.0	1.46
1921	64,257	11.2	1120	19.0	1.74
1922	69,690	12.3	1448	25.0	2.08
1923	69,452	11.7	1360	22.9	1.96
1924	71,252	12.2	1177	20.2	1.65
1925	71,863	12.2	1312	22.3	1.83

percentage mortality to total mortality. In 1922, the diabetic death-rate in Boston reached the peak of 29.1 per 100,000. In New York in 1922, the deaths from diabetes were 2.08 per cent of all the deaths. The decrease in percentage of diabetic death-rate appeared here during the war as well as the decrease in percentage of diabetic deaths to total deaths. It will be of great interest, statistically, to note whether the mortality in other sections of the

[1] Old City of New York included present Boroughs of Manhattan and the Bronx.

country continues to approach the level reached here. To a certain extent the city with the highest mortality is an index to which the mortality in other communities may be expected to rise. In Malta the rate is 38.4 per 100,000, according to Hoffman,[1] whose article upon the statistics of diabetes should be consulted.

TABLE 32.—TOTAL AND DIABETIC MORTALITY IN BOSTON.

Year.	Deaths from all causes.		Deaths from diabetes.		Diabetic deaths to total deaths, per cent
	Number.	Rate per 1000 population	Number.	Rate per 100,000 population.	
1880	8,531	23.5	[2]	[2]	[2]
1890	10,181	22.7	31	6.9	0.3
1900	11,678	20.8	77	13.7	0.7
1910	11,574	17.2	135	20.1	1.2
1915	12,018	16.1	195	26.1	1.6
1916	12,760	16.8	192	25.2	1.5
1917	12,728	16.5	148	19.2	1.2
1918	17,447	22.2	133	16.9	0.8
1919	11,689	15.6	171	23.0	1.5
1920	11,601	15.4	175	23.0	1.5
1921	10,220	13.5	149	19.7	1.5
1922	11,420	15.0	222	29.1	1.9
1923	11,503	14.9	187	24.3	1.6
1924	10,933	14.1	184	23.7	1.7
1925	11,590	14.8	166	21.2	1.4

Diabetes in Philadelphia has been carefully investigated by Anders and Jameson.[3] Whereas in 1913 diabetes occupied the twenty-second place in relative rating as a cause of death, in 1923 it had risen to twelfth place. The phenomenal rise in the death-rate among females in the last fifteen years prevailed in Philadelphia as for the country as a whole. Friedenwald and Morrison[4] have studied the question in Baltimore.

Certain foreign cities present statistics which will serve for comparison with those in this country. Berlin formerly had a higher diabetic death-rate than any of our American cities, but in the later years of the war the death-rate from diabetes was cut in half. One must not forget that the civilian population received less medical attention there as well as here, and this may partially account for the fall in death-rate, but few will gainsay that the outstanding cause for the precipitous decrease in diabetic mortality was due to undernutrition. Confirmation of this conclusion will be furnished by the mortality statistics for the next few years, during which they should rise. Today the demonstration of the importance of undernutrition in the treatment of diabetes appears to be beyond doubt.

[1] Hoffman: Boston Med. and Surg. Jour., 1922, **187**, 135.
[2] 1880 data not available.
[3] Anders and Jameson: Am. Jour. Med. Sci., 1925, **170**, 313.
[4] Friedenwald and Morrison: Arch. Int. Med., 1927, **40**, 538.

TABLE 33.—TOTAL AND DIABETIC MORTALITY IN BERLIN.

Year.	Deaths from all causes.		Deaths from diabetes.		Diabetic deaths to total deaths, per cent.
	Number.	Rate per 1000 population.	Number.	Rate per 100,000 population.	
1871–1875	..	..	..	1.7	
1876–1880	..	..	..	3.0	
1881–1885	..	..	..	3.6	
1886–1890	..	..	..	5.1	
1891	33,394	21.0	91	5.7	0.27
1892	32,696	20.3			
1893	36,038	22.1	120	7.4	0.33
1894	30,961	18.8	149	9.1	0.48
1895	33,627	20.2	131	7.9	0.39
1896	30,578	18.0	152	8.9	0.50
1897	30,622	17.7	152	8.8	0.50
1898	30,574	17.2			
1899	34,011	18.7	167	9.2	0.49
1900	35,411	19.0	193	10.3	0.55
1901	34,096	18.1	261	13.8	0.77
1902	30,741	16.2	281	14.8	0.91
1903	31,882	16.6	310	16.1	0.97
1904	33,425	17.0	395	20.1	1 18
1905	34,451	17.1	324	16.1	0.94
1906	32,648	15.9	414	20.1	1.28
1907	32,353	15.6	374	18.1	1.16
1908	32,408	15.7	367	17.8	1.13
1909	31,844	15.5	406	19.8	1.28
1910	30,152	14.6	391	19.0	1.30
1911	32,307	15.6	441	21.3	1.37
1912	29,981	14.4	459	22.0	1.53
1913	28,067	13.5	409	19.6	1.46
1914	29,664	14.6	468	23.1	1.63
1915	28,572	15.2	385	20.5	1.35
1916	27,147	15.1	332	18.5	1.22
1917	34,138	19.6	246	14.1	0.72
1918	35,764	20.7	204	12.0	0.57
1919	31,307	18.5	185	10.9	0.59
1920	30,982	18.6	178	10.9	0.57

TABLE 34.—TOTAL AND DIABETIC MORTALITY IN PARIS.

Year.	Deaths from all causes.		Deaths from diabetes.		Diabetic deaths to total deaths, per cent.
	Number.	Rate per 1000 population.	Number.	Rate per 100,000 population.	
1880	55,706	25.4	...	6.3	
1890	54,566	22.8	...	13.5	
1900	51,725	19.6	413	17.0	0.82
1910	45,814	16.2	468	18.4	1.02
1911	48,942	16.9	451	16.9	0.92
1912	47,059	16.3	483	17.7	1.05
1913	44,624	15.4	424	16.0	0.95
1914	45,972	15.9	406	14.3	0.89
1915	43,068	14.9	382	13.2	0.89
1916	43,450	15.0	387	13.4	0.89
1917	44,597	15.4	392	13.5	0.88
1918	49,658	17.4	279	9.6	0.56
1919	44,936	15.5	297	10.3	0.66
1920	43,082	14.8	280	9.6	0.65
1921	41,955	14.4	376	12.9	0.90
1922	40,583	14.0	321	11.0	0.79

TABLE 35.—DIABETIC MORTALITY IN DIFFERENT COUNTRIES AND CITIES ON DIFFERENT DATES COMPARED (RATE PER 100,000).

Countries.	1880.	1900.	1910.	1915.	1916.	1917.	1918.	1919.	1920.	1921.	1922.	1923.	1924.	1925
United States[1]	**2.8**	9.7	14.9	17.5	17.1	17.0	15.9	14.9	16.1	16.8	**18.4**	**17.9**	**16.6**	**16.9**
England[2]	**4.1**	8.6	11.0	13.0	13.0	11.2	10.6	10.5	10.0	10.8	**11.9**	**11.4**	10.9	11.2
Germany														
France														
Italy	**1.4**	**3.3**	**4.7**	**5.3**	**5.0**	**5.2**	**4.8**	**4.3**	**4.5**	**4.9**	5.4	5.4		
Japan[3]	...	...	**2.2**	3.0[4]	3.1	3.2	3.6	2.9	**3.1**	3.3	3.3			
Cuba	...	**2.4**	**2.4**	**3.4**	**3.5**									

Cities.	1880.	1900.	1910.	1915.	1916.	1917.	1918.	1919.	1920.	1921.	1922.	1923.	1924.	1925.
New York[1]	**3.6**	11.4	18.6	24.1	22.8	24.3	22.3	21.2	23.4	24.1	27.9	27.4	25.7	25.9
Boston[1]	...	15.2	20.8	27.1	26.6	21.3	19.6	23.5	24.2	19.8	29.3	24.8	**23.7**	20.9
London[5]	...	...	...	11.9	11.4	10.0	8.1	8.7	8.0	9.3	**10.4**	**9.5**	9.5	9.0
Berlin	...	**10.3**	**19.0**	**20.5**	**18.5**	**14.1**	**12.0**	**10.9**	**10.9**					
Paris	**6.3**	**17.0**	**18.4**	**13.2**	**13.4**	**13.5**	**9.6**	**10.3**	**9.6**	**12.9**	**11.0**			
Rome														
Tokyo	...	...	**2.9**	**3.2**	**2.6**	**2.7**	**2.4**	**2.5**	**2.2**	**3.0**	**2.4**			
Havana	...	**7.4**	**2.5**	**7.4**	**9.0**	**6.0**	**7.6**	**7.5**	**8.4**	**7.5**	**9.2**			

Paris shows almost as striking a variation in the statistical mortality from diabetes as Berlin, because from 1910, when the diabetic mortality in Paris reached its acme, 18.4 per 100,000 population, it fell in 1918 to 9.6, but is now on the upward trend. The reduction in the percentage of diabetic deaths to total deaths in Berlin and Paris is even more striking than the falling mortality.

Ullman[6] has carefully studied diabetic statistics, particularly in Germany. His comments upon them are already published, but the statistical article is not yet available. Many of his conclusions may be modified by data published here as will also certain of my impressions.

London[7] with a population of 7,625,461 in 1923 reports 725 deaths from diabetes; Massachusetts with a population of 3,969,536 records

[1] Registration area exclusive of Hawaii: 1900, from Mortality Statistics, U. S., 1900 to 1904; 1910, from Mortality Statistics, U. S., 1910; 1915 to 1921, from Mortality Statistics, U. S., 1921.

[2] 1900, from report Registrar-general, England and Wales, 1911; 1910, from report Registrar-general, England and Wales, 1920; 1915 to 1921, from report Registrar-general, England and Wales, 1921.

[3] Based on civilian deaths and civilian population.

[4] 1915 to 1918, from Statistique Causes de Dérès, Japan, for each year; 1919, from Résumé Statistique de Mouvement de la population, Japan, 1919; rates worked from population and deaths in each report.

[5] 1915 to 1921, from reports Registrar-general, England and Wales, for each year. Rates worked from population and deaths in each report. Figures are for London administrative county, which is Greater London, exclusive of "Outer Ring." In 1921 report *only* are deaths from diabetes shown for Greater London; Greater London, population 7,535,582, deaths from diabetes, 746, rate per 100,000, 9.9; London Administrative County, population 4,524,000, deaths from diabetes, 422, rate per 100,000, 9.3.

[6] Ullman: Deutsch. med. Wchnschr., 1927, **53**, 561. See also Die Med. Welt., 1928, **2**, 87.

[7] Joslin: Boston Med. and Surg. Jour., 1925, **193**, 707.

852 deaths. In London the diabetic death-rate per 100,000 was 9.51, in Massachusetts 21.4. In 1880 in Massachusetts 83 individuals succumbed to diabetes, by 1923 the increase in numbers had been ten-fold, and the death-rate had risen about four-fold. For the same period in England and Wales the increase in the diabetic death-rate was nearly three-fold. (4.1–11.9, rate for 1922). For the year 1880 in Massachusetts there was 1 death from diabetes in 425 deaths, for 1924 there was 1 death in 64 deaths. The doctors in Massachusetts, therefore, have a diabetic problem on their hands. Their patients are more than twice as liable statistically, I do not believe it actually, to die of diabetes as citizens of London and the increase in the incidence of diabetes among their patients is far more rapid.

TABLE 36.—TOTAL AND DIABETIC DEATH MORTALITY IN ENGLAND AND WALES.

Year.	Deaths from all causes.		Deaths from diabetes.		Diabetic deaths to total deaths, per cent.
	Number.	Rate per 1000 population.	Number.	Rate per 100,000 population.	
1850	368,995	20.8	422	2.4	0.11
1860	422,721	21.2	536	2.7	0.13
1870	515,329	21.6	735	3.3	0.14
1880	528,624	19.5	1059	4.1	0.20
1890	562,248	19.3	1863	6.5	0.33
1900	587,830	18.2	2767	8.6	0.47
1901	551,585	16.9	2964	9.1	0.54
1902	535,538	16.2	2769	8.4	0.52
1903	514,628	15.4	2844	8.5	0.55
1904	549,784	16.2	3133	9.3	0.57
1905	520,031	15.2	3174	9.3	0.61
1906	531,281	15.3	3342	9.7	0.63
1907	524,221	14.9	3360	9.7	0.64
1908	520,456	14.5	3610	10.3	0.69
1909	518,003	14.3	3698	10.4	0.71
1910	483,247	13.2	3937	11.0	0.81
1911	527,810	14.2	3853	10.6	0.72
1912	486,939	13.0	4051	11.1	0.83
1913	504,975	13.5	4311	11.8	0.85
1914	516,742	13.7	4507	12.2	0.87
1915	562,253	14.8	4658	13.2	0.82
1916	508,217	13.4	4544	13.2	0.90
1917	498,922	13.5	3816	11.3	0.77
1918	611,861	17.1	3568	10.6	0.58
1919	504,203	13.3	3857	10.5	0.77
1920	466,130	12.1	3749	10.0	0.80
1921	458,629	11.5	4092	10.8	0.90
1922	486,780	12.8	4545	11.9	0.93
1923	444,785	11.6	4366	11.4	0.98
1924	473,235	12.2	4254	10.9	0.89
1925	472,841	12.2	4357	11.2	0.92

The diabetic mortality in different countries and different cities on different dates is compared in Table 35. All data in the table,

save those in heavy type, were placed at my disposal by the Department of Commerce, Bureau of the Census, Washington, through the courtesy of William H. Davis, M.D., Chief Statistician for Vital Statistics. There are various regrettable gaps in the table which it is hoped some one can fill. The general tendency is about the same. England shares with Berlin and Paris in presenting a falling diabetic mortality for the years subsequent to 1915; but why is the diabetic death-rate so low in England? Are the English better trained in the art of living under modern conditions? Is the same diligence displayed in discovering diabetes in London as in New York? It should be an easy matter to compile the number of examinations of urine on a single day in the public clinics of New York and of London.

The detailed diabetic mortality in England and Wales is given in Table 36. It is a striking fact that the percentage of diabetic deaths to total deaths in England and Wales for 1925 was only about one-half that in Boston. What is the explanation? The total death-rate in Holland is low, but the diabetic death-rate is very high and as a result of each condition the ratio of the diabetic death-rate to the total death-rate is extraordinary.

TABLE 37.—TOTAL AND DIABETIC MORTALITY IN HOLLAND.

Year.	Deaths from all causes.	Rate per 1000.	Deaths from diabetes.	Rate per 100,000.	Per cent of total.
1915	31,686	11.4	836	30.0	2.6
1917	34,957	12.1	843	29.2	2.4
1919	36,974	12.4	854	28.7	2.3
1921	30,593	9.9	880	28.6	2.9
1923	28,376	8.9	1076	33.9	3.8
1924	28,823	9.0	1032	32.2	3.6

The data shown in Table 37 were kindly furnished me by Angeline Hamblen. They are so remarkable in showing a high percentage of diabetic deaths to total deaths that I fear I must have misinterpreted them. It is difficult to conceive of the diabetic mortality in Holland being thrice that in England.

The low total and percentage diabetic mortality in Italy, as well as the constancy in the mortality, is noticeable in comparison with the mortality in other countries. This low mortality is only exceeded by that in Japan. The same upward tendency, however, in the prevalence of diabetes is noted in Japan. In fact, the most recent diabetic death-rates obtainable in each country represent the highest rates. This is shown in Japan and Tokyo by statistics furnished by Murayama and Sakaguchi. See Iwai.[1]

[1] Iwai: Le Diabete Sucre chez les Japonais, Tokyo, translated by Le Goff, Paris, Masson et Companie, Editeurs, 1916.

TABLE 38.—TOTAL AND DIABETIC MORTALITY IN ITALY.

Year.	Deaths from all causes.		Deaths from diabetes.		Diabetic deaths to total deaths, per cent.
	Number.	Rate per 1000 population.	Number.	Rate per 100,000 population.	
1890	795,911	27.3	637	2.1	0.08
1891	795,327	27.3	680	2.2	0.09
1892	802,779	26.8	792	2.6	0.10
1893	776,713	26.3	704	2.3	0.09
1894	776,372	25.1	700	2.3	0.09
1895	783,813	25.4	771	2.5	0.10
1896	758,129	24.1	833	2.6	0.11
1897	695,602	21.9	882	2.8	0.13
1898	732,265	22.9	894	2.8	0.12
1899	703,393	21.9	1026	3.2	0.15
1900	768,917	23.8	1082	3.3	0.14
1901	715,036	22.0	1071	3.3	0.15
1902	727,181	22.2	1154	3.5	0.16
1903	736,311	22.2	1139	3.5	0.16
1904	698,604	21.2	1242	3.8	0.18
1905	730,340	22.0	1322	4.0	0.18
1906	696,875	20.9	1394	4.2	0.20
1907	700,333	20.9	1535	4.6	0.22
1908	770,054	22.8	1503	4.4	0.20
1909	738,459	21.7	1551	4.6	0.21
1910	682,459	19.9	1608	4.7	0.24
1911	742,811	21.4	1714	4.9	0.23
1912	635,788	18.2	1658	4.7	0.26
1913	663,966	18.8	1818	5.1	0.27
1914	643,355	17.9	1838	5.1	0.29
1915	741,143	20.4	1942	5.3	0.26
1916	721,847	19.7	1827	5.0	0.25
1917	682,311	19.2	1835	5.2	0.29
1918	1,166,132	32.9	1696	4.8	0.14
1919	676,329	18.8	1536	4.3	0.23
1920	681,749	18.7	1636	4.5	0.24
1921	642,234	17.4	1799	4.9	0.28
1922	660,411	17.7	2020	5.4	0.31
1923	626,453	16.6	2037	5.4	0.33

Diabetes in the adult, according to Quiñones,[1] is not very common in Mexico, and he records that he has never seen a case of juvenile diabetes although having searched for it in his own practice and that of his pediatric confreres.

In an instructive monograph Montoro[2] discusses the incidence of diabetes in Cuba[2] and especially in the city of Havana. He ascribes the increase in incidence largely to the prolongation of life.

A discussion of the increase of diabetes in the Philippines can be found in an article by Concepcion.[3] In the latter country the incidence is increasing, due apparently to a greater accuracy of vital statistics, but it is still less than that in other countries, including Japan.

[1] Quiñones: La Diabetes y Su Tratamiento, Mexico, 1925, p. 109; *see also* Gaceta Médica de México, 1926, **57**, 181.

[2] Montoro: Diabetes y Su Tratamiento Actua, Habana, 1924.

[3] Concepcion: Philippine Island Med. Assn. Jour., 1922, **2**, 57.

TABLE 39.—TOTAL AND DIABETIC MORTALITY IN JAPAN AND TOKYO.

Year.	Deaths from all causes. Number.	Rate per 1000 population.	Deaths from diabetes. Number.	Rate per 100,000 population.	Diabetic deaths to total deaths, per cent.
		JAPAN.			
1909	1,091,264	21.7	1057	2.1	0.10
1910	1,064,234	17.7	1089	1.8	0.10
1911	1,043,906	20.0	1212	2.3	0.12
1912	1,037,016	19.8	1331	2.5	0.13
1913	1,027,252	19.3	1373	2.6	0.13
1914	1,101,815	20.3	1467	2.7	0.13
1915	1,090,000	19.9	1609	2.9	0.15
1916	1,187,832	21.4	1737	3.1	0.15
1917	1,199,669	21.3	1801	3.2	0.15
1918	1,493,162	26.3	1995	3.5	0.13
1919	1,281,965	22.8	1625	2.9	0.13
1920	1,422,096	25.4	1725	3.1	0.12
1921	1,288,570	22.7	1890	3.3	0.15
1922	1,286,941	22.3	1904	3.3	0.15
		TOKYO.			
1909	36,407	22.3	44	2.7	0.12
1910	35,870	19.8	53	2.9	0.15
1911	36,789	19.3	41	2.2	0.11
1912	35,283	17.6	37	1.8	0.11
1913	36,593	18.1	43	2.1	0.12
1914	36,765	17.5	50	2.4	0.14
1915	39,270	17.5	73	3.2	0.19
1916	39,397	17.2	59	2.6	0.15
1917	42,596	18.1	64	2.7	0.15
1918	46,815	20.3	55	2.4	0.12
1919	49,198	20.9	60	2.5	0.12
1920	50,516	21.1	52	2.2	0.10
1921	44,973	20.4	67	3.0	0.15
1922	43,409	19.4	54	2.4	0.12

TABLE 40.—DIABETIC MORTALITY IN SPAIN.[1]

Year.	Population.	Deaths.	Diabetic deaths.	Men.	Women
1919	20,719,598	482,752	1545		
1920	20,783,844	494,540	1406		
1921	21,338,381	455,469	1554		
1922	21,502,768	441,330	1572	696	876
1923	21,658,222	449,683	1715	717	998
1924	21,966,641	430,560	1784	799	985

Through the courtesy of Dr. Chester Jones and Professor Blum, of Strassbourg, I am enabled to insert the data for the diabetic mortality in Strassbourg.

Total Diabetics in the United States.—For the total number of diabetics in the United States no accurate figures are available. Since approximately 1 death out of each 50 in New York and Boston is due to diabetes, one might be tempted to assume that 2 per cent of the population have or will have the disease. On this basis the

[1] The statistics for diabetic mortality in Spain were given to me by Professor G. Marañon.

number of diabetics for the United States would be nearly 2,000,000! Granted the average length of a diabetic's life to be ten years, the number of fatal cases would be 200,000 instead of the actual number reported for the registration area, which was approximately 17,385 for 1925. Support for using the New York and Boston figures for

TABLE 41.—TOTAL AND DIABETIC MORTALITY IN BARCELONA, 1901–1922.[1]

Year.	Population in registration area.	Deaths from all causes. Number.	Deaths from all causes. Rate per 1000 population.	Deaths from diabetes. Number.	Deaths from diabetes. Rate per 100,000 population.	Rate per 100 total deaths.
1901	542,144	14,884	27.9	59	10.8	0.39
1902	546,882	12,596	23.6	57		
1903	551,863	12,849	24.1	51		
1904	556,787	12,985	24.2	49		
1905	561,755	13,966	26.0	61	10.9	0.35
1906	566,768	13,945	24.6	59		
1907	571,826	13,226	23.1	56		
1908	576,729	13,287	23.0	65		
1909	581,876	14,592	25.1	51		
1910	587,284	13,546	23.1	80	13.5	0.59
1911	592,476	13,847	23.4	82		
1912	599,113	13,172	22.0	95		
1913	603,421	14,661	24.3	102		
1914	607,170	16,577	27.3	83		
1915	619,083	14,468	23.4	86	12.2	0.59
1916	623,524	14,325	23.0	89		
1917	628,144	16,253	25.9	114		
1918	628,144	22,704	25.9	105		
1919	628,144	17,685	25.9	124		
1920	709,728	16,606	23.4	90	12.7	0.54
1921	709,728	14,774	23.4	113		
1922	709,728	15,691	23.4	125		

TABLE 42.—DIABETIC MORTALITY IN STRASSBOURG.

	Total number of deaths.	Total deaths from diabetes.	Per cent due to diabetes.
1920	2745	22	0.801
1921	2758	21	0.761
1922	2596	21	0.808
1923	2601	28	1.076
1924	2777	28	1.088

an estimate of the total diabetics in the country is furnished by the statistics of Barringer,[2] based upon the frequency with which sugar was found in the urines of 72,000[3] adults examined for life insurance in New York City. His method of investigation showed that nearly 2 per cent[4] of this large group of the adult population in a city had diabetes. It would be unjustifiable to apply his statistics to the entire population, because diabetes is comparatively rare in the early part of life, but increases in frequency as age advances, and Barringer's data relate to adults. The incidence of

[1] Carrasco Formiguera: Joslin—Tratamienta de la Diabetes Sacarina, Montaner y Simon, Barcelona, 1925.

[2] Barringer: Arch. Int. Med., 1909, **3**, 295.

[3] Actually 71,729.

[4] 1.895 per cent.

diabetes might be far below 2 per cent in the early decades of life and then increase far above it from the sixth decade onward. John[1] found that of 55,939 cases seen in the Cleveland clinic 1.8 per cent were diabetics. Presumably the percentage among well persons would be lower. Today our information rests upon hypothetical grounds, but within a few years far more satisfactory information will be available. In 1923 I estimated the number of individuals in the country who either had diabetes or would develop it at about 1,000,000, but on account of the increasing duration of life of the diabetic today and the increasing longevity of the population as a whole I believe the number to be more nearly 1,400,000.

Through the courtesy of Major W. B. Borden of the Surgeon-General's Office, I am enabled to give the records for diabetes in the Army during the World War (Table No. 43).

In explanation of this table, attention is called to the fact that "admissions" should be interpreted to mean cases admitted to such report with a primary diagnosis of diabetes mellitus, and does not include any cases which may have been discovered as an associate or as complications of the primary disease.

"Deaths" should be interpreted to mean the deaths occurring among those cases primarily admitted for diabetes mellitus, regardless of whether or not they may have had any associate disease or complication which could have been a contributing cause or actual cause of deaths, that is, all deaths were charged against the primary admission."

The army percentage mortality of 3.0 per 100,000 is less than one-half that for civilian life for the age group twenty to forty-four years. (See Table 25.) This low army rate may be attributed to: (1) The initial exclusion from the army of recruits with diabetes by routine examination on enlistment. Omission of routine urinary examinations in certain training camps under the stress of preparation in time of war probably accounts for the fact that even as many as 718 cases were found in soldiers. (2) The freedom from overfeeding and sedentary living.

Dublin[2] calls attention to the preponderance of diabetes among females rather than males, in whites rather than in colored, and the definite racial evidence in Jews and Irish, and points out that other diseases have similar characteristics: namely, exophthalmic goiter and Addison's disease, which like diabetes are disorders of endocrine function. In certain southern communities, according to Dublin, in which the number of negroes is large, the rates are higher for colored than for whites (!), according to the figures for insurance in the Metropolitan Life Insurance Company.[3]

[1] John: Arch. Int. Med., 1927, **39**, 67.
[2] Dublin: Personal communication.
[3] Emerson and Larimore: Loc. cit. p. 46.

TABLE 43.—DIABETES MELLITUS. ADMISSIONS, DEATHS, DISCHARGES FOR DISABILITY, AND DAYS LOST FOR THE PERIOD OF THE WAR. APRIL 1, 1917, TO DECEMBER 31, 1919, INCLUSIVE.

Disease.	Admissions.				Deaths.				Discharges for disability.					Days lost.				
	Total Army officers and enlisted men, including native troops.	Total officers.	Total enlisted men, including native troops.	Total American troops.	Total native troops.	Total Army officers and enlisted men, including native troops.	Total officers.	Total enlisted men, including native troops.	Total American troops.	Total native troops.	Total Army officers and enlisted men, including native troops.	Total officers.	Total enlisted men, including native troops.	Total American troops.	Total native troops.	Total Army officers and enlisted men, including native troops.	Total officers.	Total enlisted men, including native troops.	Total American troops.	Total native troops.
Absolute numbers .	718	83	635	632	3	104	6	98	97	1	330	14	316	315	1	39,062	5453	33,609	33,520	89
Ratios per 1000 .	0.17	0.40	0.16	0.16	0.08	0.03	0.03	0.02	0.02	0.03	0.08	0.07	0.08	0.08	0.03	0.03	0.07	0.02	0.02	0.01

Lemann[1] compares statistics from the Charity Hospital in New Orleans for white and colored admissions for three periods, 1898 to 1909, 1909 to 1919, 1921 to 1926. These are given in Table 44. Whereas among the white patients the percentage per 1000 admissions has risen from 0.73 per cent to 2.3 per cent, or three times, the percentage among the colored admissions has risen from 0.47 per cent to 3.4 per cent, or more than seven times.

TABLE 44.—INCREASE OF INCIDENCE OF DIABETES, CHARITY HOSPITAL, NEW ORLEANS.

	Admissions.			Diabetes.			Diabetes per 1000 admissions.		
	Total.	White.	Colored.	Total.	White.	Colored.	Total.	White.	Colored.
1898 to 1909 .	101,565	61,298	40,265	64	45	19	0.63	0.73	0.47
1909 to 1919 .	160,044	92,040	69,004	194	135	59	1.20	1.40	0.86
1921 to 1926 .	148,671	91,948	66,673	439	211	228	3.00	2.30	3.40

Diabetes in the negro in the United States is less prevalent statistically than among the whites. According to the Metropolitan Life Insurance statistics it is no more frequent now than fifteen years ago among negro males, but among negro females it has increased many times as rapidly as among white females, great as has been the advancing incidence of diabetes among the latter. The greater attention paid to the investigation of the health of the negro undoubtedly explains much of this apparent change in mortality.

Urban versus Rural Incidence of Diabetes.—The rate for the registration area in the United States since 1906 has been greater in urban than rural communities. This is as one would expect. In the city opportunities for the diagnosis would seem to be better, physical exertion likewise would appear to be less and as a result obesity more frequent. Such considerations, however, do not hold for Massachusetts where the rural cases have exceeded the urban between 1900 and 1925 save for the years 1912, 1922, and 1923. This difference between the two types of localities, however, is slight. This is likewise true for density of population. For details see Hamblen and Joslin.[2]

2. **The Explanation of the Statistical Increase in Diabetes.**—(*a*) **Greater Accuracy of Vital Statistics.**—The increased accuracy of vital statistics in recent years undoubtedly explains to a great extent the apparent increase in diabetes. Particularly is this borne

[1] Lemann: Jour. Am. Med. Assn., 1927, **89**, 659.
[2] Hamblen and Joslin: Jour. Am. Med. Assn., 1927, **88**, 243.

out by the disproportionate advance encountered in women and especially in negro women. The World War introduced an entirely new factor, and the results of this gigantic etiological and therapeutic experiment in diabetes are of great significance. Time enough has elapsed to furnish the control after-period, and with an abundance of food the incidence of diabetes is rising to that of prewar days in those countries where the restriction of the food supply was greatest. The onset of diabetes in children attracts attention, because, untreated, the disease makes quick progress. The symptoms of diabetes in women begin more gradually, regrettably are tolerated because of modesty, and are frequently confused with cystitis or attributed to the results of parturition. Consequently diabetes is not becoming more frequent in children, but, with better medical supervision, appears to be more frequent in women. However, with the women there is another factor, see p. 141.

(*b*) **More Frequent Urinary Examinations.**—The chief cause for the improvement in the vital statistics upon diabetes lies in the increased frequency of routine urinary examinations. Urinary examinations are comparatively recent. This is shown by the records of a case of diabetes at the Massachusetts General Hospital for the year 1866, where the words "urine tasted sweet" may be seen in the handwriting of a house pupil, later a professor in the Harvard Medical School, and in 1927 still alert.

TABLE 45.—AVERAGE AGE AT DEATH FROM ALL CAUSES IN THE UNITED STATES.

Year.	Age, yrs.	Year.	Age, yrs.
1860	22.7	1900	35.2
1870	25.2	1910	38.7
1880	26.9	1915	42.2
1890	31.1	1920	41.9

(*c*) **General Increase in Duration of Life.**—The general increase in the duration of life throughout the world is an important cause for the apparent as well as the real increase in the frequency of diabetes. This is of more significance in studying the incidence of diabetes than it would be with the infectious diseases. The infectious diseases are common to the early years of life, and consequently prolongation of life would affect their incidence comparatively little; but with diabetes quite the opposite is the case. The general mass of the population is marching toward the age of the greatest incidence of diabetes. This is very well shown in Table 45, which presents the approximate age at death from all causes in the registration area of the United States in 1860 and for following decades. This average has risen to forty-two years. But a better figure to consider is the present average expectation of life, which is a very different matter from the average age at death. This expectation

of life in the United States is now estimated to be fifty-five years. In 1885 the average expectancy of life for a new-born baby in Massachusetts was 42.7 years; in 1924 it was 58.5 years.

The expectation of life at birth in various countries is given in Table 46.

TABLE 46.—EXPECTATION OF LIFE AT BIRTH IN VARIOUS COUNTRIES.

Country.	Year.	Males.	Females.
New Zealand	1906–1910	59.2	61.8
Australia	1901–1910	55.2	58.8
Denmark	1906–1910	54.9	57.9
Norway	1901–1910	54.8	57.7
Sweden	1901–1910	54.5	57.0
Holand	1900–1909	51.0	53.4
United States	1901–1910	49.3	52.5
United States	1924	56.7	59.6
Switzerland	1901–1910	49.3	52.2
England	1901–1910	48.5	52.4
France	1898–1903	45.7	49.1
Germany	1901–1910	44.8	48.3
Italy	1901–1910	44.2	44.8
Japan	1898–1903	44.0	44.9
India	1901–1910	22.6	23.3

The figures for 1924 in the United States may explain in part our proportionately higher diabetic death-rate, but as the table is incomplete for other countries this may not hold when they are known. At any rate, until the average age at death in the country is fifty years there will be reason to expect a climbing incidence for diabetes. That it has reached more nearly this limit for certain classes of society, the well-to-do, may account in considerable measure for their greater diabetic morbidity.

For clinical convenience I am inserting the tables of the American-Canadian Mortality Investigation from 1900–1915 which show the complete expectation of life for American men. It is interesting to compare this with the American table which I published in the second edition of this book because in that table the expectation was not given beyond the age ninety-five years.

(*d*) **Life Insurance Statistics.**—The increased frequency of urinary examinations is due to some extent to the increasing percentage of the population which is insured. In Table 48, the growth of the per cent of population to policies in force in the United States for successive periods is indicated. Further proof of the important part which insurance examinations occupy in the discovery of diabetes is shown by an analysis of my own diabetic statistics. Whereas between the years 1893 and 1916, 6 per cent of patients coming to me for treatment of diabetes reported the disease had been discovered by routine life insurance examinations, by 1923 the percentage had risen to 13. Indeed, the percentage in males, which

TABLE 47.—EXPECTATION OF LIFE. AMERICAN-CANADIAN MORTALITY INVESTIGATION, 1900–1915.

American Men.

Age.	Expectation.	Age.	Expectation.	Age.	Expectation.
15	50.06	45	25.22	75	6.69
16	49.23	46	24.41	76	6.32
17	48.40	47	23.62	77	5.96
18	47.58	48	22.83	78	5.62
19	46.75	49	22.06	79	5.30
20	45.93	50	21.29	80	4.99
21	45.11	51	20.53	81	4.69
22	44.29	52	19.79	82	4.41
23	43.47	53	19.05	83	4.14
24	42.65	54	18.33	84	3.89
25	41.83	55	17.62	85	3.65
26	41.01	56	16.93	86	3.42
27	40.18	57	16.25	87	3.21
28	39.36	58	15.58	88	3.00
29	38.53	59	14.93	89	2.81
30	37.70	60	14.29	90	2.63
31	36.87	61	13.67	91	2.46
32	36.03	62	13.06	92	2.30
33	35.19	63	12.47	93	2.15
34	34.35	64	11.90	94	2.01
35	33.51	65	11.34	95	1.87
36	32.67	66	10.80	96	1.74
37	31.83	67	10.28	97	1.61
38	30.99	68	9.77	98	1.50
39	30.15	69	9.28	99	1.34
40	29.32	70	8.81	100	1.19
41	28.49	71	8.35	101	1.07
42	27.66	72	7.91	102	0.83
43	26.84	73	7.49	103	0.50
44	26.03	74	7.08		

FIG. 48.—LIFE INSURANCE POLICIES IN FORCE IN THE UNITED STATES. RISING PERCENTAGE ACCORDING TO POPULATION.

Year.	Number of policies.	Population.	Per cent of population to policies in force.
1880	608,681	50,155,783	1
1890	1,276,167	62,947,714	2
1900	3,071,253	75,994,575	4
1910	6,040,617	91,972,266	7
1920	13,199,605	105,710,620	12
1925	18,589,631	113,000,000[1]	17

was formerly 9 per cent, had changed by the latter date to 21 per cent. In subsequent years the ratio has decreased. If one computes the actual number of true diabetics in each 1000 coming with supposed diabetes and relates these figures to diagnosis through examinations for life insurance, the percentages are somewhat similar as is shown in Table 49.

[1] Estimated.

TABLE 49.—FREQUENCY OF DISCOVERY BY INSURANCE OF DIABETES IN MALES WITH SUBDIVISION ACCORDING TO ULTIMATE CLASSIFICATION.

Period.	No. of males in each 1000 patients with glycosuria.	Discovered by Life Insurance.				
		True diabetes.	Renal glyco-suria.	Potential diabetes.	Unclass-ified.	Total
1898–1916	594	37	0	3	13	53
1916–1920	578	41	1	0	13	55
1920–1923	524	74	2	8	25	119
1923–1924	494	51	0	10	19	80
1924–1926	483	48	3	8	22	81
1926–1927	446	26	1	5	11	43

In a study of 1000 cases John[1] found that 3.9 per cent had been discovered by insurance examinations.

(*e*) **Frequency by Decades at Which Onset Occurs Now and Formerly.**—The increase in the incidence of diabetic mortality has already been shown to be quite uniform for the different decades until the beginning of treatment with insulin. Up to von Noorden's time the distribution of frequency of diabetes in the experience of men especially concerned in its treatment was approximately the same for different age groups and is shown in Table 50. These early writers lived in a period when urinary examinations were really not a part of the general routine of medical examinations. Von Noorden's statistics represent a later era and it is noticeable that he had at least 50 per cent more cases in the first decade of life than earlier writers. My own statistics, being still more recent, make this still clearer, because the percentage has risen from von Noorden's[2] 1.43 per cent to the writer's 4.6 per cent. The latter figure is based upon 5086 true cases of diabetes of all ages. For 2800 "supposed" diabetics seen prior to July, 1922, it was 5.7 per cent, and for the 2440 true diabetics in that number it was also 5.7 per cent. The incidence of diabetes in the first decade of life in my series is therefore decreasing. Among the 3078 fatal cases of diabetes in Prussia in 1923, 8.2 per cent occurred in the first two decades in contrast to my 11.7 per cent for the onset of diabetes. Of 608 cases of diabetes reported by Iwai[3] in Japan not a single case was encountered in the first decade of life. John[4] reports only 1.8 per cent of 1000 cases as beginning in the first decade. Adams[5] figures approximate mine, however. Just why Adams of the Mayo Clinic gets 4.3 per cent of his diabetic patients in the first decade and John of the Cleveland Clinic gets only 1.8 per cent is hard to explain.

[1] John: Arch. Int. Med., 1927, **39**, 67.
[2] Von Noorden and Isaac: Die Zuckerkrankheit, Berlin, 1927, 8th edition, 77.
[3] Iwai: Loc. cit. p. 117.
[4] John: Arch. Int. Med., 1927, **39**, 67.
[5] Adams: Arch. Int. Med., 1926, **37**, 861.

This increase in the percentage of cases in the first decade as compared with a generation ago speaks emphatically in favor of the better diagnostic methods of today rather than of actual increase in the frequency of the disease. This statement is confirmed by a study of diabetes for different age groups in the United States shown in Table 25.

TABLE 50.—FREQUENCY OF ONSET OF DIABETES BY DECADES. PER CENT OF TOTAL CASES FOUND IN EACH DECADE.

Decade.	1.	2.	3.	4.	5.	6.	7.	8.
Frerichs[1]	1.0	7.0	10.0	18.0	25.0	26.0	11.0	1.0
Seegen[2]	0.5	3.0	16.0	16.0	24.0	30.0	10.0	0.5
Grube[3]	...	1.7	2.8	11.2	23.1	39.5	18.1	3.4
Schmitz[4]	0.8	4.1	9.3	17.3	22.3	32.6	10.0	3.3
Pavy[5]	0.5	4.1	7.1	16.4	24.9	30.7	13.4	2.6
Külz[6]	1.0	3.0	4.6	17.2	36.0	26.8	9.2	0.1
Von Noorden[7]:								
Mild	...	0.4	2.4	10.0	21.0	17.7	4.0	0.4
Severe and moderately severe	1.4	2.4	6.0	9.6	12.6	11.0	2.1	
Murayama, Yamaguchi[8]	0.2	0.9	5.8	18.6	33.6	28.6	9.3	1.2
Adams[9]	4.3	6.1	9.5	12.3	19.7	27.4	18.2	2.4
John[10]	1.8	2.7	4.6	11.2	22.4	26.9	29.0	..
Joslin[11]	4.6	7.0	8.8	13.0	24.9	26.3	12.8	2.6

"The diabetic mortality reaches two distinct elevations, a peak at the age of fifteen years (a relative increase) and a plateau between the ages of sixty and seventy years (an actual increase)."[12] In the interpretation of this *mortality-rate* it must be remembered that the *age of onset* is distinctly earlier and so these figures correspond fairly closely with twelve years as the peak of onset in the present series and fifty-one years as the peak of onset in our series for adults. The diabetic mortality curve follows very closely the rise as shown by age at onset, beginning at about forty-five years.

It is interesting to note that Rabinowitch[13] found the patients

[1] Frerichs: Ueber den Diabetes, Berlin, 1884.
[2] Seegen: Der Diabetes Melitus, Berlin, 1870, 1st ed.; 1893, 3d ed.
[3] Grube: Diätetische Behandlung der Zuckerkrankheit, Bonn, 1898.
[4] Schmitz: Berlin klin. Wchnschr., 1873, **18**, 18; *also* Berlin, 1891, p. 373.
[5] Pavy: On Diabetes, London, 1869; Differentiation in Diabetes, L ondon,1900.
[6] Kulz: Klinische Erfahrungen über Diabetes Melitus, Herausg. von Rumpf, Jena, 1899.
[7] Von Noorden: Die Zuckerkrankheit, Berlin, 1927, 8th ed., p. 77.
[8] Murayama, Yamaguchi: Personal communication. Age unknown, 1.7 per cent.
[9] Adams: Arch. Int. Med., 1926, **37**, 861—0.1 per cent in ninth decade.
[10] John: Arch. Int. Med., 1927, **39**, 67—compiled from chart; age unknown 1.4.
[11] Joslin: Compiled to April, 1927, 5086 cases of True Diabetes (No. 1 to 6000).
[12] Thomson: Boston Med. and Surg. Jour., 1925, **192**, 532.
[13] Rabinowitch: Canadian Med. Assn. Jour., 1927, **17**, 1415.

at the age of fifty-two years were more numerous than those of any other age who visited the Montreal General Hospital Diabetic Clinic between 1921 and 1927.

(*f*) **The Importance of Recognition of the Extent of Diabetes in the Community and Its Influence upon Treatment.**—The recognition of the large number of diabetic individuals living in the United States is important. It determines the character of the treatment. The number of cases is so great that it at once becomes evident that their care must rest in the hands of the general practitioner. It is ridiculous to expect that the treatment of diabetics should be under the supervision of a specialist; neither can they all undergo hospital treatment. It is plain that a program of education not only for the diabetic patients themselves but the population as a whole must be instituted along similar lines to that which has been adopted in the treatment of tuberculosis. But first of all this program must begin with the doctor. The campaign against tuberculosis has given the community fresh air. A campaign for the prevention and treatment of diabetes should give the community a knowledge of diet, of the danger of obesity, and of the importance of physical exercise. The gain to the community from the dissemination of such knowledge will almost offset the harm caused by diabetes. In this campaign I would especially emphasize the importance of the education of the general practitioner in diabetes. To treat the 1,000,000 or more diabetic patients in the United States there were in 1925, 147,010 physicians. Formerly a physician would rarely see over 5 to 10 diabetics a year, but with the increased frequency of the disease in the future he is destined to see still more. Between 1898 and 1914, my own Naunyn Epoch, the average duration of life of my 331 fatal cases was 4.8 years; between August, 1922, and July, 1926, for 600 fatal cases it was 7.7 years or an increase of 2.9 years. Consider what this change in duration means when applied to the 1,000,000 diabetic patients in the United States. It creates an addition of nearly 3 million years of the disease diabetes which the general practitioner must treat. Furthermore, these additional years of illness for each patient with diabetes require far more treatment, and more resourceful treatment, than the earlier years. The type of diabetes one sees today is very different from what it was before the World War. This increase in the duration of life of diabetics is based upon my own experience, but I believe a similar relative change in duration of the disease will hold for the entire country. How much greater the increase in duration of life is destined to be through insulin no one can predict.

3. **Sex Incidence.**—More men than women are treated for diabetes according to the authors, but more women than men die of the disease according to mortality statistics. The first part of the

above statement has already been reversed by my own data. Prior to August, 1922, 55 per cent of my patients were males, but since August, 1922, the females are in the majority, 55.2 per cent.

In illustration of the above the following table from von Noorden[1] is cited, to which are added my own statistics, and also a table showing the deaths from diabetes according to sex in the registration area of the United States during the years 1913–1923 inclusive. (See Table 51.)

TABLE 51.—SEX IN DIABETES.

Sex in diabetes.			Diabetic deaths in registration area of United States.		
Name.	No. of cases.	Males, per cent.	Year.	No. of cases.	Males, per cent.
Grube	177	77	1913	9,660	47
Külz	692	76	1914	10,666	46
Griesinger	225	76	1915	11,775	45
Seegen	938	75	1920	14,062	45
Von Noorden	1960	73	1921	14,933	45
Frerichs	400	70	1922	17,182	44
Williamson	100	62	1923	17,357	44
Schmitz	2109	57			
Adams	1000	58			
Carrasco	350	54			
John	2000[2]	53			
Joslin (1898–1922)	2440	55			
Joslin (1922–1927)	2646	45			

The statistics for Prussia and England also exhibit the preponderance of the male sex and agree with the figures for morbidity of the authors cited in Table 51. They are approaching, however, the United States figures for mortality which now register a lesser percentage of deaths among males.

TABLE 52.—THE PERCENTAGE OF DIABETIC DEATHS IN MALES IN THE TOTAL DIABETIC MORTALITY, ENGLAND, PRUSSIA, AND THE UNITED STATES.

Years.	England, per cent.	Prussia, per cent.	United States,[3] per cent.
1861–1870	65		
1871–1880	63		
1881–1890	59	62	
1891–1900	55	61	
1901–1910	51	58	48
1911–1920	49	57	46

The apparent clinical preponderance of diabetes in men in the past may be ascribed: (1) To the greater consideration which they received; (2) to the large percentage discovered by life insurance examinations, amounting to 22 per cent of my male cases; (3) to the

[1] Von Noorden and Isaacs: Loc. cit., p. 76.
[2] Personal Communication, November, 1927.
[3] Not available until 1900.

hesitancy of women to speak about their urinary troubles and their neglect to regard them seriously; (4) to the type of practice of those who have reported large series of cases. It is suggestive that in Japan 80 per cent of the cases of diabetes reported by Iwai[1] and 85 per cent of 900 cases treated at the Kyonndo Hospital of Tokyo between 1915 and 1922 (Muryama and Yamaguchi) were males, and that 70 per cent of the German cases reported are males, save in the series of Schmitz, but only 55 per cent, according to my earlier series, and 45.3 per cent in my recent series.

Morrison's[2] figures for the city of Boston between the years 1895–1913, like the national statistics, show 45 per cent of 1775 deaths from diabetes to have been males.

The fact that more men than women receive special medical treatment for diabetes while more women than men die of the disease, is evidence in favor of the usefulness of our present therapeutic procedures.

Bouchardat, Lecorche and Pavy all noted the sharp increase in diabetes just before the menopause.[3]

John's[4] figures approximate mine in that he found 534 females in a group of 1000 patients. The males predominated in the first two decades, equalled the females in the fourth, but were less in the third, fifth, sixth, and seventh. Carrasco Formiguera[5] found that in a series of 350 cases, 189, or 54 per cent, were women. Adams of the Mayo Clinic, however, reports 58 per cent of 1000 patients to be males.

4. **Heredity Incidence.**—The influence of heredity in diabetes has always interested me, and I have taken great pains to secure data from my patients upon this point. Naunyn said that the more carefully he inquired into the family history, the more commonly he found heredity to be present, and I am quite sure that this rule holds. It is easy to exaggerate the importance of heredity, for diabetic patients naturally would be more liable to know of the presence of diabetes in the members of their families than would patients who did not have diabetes. This introduces a considerable error into the statistics of the heredity of diabetes. Among 100 non-diabetic patients, Heiburg found 7 who had relatives with the disease, and upon inquiry from 100 diabetic patients he learned that 18 had relatives similarly affected. Among 500 consecutive histories of my own non-diabetic patients, 25 had relatives with the disease. Having seen the increase in diabetes in the community to

[1] Iwai: Loc. cit., p. 177.
[2] Morrison: Boston Med. and Surg. Jour., 1916, **175**, 54.
[3] Von Noorden and Isaac: Loc. cit., p. 311.
[4] John: Arch. Int. Med., 1927, **39**, 67.
[5] Carrasco Formiguera: Footnote: Joslin: Tratamiento de la Diabetes Sacarina, Montaner y Simon, Barcelona, 1925, p. 116.

be, at least in great part, apparent rather than real, I hesitate to attach too much importance to heredity. Undoubtedly, heredity will appear more prominently in the case reports of diabetes as time goes on, but this may reflect only the greater accuracy in vital statistics. Hansen[1] believes heredity to be much greater than has been thought to be the case. He proposes the query, how often is a case of diabetes not hereditary in character? and suggests the examination of case histories from this point of view.

Evidence was not forthcoming that diabetes was transmitted as a Mendelian characteristic according to Buchanan.[2] He studied 34 families resulting from the marriage of one diabetic and one non-diabetic through the second and third generations.

Meulengracht considers the disease is dependent on a single dominant factor in contrast to Hansen who believes it caused by several factors with a similar effect. "The normal development of the pancreas is determined by several factors acting in a similar way. The severe cases of diabetes occur when many factors are lacking, the mild cases when a few are lacking."[3]

Statistics upon heredity in diabetes are susceptible to criticism because of what is included under the term "hereditary." Often by this term familial as well as hereditary cases are included. So far as my own statistics are concerned "heredity" signifies the presence of the disease in a parent, and occasionally information about a grandparent was obtained, as well as uncle, aunt or child. The term "familial," on the other hand, embraces brothers, sisters, and cousins and it is quite evident from the litérature that brothers, sisters and cousins are usually included in compiling statistics on heredity. Conjugal diabetes, of course, does not belong to either group. In securing statistics upon heredity, a record should always be made upon the history blank as to whether the information appears reliable, and is suitable for tabulation.

In compiling statistics upon heredity one is apt to forget the large number of ancestors any one of whom may stamp the patient as an hereditary case. Parents and grandparents, uncles and aunts, and children usually represent 20 souls, and it is almost to be expected that in 10 such groups at least 2 persons would have the disease, and this is about the diabetic morbidity.

In 6 cases at least of my first 1421 cases, Cases Nos. 105, 473, 503, 954, 1285 and 1421, the diabetes developed in the child or children before it occurred in the parent. This is not surprising, because it is the tendency which is transmitted and it would be immaterial whether the disease had broken out in the parent.

[1] Hansen: Acta. Med. Scand., 1925, **62**, 85.
[2] Buchanan: Am. Jour. Med. Sci., 1923, **155**, 675.
[3] Loc. cit by Holst: Arch. Int. Med., 1926, **38**, 279.

(*a*) **Author's Data.**—A history of diabetes in grandparent, parent, uncle, aunt, or child was obtained in 417 cases of my series of 2800 cases, or 15 per cent. Of this number, 211 were males and 206 females. On the other hand, the group of cases showing a

FIG. 53.—HEREDITY IN DIABETES.

Author	Date of compilation.	No. of cases.		Heredity, total per cent.
Frerichs	..	400		9.8
Seegen	..	..		14.0
Schmitz	..	..		20.0
Külz	..	692		21.6
Williamson	..	500		22.0
Bouchard	..	..		25.0
Naunyn	1906	398		17.0
Von Noorden	1917		Hereditary 18.5 Familial 6.9	25.4
Montoro[1]	1924	400	Hereditary 15.0 Familial 3.0	18.0
Seckel[2]	1925	391	Hereditary 17.4 Familial 9.0	26.4
John[3]	1927	1000	Hereditary 4.6 Familial 5.1	9.7
Joslin	1923	2800	Hereditary 15.0 Familial 7.0	21.0
Joslin	1927	2646	Hereditary 17.0 Familial 11.9	25.5

familial tendency included 189 cases, or 7 per cent of my series. Of this group 96 were males, and 93 females. If we combine the two groups, we have 606 cases showing an hereditary or familial tendency, or 21 per cent of all the cases. In this early group of

TABLE 54.—HEREDITY IN TRUE DIABETES, RENAL GLYCOSURIA, POTENTIAL DIABETES, AND UNCLASSIFIED GLYCOSURIA. CASES NOS. 2800 to 6000.

Condition.	Total cases.	Hereditary.		Familial.		Total heredity.	
		No.	%.	No.	%.	No.[4]	%.
True diabetes	2646	450	17	316	12	674	26
Renal glycosuria	31	6	19	7	23	12	40
Potential diabetes	141	31	22	22	16	46	33
Unclassified glycosuria	381	72	19	46	12	103	27

2800 cases were included 360 cases which were not true diabetics. In the more recent group of 2646 true diabetics occurring in the next 3200 cases seen for supposed diabetes the hereditary tendency was 17 per cent, the familial 12 per cent, and the combined per cent,

[1] Montoro: Diabetes Y Su Tratamiento Actual, Habana, 1924, p. 20.
[2] Seckel: Zeitsch. Klin. Med., 1925, **102**, 195.
[3] John: Arch. Int. Med., 1927, **39**, 67.
[4] Duplicates excluded.

excluding duplicates, 26 per cent. Among the 553 cases of renal glycosurics, potential diabetics, and unclassified glycosurics, the hereditary tendency was present in 19 per cent and the familial in 14 per cent. I suspect these high percentages indicate that these individuals knowing diabetes was in their family followed up a demonstrated glycosuria with unusual care. Older writers record data which are similar. Hoogslag[1] reports that in 43 per cent of 207 cases diabetes was known in the family. John's[2] figures are somewhat lower; in his cases he found 4.6 per cent with an hereditary tendency and 5.1 per cent with familial.

(*b*) **Notable Diabetic Families Showing Heredity.**—The most interesting diabetic family history that I have encountered was furnished by a nurse, who stated that her mother and her mother's 11 brothers and sisters all died of diabetes save 1, who, like the rest, has the disease but is still alive. Two of her aunts each had a child with diabetes. To my repeated inquiries about the accuracy of the information, she writes: "I am positive that diabetes was proven by examination of the urine in the case of 5 of the first generation; the others are on record as having died of diabetes. All the patients were stout." (See Table 55.)

The family showing the most marked diabetic heredity with which I have personally come in contact was that of a Jewish patient, Case No. 759, who developed diabetes at the age of fifty-five years.

A brother died of diabetes and tuberculosis at sixty-eight years; a sister of diabetic coma at fifty-five years; a sister of acute indigestion at fifty-eight years, having had diabetes for many years; a sister of Bright's disease at fifty-six years, having had diabetes for ten years; a sister, who is living, has had acute indigestion and also has diabetes; finally a brother died of influenza at sixty-two years, having had diabetes eight years. The father succumbed to paralysis at sixty-two years, and the mother to heart disease at sixty-five years. A niece, Case No. 436, also has had diabetes since 20.3 years of age in 1909, when a noted German clinician found 8 per cent sugar and naturally gave a very unfavorable prognosis. Despite the prognosis, she married. She has been under my observation for sixteen years. She became pregnant in 1915, and the carbohydrate balance, which amounted to 15 grams for a year or more before pregnancy began, rose to about 65 grams. She had a normal delivery in April, 1916, nursed her baby for several months, and both mother and child are in excellent condition and were kind enough to go on to a Clinic at the Academy of Medicine in New York in May, 1923. The tolerance for carbohydrate fell after

[1] Hoogslag: Cit. Jour. Am. Med. Assn., 1922, **2**, 1934.
[2] John: Arch. Int. Med., 1927, **39**, 67.

delivery and again when nursing was given up. No sudden change in tolerance, however, was observed.

This patient has seldom dieted rigidly, but she has maintained her vigor and would not be suspected of having diabetes although now in 1927 she is thirty-eight years old and the diabetes is of eighteen years' duration. Her present height is 62.5 inches without heels and her weight is 133.5 pounds without clothes. On June 3, 1927 the urine before insulin in the fasting state contained 0.3 per cent sugar, 0 diacetic acid, extremely slight trace albumin, 0 casts. The blood sugar was 0.27 per cent, the non-protein nitrogen 40 mgs. per 100 cc. blood, and the cholesterol 175 mg. per 100 cc. The insulin was 5-0-7 units. Upon physical examination there was slight if any arteriosclerosis, but the Roentgen-ray examination showed it to be beginning in the vessels of the legs and quite marked in the popliteal arteries. The heart is of normal size.

TABLE 55.—A FAMILY WITH A DOZEN FAT DIABETIC BROTHERS AND SISTERS.

Preceding generation.	Date of birth.	Date of death.	Duration of life, years.	Cause of death.
Andrew	Oct. 18, 1803	1853	50	Lockjaw
Hannah his wife .	Aug. 9, 1805	1848	43	Childbirth
First generation:				
Emily	Feb., 1827	1881	54	Diabetes
Daniel	Aug., 1828	1843	15	"
Hannah	Mar., 1830	1905	75	"
George	Aug., 1831	1890	59	"
Elizabeth . . .	Jan., 1833	1883	50	"
Andrew	May, 1834	1874	40	"
Jane	Feb., 1836	1896	60	"
Addie	Dec., 1837	1904	67	"
Rachel	Oct., 1841	1873	32	"
William	Dec., 1843	1895	52	"
John	July, 1845	1878	33	"
Catherine . . .	Mar., 1848	Living	52 to date, December, 1915.	
Second generation:				
Jennie, daughter of Elizabeth			18	
Jane, daughter of Emily			42	

Landis[1] has reported a diabetic family in which the disease was transmitted to the 5 blonde but not to the 4 brunette children of a diabetic mother.

Eight relatives of Case No. 4565 died of diabetes: to wit, maternal great grandfather, maternal grandfather, maternal grandmother, maternal aunt, mother, one cousin, two second cousins.

(*c*) **The Favorable Influence of Heredity.**—The influence of heredity upon the disease is not uniform. It may be serious, or it may be favorable. Naunyn has pointed out that the onset of the disease in successive generations is apt to take place at a suc-

[1] Landis: Trans. Assn. Am. Phys., 1921, **36**, 293.

cessively earlier age, and consequently the diabetes is more apt to be severe. Von Noorden has emphasized the importance of the character of the diabetes in the progenitor as indicative of the character of the disease in the offspring. My cases of hereditary diabetes have usually been mild, so that I always look upon heredity as a favorable omen. I have seen no reason to change this opinion notwithstanding the comment of von Noorden and Isaac[1] upon it. I suspect that their cases may date back to an earlier period. Several cases in young people have been unusually favorable.

All cases which have come to my attention of youthful patients with diabetes living for very long periods of time have been hereditary. The case of Schmitz quoted by Naunyn[2] was hereditary, and deserves regard because of its encouraging features. This was a four-year-old child, whose mother and older sister were diabetics. The urine was frequently examined for sugar, and always found sugar-free, the last examination being November 22, 1871. November 26, 1871, a febrile attack, and evening urine of November 27, contained 5.8 per cent of sugar. Patient put upon a strict diet. December 3, 3.5 per cent; December 8, 2 per cent, and on December 13, was sugar-free. The strict diet was continued for some time, and then gradually some bread and milk were allowed. Sugar was constantly absent from the urine, and the child felt well. The diet was made more liberal from year to year, and finally included the diet which most children much enjoy, fruit, chocolate, and puddings. Everything went well, and at eighteen the strong, well-developed girl was married, and in 1892, presented the appearance of blooming health, and was the mother of two healthy children, sugar having never reappeared.

Naunyn's own famous cases Nos. 124, 173 and 32 were all hereditary cases and he refers on pages 96 and 97 of his book to other cases of long duration in which I find that heredity was manifest.

Teschemacher[3] has reported several cases of apparently cured diabetes. The most remarkable feature is the simultaneous occurrence of diabetes in all four members of a family, father, mother, and two young children. It is doubtless a coincidence rather than an evidence of the infectiousness of diabetes. The father slowly became worse; the mother and both children apparently recovered completely; at any rate they remained sugar-free on a mixed diet for two years.

Riesman[4] has emphasized the mild character of some cases of diabetes in children. Of the 4 cases which he reports one again

[1] Von Noorden and Isaac: Loc. cit., p. 79.
[2] Naunyn: Loc. cit., p. 102, see p. 384.
[3] Teschemacher: Deutsch. med. Wchnschr., 1910, **36**, 401.
[4] Riesman: Am. Jour. Med. Sci., 1916, **161**, 40.

finds the presence of a familial or hereditary history in 3. Cases I and II were brother and sister; Case III showed neither familial nor diabetic heredity, but the mother of Case IV had had diabetes for nine years.

Wagner[1] states that if there are several children in a family and a younger develops diabetes, the older one will not do so. I have not investigated this point, but the older brother of Case No. 2615 developed diabetes in 1905 at the age of ten years, the patient in 1922 at twenty-four and eight-tenths years, and a younger sister in 1926 at sixteen years.

See p. 821 for further data on the favorable effect of heredity on the duration of diabetes in children.

The duration of life of the fatal cases of my earlier series of hereditary diabetes is shown in Table 56 and in Table 58 are collected the data of those with a familial history.

The average duration of life of 96 fatal cases of hereditary diabetes seen between 1894 and September, 1922, was 6.4 years, in contrast to the average duration of life of all fatal cases at that time, which was 5.6 years. The average duration of life of 94 fatal cases of familial diabetes seen between 1894 and September, 1922, was 5.5 years, in contrast to the average duration of life of all fatal cases at that time, which was 5.6 years. For 33 fatal cases of hereditary diabetes between September 1, 1922, and July 1, 1926, the average duration was 7.5 years and for 35 fatal cases of familial diabetes for the same period the average duration was 8.1 years.

The interrelationship of the various endocrine glands leads von Noorden and Isaac[2] to point out the desirability of seeking information from diabetic patients not only of a diabetic heredity, but also of the incidence in progenitors of disturbances of the pineal gland, pituitary, thyroid, adrenal, thymus, spleen, and genitalia.

5. **Conjugal Incidence.**—Twenty-four instances (27 cases) of conjugal diabetes occurred in my first 3000 cases. Oppler and C. Külz found 10 such instances in 900 cases of E. Külz; Senator, among 770 cases, found 9 diabetic couples. Naunyn observed 8 instances in 775 cases. All agree that similarity of living rather than contagion accounts for this condition, and I subscribe to this opinion. It is exposure to good food rather than to one another.

Twenty-seven of the 48 individuals concerned were seen by me, and only 1 of these was thin; information is lacking about the weights of 15, 7 of the patients weighed 165 to 190 pounds, and 14 from 190 pounds to 251 pounds. (These facts, together with the duration of the disease, are recorded in Table 60.) Thirty-eight other conjugal cases appear in the records as far as Case No. 5095. The

[1] Wagner: Wien. klin. Wchnschr., 1927, Jahrgang **40**, Heft 41, Sonderbeilage.
[2] Von Noorden and Isaac: Loc. cit., p. 81.

TABLE 56.—DURATION OF LIFE OF 96 FATAL CASES OF HEREDITARY DIABETES, 1894 TO SEPTEMBER 1, 1922.

Decades.	Under 1 yr.	1 yr.	2 yrs.	3 yrs.	4 yrs.	5 yrs.	6 yrs.	7 yrs.	8 yrs.	9 yrs.	10 yrs.	11 yrs.	12 yrs.	13 yrs.	14 yrs.	15 yrs.	16 yrs.	17 yrs.	18 yrs.	19 yrs.	20 yrs.	21 yrs.	24 yrs.	35 yrs.	Total
0–10	3	1	1	..	..	1	1	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	7
11–20	1	1	3	..	1	1	..	..	..	1	..	..	1	..	..	..	..	..	..	..	..	1	..	..	10
21–30	2	..	2	1	4	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	9
31–40	2	2	..	2	1	..	2	..	..	..	..	..	..	..	..	..	..	1	1	..	..	..	..	1	12
41–50	3	2	2	1	2	3	2	1	3	1	4	3	1	..	..	1	..	1	..	1	..	..	..	..	31
51–60	1	2	1	..	..	1	1	..	..	4	..	..	..	..	1	..	..	2	..	..	1	..	..	..	14
61–70	1	..	2	..	..	2	..	..	2	..	..	..	..	..	..	1	..	..	..	..	..	1	..	..	9
71–80	1	..	1	..	..	..	2	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	4
Total	14	8	12	4	8	8	8	1	5	6	4	3	2	..	1	2	..	4	1	1	1	2	..	1	96
Per cent	14.5	8.3	12.5	4.2	8.3	8.3	8.3	1.0	5.2	6.3	4.2	3.1	2.1	..	1.0	2.1	..	4.2	1.0	1.0	1.0	2.1	..	1.0	

Average duration of 96 fatal cases of hereditary diabetes, 6.4 years.

TABLE 57.—DURATION OF LIFE OF 33 FATAL CASES OF HEREDITARY DIABETES, SEPTEMBER 1, 1922 TO JULY 1, 1926.

Decades.	Under 1 yr.	1 yr.	2 yrs.	3 yrs.	4 yrs.	5 yrs.	6 yrs.	7 yrs.	8 yrs.	9 yrs.	10 yrs.	11 yrs.	12 yrs.	13 yrs.	14 yrs.	15 yrs.	16 yrs.	25 yrs.	34 yrs.	Total.
0–10	..	..	1	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	1
11–20	..	..	1	1	1	..	..	..	..	..	..	..	..	..	..	..	..	..	..	3
21–30	1	..	1	..	..	..	..	1	..	..	..	..	..	..	..	..	..	1	1	5
31–40	..	..	..	..	..	..	..	..	..	..	..	..	1	..	..	..	1	..	..	2
41–50	..	1	1	..	..	..	..	..	..	..	..	..	..	2	1	..	..	..	1	6
51–60	..	1	2	..	1	1	..	..	1	..	..	1	..	..	1	..	..	..	..	8
61–70	..	2	1	..	..	1	1	..	..	..	..	..	..	..	..	..	..	..	..	5
71–80	1	1	..	1	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	3
Total	2	5	7	2	2	2	1	1	1	..	..	2	..	2	2	..	1	1	2	33
Per cent	6.1	15.1	21.1	6.1	6.1	6.1	3.0	3.0	3.0	..	..	6.1	..	6.1	6.1	..	3.0	3.0	6.1	

Average duration of 33 fatal cases of hereditary diabetes 7.5 years.

TABLE 58.—DURATION OF LIFE OF 94 FATAL CASES OF FAMILIAL DIABETES, 1894 TO SEPTEMBER 1, 1922

Decades.	Under 1 yr.	1 yr.	2 yrs.	3 yrs.	4 yrs.	5 yrs.	6 yrs.	7 yrs.	8 yrs.	9 yrs.	10 yrs.	11 yrs.	12 yrs.	13 yrs.	14 yrs.	15 yrs.	16 yrs.	17 yrs.	18 yrs.	19 yrs.	20 yrs.	21 yrs.	24 yrs.	35 yrs.	Total.
0–10	2	2	..	..	1	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	5
11–20	1	4	2	..	2	..	2	1	1	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	13
21–30	..	2	2	..	2	..	..	..	..	..	..	..	..	..	..	..	..	..	..	1	..	..	..	..	7
31–40	..	2	3	..	1	..	1	1	1	..	..	..	1	..	..	1	..	..	..	..	..	..	..	..	11
41–50	..	2	..	3	3	1	1	1	2	..	1	..	3	..	1	..	1	1	..	..	..	..	..	1	21
51–60	1	1	3	4	..	2	2	1	2	..	..	1	..	..	1	..	..	..	..	..	..	..	..	..	18
61–70	1	2	1	2	..	4	1	2	..	1	1	..	1	..	..	1	..	..	..	..	..	..	..	..	17
71–80	..	..	..	1	..	..	..	..	1	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	2
Total	5	15	11	10	9	7	7	6	7	1	2	1	5	..	2	2	1	1	..	1	..	..	1	..	94
Per cent.	5.3	15.9	11.7	10.6	9.6	7.4	7.4	6.4	7.4	1.1	2.1	1.1	5.3	..	2.1	2.1	1.1	1.1	..	1.1	..	..	1.1		

Average duration of 94 fatal cases of familial diabetes, 5.5 years.

TABLE 59.—DURATION OF LIFE OF 35 FATAL CASES OF FAMILIAL DIABETES, SEPTEMBER 1, 1922 TO JULY 1, 1926.

Decades.	Under 1 yr.	1 yr.	2 yrs.	3 yrs.	4 yrs.	5 yrs.	6 yrs.	7 yrs.	8 yrs.	9 yrs.	10 yrs.	11 yrs.	13 yrs.	14 yrs.	17 yrs.	18 yrs.	20 yrs.	25 yrs.	26 yrs.	27 yrs.	Total.
0–10	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	.
11–20	..	1	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	1
21–30	1	..	..	..	..	..	..	..	1	..	..	..	..	..	..	..	..	1	..	..	3
31–40	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	1	1
41–50	..	1	..	1	1	..	..	..	..	..	..	1	..	4	1	..	..	..	..	..	9
51–60	..	1	1	1	..	1	1	..	1	1	1	1	..	1	..	..	..	..	..	..	10
61–70	..	1	..	..	2	1	2	1	..	1	..	..	1	..	..	..	..	..	..	..	9
71–80	1	..	..	..	..	1	..	..	..	..	..	..	..	..	..	..	..	..	..	..	2
Total	2	4	1	2	3	3	3	1	2	2	1	2	1	5	1	..	..	1	..	1	35
Per cent.	5.7	11.4	2.9	5.7	8.5	8.5	8.5	2.9	5.7	5.7	2.9	5.7	2.9	14.3	2.9	..	..	2.9	..	2.9	

Average duration of 35 fatal cases of familial diabetes, 8.1 years.

average age at onset of the 14 males was 50.4 years, the average height 5 feet 5 inches and the average weight 203 pounds. The average age at onset of the 24 females was fifty-three years, the average height 5 feet 4 inches and the average weight 180.8 pounds.

TABLE 60.—CONJUGAL CASES OF DIABETES.

Case No.	Sex.	Age at onset, years.	Height, feet and inches.	Weight, pounds.	Weight above standard, per cent.	Duration,[1] years.	Weight of conso rt, pounds.
2	F.	54	...	171	....	9.0	165
10	M.	38	...	147	....	12.0	248
111	F.	46	...	248	....	9.0	147
234	M.	77	...	165	....	2.0	171
403	F.	55	...	192	....	6.1	
730	F.	57	5′ 5″	205	+40.5	13.5	
778	M.	54	5′ 8¾″	204	+23.7	10.0	
830	M.	45	...	196	....	20.0	Obese
832	F.	54	5′ 3½″	251	+76.4	17.3	200
905	M.	55	...	205	....	11.0	
1007	F.	39	5′ 4″	139	+ 4.9	26.0	
1024	F.	69	...	163	....	10.0	
1072	M.	63	...	175	....	11.0	
1232	F.	30	5′ 5″	113	−10.9	9.6	
1520	F.	61	4′ 11″	135	+ 9.0	8.9	
1558	M.	56	6′	190	+ 4.7	2.7	
1645	F.	58	...	220	....	4.6	
1903	F.	59	5′ 5″	208	+42.5	10.0	Obese
2139	F.	51	5′ 5″	184	+27.6	10.7	
2294	F.	48	5′ 3¾″	199	+42.2	11.2	
2574	F.	58	5′ 2″	173	+29.8	6.0	
2657	M.	49	5′ 7¼″	185	+21.2	3.0	
2694	F.	55	...	208	....	15.2	170
2701	F.	57	5′	142	+12.6	4.2	200
2775	M.	53	5′ 7″	243	+56.2	9.1	200
2864	M.	46	5′ 4½″	170	+21.6	5.9	299
2865	F.	34	5′ ½″	229	+88.2	7.9	170

The information given above offers no support to the infectious theory and makes it appear quite plainly that obesity, probably associated with lack of exercise, led to the development of the diabetes. None of the cases suggested to me at the time the presence of syphilis.

6. **Racial Incidence.**—The evidence of heredity should be greatest among Jewish patients. Unfortunately comparatively few of these patients are accurately informed about the causes of death of their antecedents. However, my statistics since November 26, 1920, are as follows: Among 366 Jewish patients with true diabetes,

[1] Compiled to August, 1926.

there were 55, 15 per cent, with hereditary diabetes, and 43, 12 per cent, with familial diabetes. These are comparable figures to those obtained for all my diabetics. Thus, so far as my recent statistics go the incidence of diabetes in the Jewish race does not favor the etiological importance of heredity. However, as said above, many of these patients may not have been in a position to know the causes of death of their relatives. Evidence of heredity is no greater in Hebrews than in Gentiles. This conclusion finds support from a study of my cases of diabetes with onset under twenty years. Thus 11.6 per cent of 5086 cases developed diabetes under the age of twenty years, but only 7.5 per cent of 572 cases of Jewish extraction. Diabetes, therefore, is a disease of the old Jew rather than of the young Jew even to a greater extent than it is in Gentiles. It is an acquired rather than a congenital Semitic characteristic. The Hebrew race ought to exercise more and eat less.

TABLE 61.—SEX AND THE ONSET OF DIABETES IN THE JEWISH RACE.[1]

Age at onset, years.	Males.		Females.		Total.	
	Number.	Per cent.	Number.	Per cent.	Number.	Per cent.
0– 9	7	2.9	10	3.0	17	3.0
10–19	9	3.7	17	5.1	26	4.6
20–29	27	11.2	18	5.4	45	7.9
30–39	55	22.8	58	17.5	113	19.8
40–49	80	33.2	122	36.9	202	35.3
50–59	46	19.1	83	25.1	129	22.6
60–69	15	6.2	22	6.7	37	6.5
70–79	2	0.9	...	....	2	0.3
Unknown	....	....	1	0.3		
Total cases	241	42.1	331	58.9	572	

The frequency with which diabetes occurs in the Jewish race is proverbial. Wallach[2] found that the death-rate from diabetes among the Jews in Frankfort, as compared with the deaths from all other causes, was six times greater among the Jews than among the other inhabitants. Thus of the diabetic patients treated by von Noorden[3] 40 per cent are Hebrews.

Morrison[4] found 1775 deaths from diabetes in Boston between 1895–1913. Among Jews the ratio of deaths from diabetes to the total number of deaths was 0.018 in contrast to 0.007 among non-Jews. In other words, diabetes is nearly twice and a half as common in this vicinity among Jews.

The number of Jewish patients in my series is 545. Of this

[1] True diabetics, Cases 1 to 5200 ,first seen between 1898 and April 24, 1926.
[2] Wallach: Deutsch. med. Wchschr., 1893, **19**, 779.
[3] Von Noorden and Isaac: Loc. cit., p. 75.
[4] Morrison: Loc. cit., p. 125.

number there are 228 males and 317 females, an interesting contrast to the preponderance of males among the total group of patients which has been above recorded. The number of Jewish patients seen in each successive 1000 supposed diabetics coming for advice as well as the number of true diabetics in each 1000 is given in Table 62.

TABLE 62.—PERCENTAGE OF JEWISH CASES AMONG 4262 TRUE DIABETICS FOUND IN SUCCEEDING GROUPS OF 1000 PATIENTS.

Groups of 1000 supposed diabetics.	True diabetics.	Percentage of Jewish cases.	Sex.		
			Male.	Female.	Total.
1st	906	8	30	42	72
2d	865	12	46	61	107
3d	839	17	58	82	140
4th	843	13	40	68	108
5th	809	14	54	64	118
5000	4262	13	228	317	545

What is, however, of much more interest than the percentage of Jewish patients to the total number is the course which the disease has taken among these individuals. This is shown in Tables 63 and 64.

The statistics for the Jewish patients are here arranged in a table showing onset by decades. The duration of life of the fatal cases up to September 1, 1922, is given in Table 63 and that of the known fatal cases since that date in Table 64. It will be noted that the duration of the disease in the fatal Jewish cases up to September, 1922, was 5.2 years, which was somewhat less than that for all my cases. Since the above date, the duration has risen to 10.2 years, a surprising increase and one that is not easily explained, unless it is that the Jewish patient now is in a considerably higher social scale than ten to twenty years ago.

The causes of death of the 143 fatal Jewish cases is given in Table 65. The most striking changes in causes of mortality are first the fall in the percentage of deaths from coma from 63.6 per cent in the Naunyn Era and 37.3 per cent in the Allen Era to 11.3 per cent in the Banting Era. This is confirmatory proof of the mildness of diabetes in the Hebrews and their present readiness to take advantage of insulin. Arteriosclerotic conditions have replaced coma. Grouping under this heading deaths recorded as due to cardiac disease, nephritis, apoplexy, arteriosclerosis, and gangrene, the percentage to the total mortality has risen from 36.4 in the Naunyn Era, 24.5 in the Allen Era, to 42.2 per cent in the Banting Era. Particularly noticeable is the increase in deaths from heart disease and gangrene.

TABLE 63.—DURATION OF LIFE OF 57 FATAL CASES OF DIABETES IN JEWISH RACE. SEPTEMBER 1, 1922.

Decades.	Under 1 yr.	1 yr.	2 yrs.	3 yrs.	4 yrs.	5 yrs.	6 yrs.	7 yrs.	8 yrs.	9 yrs.	10 yrs.	11 yrs.	12 yrs.	13 yrs.	14 yrs.	15 yrs.	16 yrs.	17 yrs.	20 yrs.	22 yrs.	Total.
0–10 . .	2	1	1	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	4
11–20 . .	..	1	2	..	4	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	7
21–30 . .	3	3	3	1	..	..	..	..	2	1	..	..	..	..	..	..	..	..	..	..	13
31–40 . .	..	1	2	1	..	..	1	..	..	..	..	1	..	..	..	..	..	..	1	1	8
41–50 . .	..	..	3	1	2	..	1	..	..	..	..	..	1	..	1	..	1	2	..	..	12
51–60 . .	..	1	4	..	..	..	2	..	1	..	..	1	..	..	..	1	..	..	..	..	10
61–70 . .	1	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	1
71–80 . .	..	..	..	..	..	1	..	1	..	..	..	..	..	..	..	..	..	..	..	..	2
Total . .	6	7	15	3	6	1	4	1	3	1	..	2	1	..	1	1	1	2	1	1	57
Per cent .	10.5	12.3	26.3	5.3	10.5	1.7	7.0	1.7	5.3	1.7	..	3.5	1.7	..	1.7	1.7	1.7	3.5	1.7	1.7	

Average duration of life of 57 fatal cases of diabetes in Semitics, 5.2 years.

TABLE 64.—DURATION OF LIFE OF 68 FATAL CASES OF DIABETES IN JEWISH RACE. SEPTEMBER 1, 1922 TO JULY 1, 1926.

Decades.	Under 1 yr.	1 yr.	2 yrs.	3 yrs.	4 yrs.	5 yrs.	6 yrs.	7 yrs.	8 yrs.	9 yrs.	10 yrs.	11 yrs.	12 yrs.	13 yrs.	14 yrs.	15 yrs.	16 yrs.	17 yrs.	18 yrs.	19 yrs.	20 yrs.	22 yrs.	26 yrs.	Total
0–10	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	.	.
11–20	..	..	..	1	1	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	.	2
21–30	1	..	..	1	..	..	..	1	..	..	1	..	..	..	..	..	..	..	1	..	..	..	..	5
31–40	..	..	1	1	1	..	..	1	1	..	..	..	..	1	..	..	1	..	..	..	1	1	1	10
41–50	..	..	1	1	1	2	..	..	1	2	1	2	6	1	2	4	1	2	..	..	..	..	1	28
51–60	..	..	2	..	1	1	..	2	1	2	1	1	3	..	1	..	..	..	..	1	..	..	..	16
61–70	..	1	..	..	2	..	..	1	2	..	..	..	..	1	..	..	..	..	..	..	..	..	..	7
71–80	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	.
Total	1	1	4	4	6	3	0	5	5	4	3	3	9	3	3	4	2	2	1	1	1	1	2	68
Per cent.	1.5	1.5	5.9	5.9	8.7	4.4	..	7.4	7.4	5.9	4.4	4.4	13.2	4.4	4.4	5.9	2.9	2.9	1.5	1.5	1.5	1.5	2.9	

Average duration of life of 68 fatal cases of diabetes in semitics, 10.2 years.

TABLE 65.—CAUSES OF DEATH OF THE 143 FATAL JEWISH CASES.

Cause.	Naunyn Era, 1894 to June, 1914.		Allen Era, June, 1914 to August, 1922.		Banting Era, August, 1922 to July, 1926.	
	Cases.	Per cent.	Cases.	Per cent.	Cases.	Per cent.
Coma	7	63.6	23	37.7	8	11.3
Cardiac	2	18.2	5	8.2	19	26.8
Nephritis	1	9.1	3	4.9	7	9.9
Apoplexy	1	9.1	3	4.9	8	11.3
Arteriosclerosis	..	..	1	1.6	2	2.8
Pneumonia	..	..	2	3.3	2	2.8
Influenza	..	..	2	3.3	2	2.8
Meningitis	..	..	..	..	2	2.8
Dysentery and gastro-enteritis	..	..	..	..	1	1.4
Gall stones	..	..	1	1.6	1	1.4
Carbuncle	..	..	..	..	1	1.4
Empyema	..	..	1	1.6		
Gangrene, sepsis	..	..	3	4.9	7	9.9
Pulmonary tuberculosis	..	..	4	6.7		
Cancer of thyroid	..	..	..	..	1	1.4
Cancer of breast	..	..	..	..	1	1.4
Cancer of liver	..	..	2	3.3		
Cancer of pancreas	..	..	..	..	1	1.4
Cancer of kidney	..	..	1	1.6		
Cancer of prostate	..	..	..	..	1	1.4
Inanition	..	..	3	4.9	1	1.4
Gastric ulcer	..	..	..	..	1	1.4
Suicide	..	..	1	1.6	1	1.4
Accidental	..	..	..	..	1	1.4
Myelitis	..	..	..	..	1	1.4
Diabetes	..	..	6	9.9	2	2.8
Total	11		61		71	

The high incidence of diabetes in New York City has been attributed to the Jews. This explanation is not wholly satisfactory, because although the percentage of Jews in the population of New York City is far greater than in Boston, the diabetic death-rate in the two cities is approximately the same.

TABLE 66.—DEATH-RATES FROM DIABETES IN RELATION TO PERCENTAGE OF JEWS IN POPULATION.

	New York City.		Boston.	
	Jews in population,[1] per cent.	Diabetes death-rate per 100,000 total population.	Jews in population,[2] per cent.	Diabetes death-rate per 100,000 total population.[2]
1910	26.28	16.0	8.8	21.4
1920	29.23	18.9		

[1] American Jewish Year Book, 1923–1924; Greater New York, 1920, N. Y. C. 1920 Census Committee, p. 838.

[2] Morrison: Boston Med. and Surg. Jour., 1916, **175**, 54.

F. ETIOLOGY.

Diabetes centers around the islands of Langerhans, but why should they become diseased or cease to function? This is clear in experimental hemochromatosis, where Mallory has produced the destruction of the islands by injections of copper, but bronze diabetes is rare. This does not explain the hyaline degeneration and atrophy of the islands which is the far more common condition or does it explain those cases in which the etiology must be considered largely functional, because of our inadequate methods of investigation. An antecedent pancreatitis would appear to be the most logical explanation, but the existence of such can seldom be proved. In lieu of the true cause attention can be directed with profit to the predisposing causes and among these obesity is preëminent.

1. **Obesity and Its Relation to the Diverse Etiology of Diabetes.**[1]—(*a*) **Relation to Diabetes.**—The association of obesity and diabetes has long been noted. Conversely, in the presence of a wasting disease, diabetes is practically unknown. A few years ago an analysis of 1063 of my own cases showed that in more than 40 per cent of the number marked obesity preceded the outbreak of the disease, and the prediction was made that if more exact data were available the percentage would be fully twice as great. Writers generally have observed this connection, and von Noorden not only emphasized the necessity of examining the urines of fat persons for sugar, but also suggested that examinations of the blood sugar of fat persons would disclose their approach to the disease when the urine was sugar-free. In other words, a prediabetic stage in fat persons has been recognized and demonstrated by Paullin,[2] Beeler and Fitz,[3] Labbé and Boulin[4] and John.[5] But the closeness of the dependence of diabetes on obesity demands still more elucidation.

"While compiling the data for age, height and weight of a series of 118 diabetics whose respiratory metabolism had been studied at the Nutrition Laboratory of the Carnegie Institution, it was found that persons above the age of fifty rarely acquired diabetes if their weight remained a little below normal. These statistics, although striking, were too few for generalities. Therefore, data from 1000 successive cases of diabetes in which the age, weight and height were known were compiled and are here reported.

"Such extensive and inclusive data have not been published heretofore. Even if one searches the best of the monographs on dia-

[1] Joslin: Jour. Am. Med. Assn., 1921, **76**, 79.
[2] Paullin: Southern Med. Jour., 1922, **15**, 249.
[3] Beeler and Fitz: Arch. Int. Med., 1921, **28**, 804.
[4] Labbé and Boulin: Bull. de la Soc. méd. d. Hôp., 1925, **49**, 649.
[5] John: Am. Jour. Med. Sci., 1927, **173**, 184.

betes it will be found that the case records, while giving the weight frequently fail to give the height. This unfortunate practice is not limited to diabetes. Indeed, it is only too true that during life patients are weighed, and at death they are measured, but in neither life nor death are both height and weight taken. This may explain why the data in this series of 1000 cases throw additional light on obesity as a predisposing cause of diabetes, and at the same time suggest how the disease may be prevented."

TABLE 67.—VARIATION FROM NORMAL OF MAXIMUM WEIGHTS, AT OR PRIOR TO ONSET, OF 1000 CASES OF DIABETES, CALCULATED FOR HEIGHT, AGE AND SEX.

First Series 1923.

Age, years.	Number of cases.	Below standard weight, per cent.			Normal average zone, per cent. +5 −5	Above standard weight, per cent.								Percentage of each decade below normal zone.
		30–21.	20–11.	10–6.		6–10.	11–20.	21–30.	31–40.	41–50.	51–60.	61–70.	71 +.	
1–10	16	0	3	2	5	3	2	..	..	1	..	..	..	31
11–20	59	2	11	8	24	6	4	2	1	..	1	..	..	36
21–30	131	..	15	13	41	15	29	9	4	..	3	..	2	21
31–40	178	1	9	12	28	22	34	25	15	14	10	6	2	12
41–50	291	2	8	7	31	19	59	59	40	30	18	10	8	6
51–60	233	..	4	7	16	28	39	48	45	14	13	5	4	5
61–70	84	..	..	2	8	10	17	23	14	7	1	1	1	2
71–80	18	..	..	1	6	3	2	3	2	1	..	..	..	6
1–80	1000	5	50	52	159	106	186	169	121	67	46	22	17	

TABLE 68.—VARIATION FROM NORMAL OF MAXIMUM WEIGHTS AT OR PRIOR TO ONSET, OF 1000 CASES OF TRUE DIABETES, CALCULATED FOR HEIGHT, AGE AND SEX.

Second Series 1926.

Age. years.	Number of cases.	Below standard weight, per cent.			Normal average zone, per cent. +5 −5	Above standard weight, per cent.								Percentage of each decade below zone.
		30–21.	20–11.	10–6.		6–10.	11–20.	21–30.	31–40.	41–50.	51–60.	61–70.	71 +.	
0–10	43	1	10	8	16	4	4	..	..	..	..	..	..	44
11–20	84	4	12	8	33	9	7	7	1	2	..	1	..	29
21–30	112	1	6	4	21	16	25	11	9	12	2	1	4	10
31–40	172	1	1	6	11	10	28	39	25	22	18	4	7	5
41–50	244	..	3	4	30	13	37	48	51	24	14	10	10	3
51–60	252	..	2	..	30	19	44	65	45	24	9	7	7	1
61–70	79	3	2	..	8	8	17	19	10	8	4	..	..	6
71–80	14	..	..	1	2	..	1	4	3	2	1	..	..	7
1–80	1000	10	36	31	151	79	163	193	144	94	48	23	28	

Based upon the table as a whole the statement is justified that of the 1000 diabetics considered the maximum weights of only 10 per

cent were below the standard weight zone while 15 per cent were in that zone and 75 per cent were above it.

To reinforce my original table of the relation of weight to diabetes a second and more recent 1000 of my diabetics, this time all true cases of diabetes, have been studied and the results appear in Table 68. Again one sees that 15 per cent are in the normal zone of weight, but this time there are but 8 per cent below it, leaving 77 per cent above it. Between the years fifty-one and sixty there were but 2 diabetics in 252 whose maximum weights were below the normal zone prior to the onset of the disease.

Von Pirquet[1] has called attention to the extraordinary increase in diabetes after forty years of age, reaching its maximum in England between sixty and seventy years. On account of this he suggests another pathogenesis for this form of diabetes in contradistinction to that of earlier decades. This seems still more probable from the facts brought out in the next paragraph.

Among the 2000 cases of diabetes, not one occurred who was more than 30 per cent underweight, and in Adams' series[2] of 1000 cases at the Mayo Clinic no patient developed the disease who was more than 20 per cent underweight. The almost exclusive limitation of the underweight diabetics to the early decades of life will receive later comment.

The average percentage overweight in a series of cases of diabetes of Anders and Jameson[3] is higher among females than males, and while this is true in both Gentiles and Jews, the latter race shows a higher percentage of overweight. However, their statistics do not show a preponderance of cases of adiposity of females over males, but simply a higher average per cent overweight. The incidence of diabetes among obese Jews is higher than among obese Gentiles, the ratio being 12 to 8 in favor of the former. These authors believe that the difference in the average percentage of overweight between the two races is not great enough to account for the difference in incidence. They do, however, believe that obesity among females is unquestionably the most potent single predisposing factor in the recently increasing incidence of diabetes in this sex.

To the relation between obesity and diabetes, Mr. Mead of the Lincoln National Life Insurance Company has also offered a valuable contribution. He finds that the frequency of constitutional diseases in general increases as age advances and particularly as obesity advances, but that diabetes is to this extent an exception to the rule; its incidence increases with age only in the fat, while in the thin it remains constant throughout life. This shows that

[1] Von Pirquet: Wien. klin. Wchnschr., 1924, **37**, 1277.
[2] Adams: Proceedings Mayo Clinic, 1926, **1**, 189.
[3] Anders and Jameson: Am. Jour. Med. Sci., 1925, **170**, 313.

diabetic patients, young and old, are akin, and the earlier clinicians were right in sharply differentiating the fat and the thin patient with diabetes. The effect of body weight on the death-rate in general deserves emphasis. Until thirty-five years of age the mortality is low for the overweights. The most favorable weight for longevity in middle life is 10 to 20 pounds below the average weight and even 30 pounds below the average is safer than the average weight itself.

"(*b*) **Diabetes—A Penalty of Obesity.**—Diabetes, therefore, is largely a penalty of obesity, and the greater the obesity, the more likely is Nature to enforce it. The sooner this is realized by physicians and the laity, the sooner will the advancing frequency of diabetes be checked. The penalty of taking too much alcohol is well known, and a drunkard is looked on with pity or contempt. Rarely persons who become fat deserve pity because of a real tendency to put on weight despite moderate eating, but usually most should be placed in somewhat the same category as the alcoholic. In the next generation one may be almost ashamed to have diabetes. Jewish patients, sometimes hypersensitive to physical ills, but often rightly anxious to take things in time, are already beginning to realize this fact.

Loss of Weight a Cause of Diabetes.—Rapid loss of weight by a fat individual, strange to say, may be followed by diabetes. How frequently this occurs I cannot say, but it may be of considerable importance for I recall several instances, Cases Nos. 406 and 6338. The fat society woman in her zeal for fashion's lines takes black coffee for breakfast, bouillon and a few green vegetables at noon in order to indulge in a liberal dinner. The total calories for the day, it is true, are lowered and weight is lost, but by this dietetic plan a heavy load of carbohydrate is cast upon pancreas and liver, when the former's insulin-producing capacity has not been trained by previous meals to convert it into harmless glycogen and when the latter's store of glycogen is so low that it functions with difficulty.

Support of the above explanation and the danger of a low-carbohydrate diet followed by high-carbohydrate feeding will be found on page 200 in the observations of Odin and the others there cited. Indeed it may also be true that the scant European breakfast after the long night's fast is safer than our heavier American breakfast. At any rate after abstinence from food one should begin eating with small quantities of food in which carbohydrate finds a moderate place, and in losing weight, while one may omit all fat because the body has enough in store, one should never omit all carbohydrate from a meal.

"(*c*) **The Substandard Weight Patients.**—Patients in Tables 67 and 68 who developed diabetes, though underweight, furnish a group

for very particular study. They should represent a purer, simpler type of the disease. As this fact is now realized, subsequent cases falling into this class will be better analyzed and the number possibly reduced in size. This proved to be the case in the second series, and the number fell from 107 in the first 1000 to 77 in the second 1000. Investigation of the original series proved that 29 of the 107 were really doubtful diabetics according to the more accurate standards of today. They include that dangerous group, "renal" diabetics, "insurance" diabetics who are sometimes accepted as risks, and other extremely mild cases. An hereditary and familial element was present in 24, and among these there were 8 examples of more than 1 case in the family. Several cases showed stigmas of degeneracy, and it is my impression that greater familiarity on my part with such signs would increase the number that should be classed in this way. Conversely, there were several extraordinarily severe cases, and yet in some of these very cases in which the disease appeared severe, the patients withstood it for an unusually long period. Indeed, it would seem justifiable to formulate this diabetic law: *It is rare for diabetes to develop in an individual above the age of twenty years who is habitually underweight, and when it does so develop the case will usually be found to be either extremely severe, extremely mild, or associated with a marked hereditary taint or degenerative stigmas.* The tendency to diabetes appears to be congenital. It is most intense in childhood; but, escaping that period, the individual is less and less likely to acquire the disease if he remains underweight, whereas in the obese the tendency finds a fertile soil. In the fat the predisposition may be no greater, but the external cause is more provocative."

(*d*) **Obesity Predominant in Other Factors Often Mentioned in the Etiology of Diabetes.**—The preponderating influence of obesity in the development of diabetes explains various peculiarities in diabetic case histories and furnishes a new point of view from which to regard them.

1. *Conjugal Diabetes.*—Of 27 persons concerned in my original series there was but 1 who was thin. Husband and wife were alike fat, and the implication is strong that they contracted the disease from exposure to good food rather than to one another.

2. *Frequency of Diabetes in the Jewish Race.*[1]—One has only to visit the Jewish quarter of a large city to be impressed with the frequency of obesity. Over-feeding begins in childhood and lasts to old age. Very likely with the increasing affluence of the Jewish race in this country, permitting indulgence in their well-known fondness for style, obesity will tend to diminish and along with it

[1] See also page 150.

diabetes. Already it is as rare to see a Jewish doctor who is above normal weight as it is an educated Jewish boy or girl, man or woman, who is fat. The fashion-plate makers are far ahead of insurance company presidents in their propaganda for a normal weight. All one needs to do is to glance at the morning paper to see ladies and gentlemen portrayed for our benefit whose sylph-like figures are models of weight and height—nay, more, they are invariably a trifle below the standard weight and so might bear the legend: "Immune to diabetes."

Emerson and Larimore[1] did not find obesity notably more frequent among Jewish workers in New York. Their information would represent the younger individuals in the community.

3. *Frequency of Diabetes Among the Richer Classes of Society.*—"On the broad street of a certain peaceful New England village there once stood three houses side by side, as commodious and attractive as any in the town. Into these three houses moved in succession 4 women and 3 men—heads of families—and of this number all but 1 subsequently succumbed to diabetes. The remaining member of the group died of cancer of the stomach at the age of seventy-seven years. A search for the cause of these deaths, untimely in the majority of instances, led to the accumulation of the data on which this study of obesity was based.

"Although 6 of 7 persons dwelling in these adjoining houses died from a single cause, no one spoke of an epidemic. Contrast the activities of the local and state boards of health if these deaths had occurred from scarlet fever, typhoid fever or tuberculosis. Consider the measures that would have been adopted to discover the source of the outbreak and to prevent a recurrence. Because the disease was diabetes and because the deaths occurred over a considerable interval of time, the fatalities passed unnoticed. Even the insurance companies failed to grasp their significance, and yet probably no group of individuals in the community carried *pro rata* a higher amount of insurance than did these 6 diabetics." At the time these individuals lived, ideas of exercise for pleasure and the benefit of the body had not penetrated this rural region. Consequently, in this as in many other New England villages, though fortunately to a less extent now, the well-to-do were unusually fat. In fact, even today it is a common observation to note that country families tend more to obesity than their city cousins of similar means.

It is possible also that the age at death of affluent members of the population is greater than that of the poorer.

[1] Emerson and Larimore: Loc. cit., p. 24.

4. *Heredity.*—This may simply mean unusual exposure to an obetic environment. One should not forget that obesity is usually an acquired characteristic, and acquired characteristics are little subject to transmission from parent to child. The handicap of a diabetic heredity may be to a considerable extent counteracted by avoidance of overweight. What a comfort and stimulus to diabetic parents and gain to their children!

5. *Mental Workers in Contradistinction to Physical Workers.*—The former are more likely to be fat. But the probability of more frequent urinary examinations among the more intelligent and city dwellers might explain the apparent increase in frequency. Worms said that diabetes was so frequent among the mentally active in Paris that 1 in 10 had the disease.

Emerson and Larimore[1] cite data for England and Wales and for France which indicate that those occupations which involve hard manual and body labor show low diabetic death-rates. They express doubt, as do Kober and Hayhurst, that occupations involving nervous strain and worry cause a high prevalence of diabetes. "The question of first importance is whether such persons are not overeating and underexercising, a hygienic sin particularly common among people of sedentary, highly skilled trades or professional occupations."

Locomotive engineers are said to be especially prone to diabetes. The chief surgeon of one railroad has informed me that among 1673 engineers glycosuria was found in 44 instances. Further study showed that a majority of them were really diabetics. Their average weight was 191 pounds. About 20 per cent of all the engineers were overweight.

At the meeting of the Medical and Surgical Section of the American Railway Association (Circular No. M. and S. 61) it was stated that the chief surgeon of a certain railroad employing approximately 50,000 men in its train operations and movements reported that 0.05 per cent of all train men have diabetes; of the engine men alone 1.07 per cent were diabetic and of the other trainmen in engine service not including the engine men 0.03 per cent have the disease. The age factor may be of much importance in evaluating these statistics.

Patients with diabetes cannot engage as satisfactorily in railroad pursuits as in occupations where they get regular meals and meals at home. Intelligent diabetics often overcome these handicaps, and I have a considerable number who work on railroads, but none taking insulin, who are engineers.

The condition of a diabetic is liable to sudden change. If he is

[1] Emerson and Larimore: Loc. cit., p. 28.

careless, diabetic coma may result from errors of diet or the addition of an infection. If he is faithful and maintaining efficiency by insulin, he is liable to have an insulin reaction at such short notice, because of unexpected exertion or insufficient food, as to impair or prevent work. Occasionally no warning of an insulin reaction is recognized by the patient and he becomes unconscious. See p. 49.

6. *A Sequel to Infectious Diseases.*—Convalescents have big appetites, and unfortunately are almost fanatically overfed during a period of forced inactivity and at the very time when the pancreas must necessarily, like the rest of the body, be in a vulnerable state.

7. *Diabetes and Gout.*—Is it usual to see gout in the thin?

8. *Rarity of Syphilis in Diabetes.*—Statistics of the Peter Bent Brigham Hospital, those of von Noorden, and my own all agree in this regard—that syphilis is less common in diabetics than in the general population. Although data on the weights of syphilitic patients are not known to me, it is possible, first, that those who acquire the disease are more often thin than fat, and secondly, that they more often lose than gain weight after the disease has fully developed. Who weighs and measures syphilitics? However, the shorter duration of life of patients with tuberculosis, cancer and syphilis in part explains the decreased frequency of diabetes in their presence.

9. *Age.*—The second decade of Table 67 and the first decade of Table 68 prove exceptions to those which follow in that there were more patients who developed diabetes below the standard weight than above it. In fact, obesity appears to play no part at this age, and so far as present evidence is available it must be acknowledged that these decades constitute an argument against the importance of obesity as a predisposing factor in the development of diabetes. In explanation of the many cases of diabetes in children who were not obese is Naunyn's conception of the virulence of the diabetic tendency in childhood which leads it to break forth without an external stimulus. Of the correctness of this interpretation, however, I am not quite convinced. The subsequent histories of children once overweight should be compared with those of normal weight or below weight, and the incidence of diabetes in each group determined.

Another stimulus to diabetes in children than obesity may exist, and in seeking for more accurate data about the growth of diabetic children such a stimulus was found by Priscilla White.[1] Upon examining children's records for height prior to onset of diabetes, it developed that overheight was more frequent a precursor of diabetes in children than was overweight in adults.

[1] White: Jour. Am. Med. Assn., 1927, **88**, 170.

Ninety per cent of our 100 diabetic children were overheight in contrast to 80 per cent of 925 adults who were overweight prior to the disease. It is generally admitted that overweight is a precursor of diabetes in an adult, and now we have evidence even more striking of overheight in a child. This deviation of height from the normal average, when based on Wood's table,[1] amounts to an excess of 2.7 inches.

If the Holt[2] standard is used, 87 per cent are above standard and the average height of the entire group exceeds the standard by2 .2 inches.

Our children are predominantly of the public school class. Indeed only 3 children of the series have attended private schools in a vicinity where private schools are numerous. Therefore, it would not be fair to compare their heights with the standard based on children from private schools. Should this be done, however, it would be found that they exceed Baldwin's[3] selected group from the Francis W. Parker School (well-to-do class) by 0.8 inch. They are in turn exceeded by the Bendict and Talbot[4] private school children by 0.3 inch and by Gray's[5] recent standard, which is the highest published standard for American school boys, by 0.7 inch.

The symptomatology of diabetes in the adult and the child is the same. I cannot accept the idea of an etiology which is fundamentally different in character for adults and for children. There must be some significance in the fact that so striking a precursor of the disease as overweight should be rare in the child yet common in the adult. Our records show that obesity is rare before diabetes breaks out in children. There were only 5 who were as much as 10 per cent overweight for height, and only 2 reached the obese class of 20 per cent overweight. Compared with Gray's standard, they weigh for their height 0.9 pound less than the slender private school child. See p. 824.

Kisch[6] directed attention to the frequency of the development of diabetes in the later lives of fat children, and I never see a fat child without thinking of this possibility, for a fat child, like a fat man, is prone to diabetes. Particularly serious must it be for a child or adult of slight stature to put on weight which would be excessive even for a man of large frame. Case No. 1142 first consulted me at the age of forty-one years, and I can just remember his little spindling legs and delicate frame as a boy before he entered the primary school; many years later he entered a grocery store, "worked

[1] Wood: The Ninth Year-Book of the National Society for the Study of Education, Pt. 1, Health and Education, Chicago, 1910, p. 34.

[2] Holt: Diseases of Infancy and Childhood, Ed. 7, New York, D. Appleton & Co., 1916, p. 20.

[3] Baldwin: Physical Growth of Children, University of Iowa, 1922, **1**, 261.

[4] Benedict and Talbot: Pub. 302, Carnegie Inst. Washington, 1921, p. 32.

[5] Gray and Fraley: Growth Standards: Height, Chest-girth, and Weight for Private School Boys, Am. Jour. Dis. Child., 1926, **32**, 554.

[6] Kisch: Jour. Am. Med. Assn., 1915, **64**, 1038.

like the dickens and ate the same way," until at the age of forty he was 60 pounds above the average weight, and sugar was found at a life insurance examination. (See also p. 825.)

One of the most striking instances is that of a little child, Case No. 1139, a healthy baby until his second year, when he entered upon a series of rhinopharyngeal and bronchial attacks, including a mild bronchopneumonia. During eleven of the feverish illnesses exercise was curtailed and he was kept abed to safeguard his heart. A cow was bought that he might have fresh, rich milk, and to the 50 ounces of this milk which he daily consumed were added 3 tablespoonfuls of a malt preparation, amounting in nutritive value to 120 or more calories. At the end of his first year he was of normal weight, but at eighteen months his weight was above that of a child of two years. When two years old his weight had increased to that of a child of three years and a half, and when two years and a half old, his weight was above that of a child of four years. Is it surprising that when mumps developed in 1915, glycosuria appeared to the extent of 3.1 per cent. It vanished with a change in diet, to return three months later, during the presence of another mild febrile disorder, and again in six months after the removal of adenoids, but since this occasion the urine has remained sugar-free to date, 1928.

A poor musculature usually accompanies obesity. One-half of the carbohydrate in the body is stored in the muscles and a large part of the sugar of the body is burned in them. Therefore it does not appear strange that fat people develop diabetes. It would almost seem as if the muscles became so loaded with fat that they were unable to burn carbohydrate. At one time fat and glycogen in the liver were thought to be antagonistic to one another. Under the influence of insulin, the Toronto investigators found they could exist together.

10. *Dietary Excesses.*[1]—Chronic dietary excesses precede obesity and figure quite prominently in my records as precursors of diabetes. Allen's dogs artificially predisposed to diabetes by removal of a considerable portion of the pancreas became diabetic when overfed. It is, however, the excess of food rather than of carbohydrate which does the harm.[2] Indeed, a high percentage of carbohydrate in the diet does not appear to predispose to diabetes. Thus, the Japanese live upon a diet consisting largely of rice and barley, yet so far as statistics show, the disease is not only less frequent but milder in that country than in this. With the adoption of Occidental tastes both the frequency and severity of the disease have increased, according to my Japanese visitors.

In 1913 Germany consumed half as much sugar as was eaten in

[1] See Die Zunahme der Zuckerkrankheit; Eine Ernährungsfrage, by Ullman in Die Medizinische Welt, 1928, **2**, 87.

[2] See Jour. Am. Med. Assn., 1928, **90**, 782 for statistical evidence based on Registrar General's Decennial Supplement for England and Wales.

the United States, and yet diabetes was quite as prevalent there as here. Australia in 1922 consumed more sugar, 112 pounds per capita, than the United States, 103.2 pounds per capita, and had less diabetes—indeed little more than in England where the sugar consumption per inhabitant is 70 pounds. The increase in the quantity of sugar consumed per capita in the United States during the last century is very great, as shown by Table 69, and if one compares this table with the rising incidence of diabetes shown in Tables 23 to 32, it would seem as if the two must stand in relation. On the other hand the dietary habits and the statistics upon diabetes of Japan and the data upon sugar consumption in Australia, England, Germany and the United States point in the opposite direction.

TABLE 69.—THE CONSUMPTION OF SUGAR IN THE UNITED STATES.

Years.	Population average for decade.	Pounds per capita, yearly average.	Diabetic death-rate per 100,000.
1800–1810	6,146,343	11	First and last years of decades.
1810–1820	8,280,041	8	
1820–1830	11,038,448	9	
1830–1840	14,720,126	12	
1840–1850	19,824,542	2	
1850–1860	26,905,025	26	
1860–1870	34,645,094	23	
1870–1880	43,777,206	33	
1880–1890	55,912,152	44	2.8– 5.5
1890–1900	68,818,801	56	5.5– 9.3
1900–1910	83,275,548	65	9.7–14.9
1910–1920	98,796,383	82	14.9–16.1
1920–1925	110,509,736	98	16.8–16.9

The marked increase in the consumption of sugar, largely sucrose, shown in Table 69 might appear of great significance in seeking for a cause of the greater frequency of diabetes today were it not for the fact that whereas the consumption of sugar per capita between 1900 and 1925 has increased 35 per cent, the mortality from diabetes has increased 75 per cent. Contrariwise, between 1910–1920 and 1920–1925 the consumption of sugar increased approximately 20 per cent while the mortality from diabetes rose less than 10 per cent. Nevertheless, such a marked alteration in the diet of a nation is noteworthy and deserves attention. During 1927 the consumption of sugar has decreased in this country from its peak of 104 pounds.

Emerson and Larimore cite statistics from the Bureau of Animal Industry of the U. S. Department of Agriculture to show that, whereas the consumption of sugar in the United States has increased, that of meat has fallen in the last fifteen years from 179 pounds to 155 pounds, this reduction having been replaced by an increase in

the use of cereals, sugar, milk, and fruits. Inspection of the menu cards of a well-known chain of restaurants would indicate that the lower limit has not yet been reached

TABLE 70.—CONSUMPTION OF SUGAR PER CAPITA AND DEATH-RATE OF DIABETES PER 100,000 IN AUSTRALIA, ENGLAND, AND THE UNITED STATES.

Country.	Diabetes death-rate per 100,000.	Sugar consumption in pounds per capita.
FOR THE YEAR 1913.		
Australia	..	..
England and Wales	11.8	78.5
United States	15.3	85.4
FOR THE YEAR 1922.		
Australia	12.3	112.0
England and Wales	11.9	70.0
United States	18.4	103.0

Acute dietary excesses are rarely if ever associated with the advent of diabetes. The incidence of diabetes in the employees of candy factories and candy shops would be of interest in this connection. Even yet this question has not been thoroughly investigated.[1] The development of diabetes after glucose tolerance tests has not yet been reported.

2. **Multiple Etiology.**—The majority of diabetic patients present multiple causes for their diabetes. This is well exemplified by the history of a gentleman, aged forty-nine years, Case No. 954, who consulted me on December 12, 1915. One of his children died in 1901 at the age of two years, and another in 1913 at the age of twelve years, both of diabetes. As a child he had measles, scarlet fever, and whooping-cough, and at twenty-four years was ill for eighteen months with inflammatory rheumatism, and the pericardium was tapped twice.

At the age of thirty-three years his weight was 200 pounds, and for his height—5 feet 11 inches—was 17 per cent above normal. Prior to this time he indulged in considerable alcohol three evenings a week, and his use of tobacco was more than moderate. He was fond of sweets and occasionally ate half a pound of candy in an evening. During the last two years he took little exercise, and recently led a strenuous life on account of his active business. An attack of gall stones, which was accompanied by an infection of the biliary tract, led to an operation on November 15, 1915. Prior to the operation the urine was examined and found normal. The anesthetic was ether. Convalescence from the operation was satisfactory, but while at the hospital his friends, knowing his fondness for sweets, sent him much candy, which he ate. On

[1] Von Noorden: Die Zuckerkrankheit, Berlin, 1917, 7th ed., p. 331.

December 11, 1915, he observed polyuria, and later he recalled that when nervous and working hard this symptom had occurred off and on for a day's duration during several years. On December 11, 1915, sugar was demonstrated in the urine, and upon the following day, when he came for treatment, the specific gravity was 1045 and the percentage of sugar was 7.2. The weight of the patient was approximately 185 pounds shortly after the operation, and on December 13 was 177 pounds naked. The patient began fasting by omitting his supper on December 12, and the twenty-four-hour quantity of urine ending December 14 contained only a trace of sugar, and even this was absent the following day. Improvement was uninterrupted but (Moral!) he dropped from observation and I learned of his death from pneumonia in 1920.

The important etiological factors were all present in this case: namely, the optimum age, an hereditary tendency to diabetes, and obesity. Furthermore he has led a strenuous life, had indulged in dietary excesses, and had taken little exercise. Lastly there was the excitement connected with the operation, the trauma of the operation, and the presumable local interference with the normal action of the pancreas and liver.

It was interesting that the disease did not break out earlier in the case of this patient, when one realizes that obesity had existed several years before. It plainly suggested that obesity and the diabetic *anlage* were not sufficiently strong factors to lead to the disease. Even when to these were added dietary excesses and the strenuous life, the disease still remained latent and only a multiplicity of influences, such as were brought about by the operation were sufficient to make it declare itself.

3. **Heredity.**—The influence of heredity is elsewhere discussed. (See pp. 821 to 823 in children's section.)

4. **Nervous Element.**—A strenuous life has been considered by most writers as of importance in the etiology of diabetes, and it has so impressed me. Von Noorden records that 8 per cent of all his mild diabetic patients were physicians, and this can easily be connected with the strenuous life which medical work entails. The frequency of diabetes, among physicians, however, is undoubtedly in part due to the opportunity they have for detecting the disease. In my own series of male patients ending 1916, above the age of twenty, 10 per cent were physicians. Of these 15 had died by 1917, and the average duration of the diabetes was seven years; 47 were alive, and the average duration of the diabetes up to December 1, 1916, was likewise seven years.

The nervous element in diabetes has gained additional importance since the publication of the work of Cannon, Shohl and Wright[1] and

[1] Cannon, Shohl and Wright: Am. Jour. Phys., 1911, **29**, 280.

the investigations of Folin, Denis and Smillie[1] upon the appearance of sugar in the urines of 192 insane patients. Of these, 22 showed sugar with the standard tests. The latter investigators also examined the urines of students after important examinations. "Of 34 second-year medical students examined before and after an examination, 1 had sugar both before and after the examination. Of the remaining 33, 6, or 18 per cent, had small but unmistakable traces of sugar in the urine passed immediately after the examination. A similar study was made on second-year women students at Simmons College. Since these students were younger, and presumably much more excitable than our medical students, it was thought that even more striking results might be obtained. This expectation did not prove to be well founded. Out of 36 taking the examination and showing no sugar in the urine on the day before, 6, or 17 per cent, eliminated sugar with the urine passed immediately after the examination." Even emotion caused by securing samples of blood for analysis may lead to a rise in blood sugar percentage. Case No. 10 developed severe diabetes when on an unusual business trip from Boston to New York involving much responsibility. The appearance of polyuria and polydipsia was acute—in fact, while turning a street corner—but he lived twelve years. Carrasco Formiguera[2] cites the following tragic case, No. 34 of his series: Diabetic symptoms (polydipsia, polyuria, physical and mental depression) appeared suddenly and with extraordinary intensity in a man a few hours after suffering a double emotion. First, he saw die on the seat beside him a fellow-worker whom he was accompanying from the shop because of sudden illness, and second, he was held as the alleged slayer until the true circumstances were established a few hours later. The patient had suffered in his early childhood a serious traumatism with cerebral concussion. When the disease began, he was eighteen years of age, and until then he felt sound and strong. He died two years later in diabetic coma. In comparatively few instances in this series was the presence of an organic nervous disease demonstrated. Allen's conception of the functional nature of diabetes shows how the disease may be brought about through the nervous system by its action upon the pancreas. Thus the Claude Bernard puncture produced diabetes in one of Allen's dogs, predisposed to the same by the removal of a portion of the pancreas, and yet proved to be non-diabetic before the puncture. In this dog characteristic changes were found in the islands of Langerhans at autopsy.

The Jewish race is indicted as proof of the relation between a

[1] Folin, Denis and Smillie: Jour. Biol. Chem., 1914, **17**, 519.

[2] Carrasco Formiguera: Footnote, Joslin: Tratamiento de la Diabetes Sacarina, Montaner y Simon, Barcelona, 1925, p. 141.

nervous disposition and diabetes. Until the incidence of diabetes in Hebrew children is as great or greater than in Gentiles such evidence falls flat. I believe Jewish adults are more prone to diabetes because they overeat and underexercise.

Soldiers returning from the front did not show sugar in the urine. About 40,000 passed through the hospital center in Mesves, France, where I was consultant; yet, though the urines were systematically examined, but 2 cases of diabetes were discovered, or at least came to my attention. It would be instructive to note the incidence of diabetes in the same soldiers at a period some months later when added weight was the rule.

Children who have stood exceptionally high in their classes at school have figured largely among those children who have come under my observation with the disease. Because of the frequency of this association I have cautioned my medical friends whose children were exceptionally brilliant. Statistics are not of great service in this regard, but my associates, H. Gray, H. F. Root and P. White confirm my observation. In August, 1923, a boy of seventeen years came with diabetes who had just been admitted to Harvard without examination and already had two scholarships at his disposal! In 1928 he remains in excellent condition.

5. **Infections.**—Infections could be the etiological factor in diabetes, but if *the* factor, why is it that an infection should attack the obese almost exclusively, and why should infections which are so frequent in youth so seldom be followed by diabetes? Furthermore, if an infection attacked the pancreas, it would presumably attack all the islands, not just a few of the islands, and if it attacked all the islands, it would make the diabetes violently severe at the very start. There is a great distinction to be drawn between an infection as an etiological factor in diabetes and the well-known fact of the effect of an infection upon the diabetes. An explanation of the manner in which an infection can affect the diabetes has been outlined by Lawrence.[1] He cites his experiments which show that diphtheria toxin will practically annihilate the action of insulin. He shows that an infection acts deleteriously upon the thyroid and adrenal, and he would explain its harmful influence upon the diabetes through the stimulation of the secretions of these respective glands. Frequently. though not invariably, an infection exaggerates the symptoms of hyperthyroidism.

Tisdall, Drake and Brown[2] have shown that in young animals the ability of the animal to remove injected glucose from the blood at a normal rate was impaired by certain bacterial and chemical toxins injected subcutaneously.

[1] Lawrence and Buckley: British Jour. Exp. Path., 1927, **8**, 58.
[2] Tisdall, Drake and Brown: Am. Jour. Dis. Child., 1926, **32**, 854.

It has been very difficult in my cases to associate the onset of diabetes with an infection. Frissell-Hajek[1] believe that they traced the onset in a series of 30 cases to an infection in 6 and Strouss and Schjerning[2] believe that during the World War 45 of 2000 cases of diabetes were preceded by infections. But infections come on rapidly not gradually. In a recent painstaking analysis of successive cases of true diabetes I subsequently rechecked the type of onset of each case as recorded. In 7 cases the onset appeared quite definitely to have occurred during the course of twenty-four hours, in 24 cases it could be assigned to a definite week, in 86 cases the disease quite surely developed within a period of two months, but the onset of the disease in the remaining 383 patients was indefinite and at least could not be assigned to any two months' interval. See Table 205.

Onset.—In contrast with the above are the statistics of Adams[3] from the Mayo Clinic who reports that 317 cases of 1000 diabetic patients "could be classified as acute and in which the disease began so suddenly there could be no question as to the time. Case records were discarded when there was any question about this point. In examining these records I was constantly mindful of the possibility that a mild chronic case of diabetes might suddenly become more severe from some cause and the usual symptoms of diabetes not be forcibly brought to the patient's attention until then."

Seasonal variation as to onset of diabetes was also found to be a factor by Adams at the Mayo Clinic. Of 317 cases of "acute diabetes" he found the onset most common during the fall, winter and spring, which he attributed to the long winter season in which many persons led sedentary lives, ate more, and acute respiratory infections were more common. He also points out that "if one divides the United States at 37 degrees latitude he finds that the states above the line have a diabetic death-rate of 19.3 per 100,000 and the states below a death-rate of 8.5. It might be asserted that this discrepancy is due to the greater reliability of the mortality statistics of the northern states, but I cannot believe that this accounts for it entirely."

An infection lowers a diabetic's tolerance for carbohydrate and visibly increases the severity of the disease due, Richardson and Levine[4] believe, to an actual reduction in the amount or proportion of glucose oxidized rather than to a disturbance in the ketogenic balance. In only a few instances have I been able to associate infectious diseases with diabetes. In fact the more seriously I

[1] Frissell-Hajek: Arch. Int. Med., 1924, **33**, 230.
[2] Schjerning: Schjerning's Handbuch der artzlichen Erfahrungem im Weltkriege.
[3] Adams: Arch. Int. Med., 1926, **37**, 861.
[4] Richardson and Levine: Jour. Biol. Chem., 1925, **63**, 465.

search for them the more rarely do I find trustworthy instances. Concerning the 100 children in my series studied so carefully by Dr. White,[1] she writes: "The results of an infection may be latent, and the harmful end-results might not appear until the lapse of a period of years. For this reason in the accompanying table are represented all infections that occurred prior to onset. Two per cent did not have infections. Sixty per cent were without infections in the year preceding the onset, and in the remainder the association appears incidental rather than causal."

TABLE 71.—TOTAL INFECTIONS OF 100 DIABETIC CHILDREN PRIOR TO ONSET OF DIABETES.

	Infections in life history, per cent of children.	Infections in the year preceding onset, per cent of children.
Tonsillitis	70	15
Measles	65	10
Whooping cough	48	15
Mumps	30	10
Pneumonia	16	0
Scarlet fever	7	7
Chickenpox	7	0
Jaundice	5	0
Appendicitis	1	0

Geyelin[2] has seen only 8 cases of diabetes originating in patients within five weeks of the beginning of the infection and all of these patients were known to be sugar-free before the infection commenced. Coleman, who with DuBois has had much experience with high diets in typhoid fever, tells me that in none of their cases did diabetes develop. Barach[3] obtained a history of preceding tonsillitis more frequently in a diabetic than in a non-diabetic group of patients. Patrick[4] reports acute diabetes following mumps and Gundersen[5] states that following epidemics of mumps there is a rise in the death-rate from grave diabetes in the young age group. When one considers the frequency of infectious diseases in a community and the rarity with which diabetes develops after the same, one is not inclined to assign great importance to infections.

The loss of tolerance of carbohydrate by the diabetic during an infection is temporary, not permanent, and was recently discussed by Peters.[6] He reported several cases with striking decrease in

[1] White: Jour. Am. Med. Assn., 1927, **88**, 170.
[2] Geyelin: Annual Meeting of Connecticut State Medical Society, New Haven, Conn., 1923.
[3] Barach: Arch. Int. Med., 1927, **39**, 636.
[4] Patrick: British Med. Jour., 1924, ii, 802.
[5] Gundersen: Jour. Infec. Diseases, 1927, **41**, 197.
[6] Peters: Annual Meeting of Connecticut State Med. Soc., New Haven, Conn., 1923.

tolerance during acute illness and later a recovery of tolerance even up to 275 grams carbohydrate. With another patient tolerance successively failed following a series of infections, but this could be related to breaking diet. With adherence to diet the loss of tolerance did not disappear. I can confirm his conclusions. It is certainly significant that even in a diabetic an infection does not permanently increase the severity of the disease.

The association of acidosis with an infection was also emphasized by Peters in a considerable series of cases of diabetic coma treated at the New Haven Hospital. There was but one admission of a patient with whom a recent infection did not play a factor. According to Peters an infection in a diabetic means—go to bed.

The importance which diseases of the teeth and gums play in the etiology of diabetes is often raised. The evidence in my data is pro and con. It is a routine practice at the hospital to have the teeth of all patients promptly cared for. I have noted in taking diabetic histories that in certain cases diabetes has appeared shortly after many teeth have been extracted. Such patients are apt to take an increased proportion of carbohydrate in the diet, but they are also apt to lose weight. The coincidence is not explained.

The work of Bergey[1] in Philadelphia upon the bacterial transmissibility of diabetes has not been substantiated.

6. **Arteriosclerosis.**—The frequency of arteriosclerosis with diabetes is perhaps best explained by the increasing incidence of the disease as age advances quite as much as any effect the arteriosclerosis may have upon the blood supply of the islands of Langerhans. The longer the duration of the diabetes, the greater the degree of arteriosclerosis, and in the old the less severe the diabetes and I hope in the young as well. Arteriosclerosis is a bad enough foe of the diabetic without blaming it with the causation of his disease. (See p. 675.)

7. **Syphilis.**—See pp. 753 to 760. Syphilis is a rarity in a diabetic clinic.

8. **Trauma.**—If trauma were a factor in the causation of diabetes the war would have shown it. Above, see p. 170, attention is drawn to the infrequency of diabetes in soldiers returning from the front. My experience was not unusual. Von Noorden writes: ". . . . . neurogenen Diabetes gibt es überhaupt nicht; die Kriegserfahrungen haben ihn vollends zu Grabe getragen."[2] [3]

A definite history of trauma immediately preceding the disease was present in Cases Nos. 7 and 982 of my series. In Case No. 7 the

[1] Bergey: Proc. Soc. Exp. Biol. and Med., 1926, **24**, 229.

[2] This statement occurs in an instructive address by von Noorden before the Berlin Medical Society, December 13, 1922, and was published by Julius Springer, Berlin, 1923.

[3] Labbé is said to have "stated that he never encountered a single authentic case." Jour. Am. Med. Assn., 1927, **89**, 1886.

patient observed the first symptoms of diabetes directly after being injured by a cow. He was seen by me once on October 25, 1898, four weeks later, and died in coma five months after the onset. No record of a previous urinary examination exists. Case No. 982 was seriously hurt in his back in a foot-ball game, in the fall of 1913, and became unconscious. A broken neck was suspected. In the following January he again had a serious fall in the woods and again injured his back, so that he was incapacitated for three weeks. At the expiration of this time he observed that his mouth was dry, and in February, sugar was found in the urine. This case too, ran a rather severe course and the patient died six years after onset in coma.

Case No. 954 (See p. 167) developed the diabetes after the trauma of an operation but there were many other etiological factors present, and furthermore such an event must be extremely rare. An operation represents trauma, yet after operation even with ether for an anesthetic, diabetes is almost unknown. However, in a recent compilation of urinary reports in surgical operations upon 500 non-diabetics and non-thyroids, Middleton discovered that in 13.6 per cent the urine contained 0.1 per cent or more sugar before operation and 0.5 per cent or more after operation.

Case No. 1188 probably represents best of all the indirect harm which may result from trauma, though his case resembles most cases of the supposed influence of trauma upon diabetes by lack of evidence showing its absence before the accident. This patient was an ice-cream manufacturer in 1915, at the age of thirty-one, and weighed 242 pounds. He was in the habit of eating, in addition to his regular meals, two quarts of his own ice-cream. During the subsequent year, his weight fell to about 212 pounds, when on October 27, he was accidentally shot with a rifle, and his leg badly shattered, requiring frequent painful dressings. The urine was first examined on November 27, 1916, and sugar found. The quantity amounted to 3780 cc. and the percentage of sugar was large. Under treatment he gradually became sugar-free and acquired a tolerance for about 80 grams carbohydrate. He is (1927) alive and in good condition.

Richard T., aged thirteen years, went fishing through the ice and fell in, but was rescued by his setter dog, Laddie. That night, January 2, 1927, for the first time polyuria began, and on January 14, I found 9 per cent of sugar in the urine. On January 26, the urine was sugar-free and the blood sugar normal both before and after meals. On the preceding day the diet was carbohydrate 99 grams, protein 71 grams, fat 104 grams, insulin 10–0–5; his weight was 77 pounds, a gain of 4 pounds. On May 3 with the same dosage of insulin the blood sugar was normal, the diet was carbohydrate 101 grams, protein 74 grams, fat 117 grams; the weight 85½ pounds.

The fracture of an extremity is often accompanied by glycosuria. Among 61 cases at the Surgical Clinic at Kiel, 24 showed alimentary glycosuria, and in 3 unsuspected diabetes was discovered. Hyperglycemia was present in 31 out of 36 of the cases examined.[1] It would not seem strange if many of the cases of diabetes following trauma might be due to the enforced idleness and rest combined with forced feeding at the hands of friends.

9. **Hypophysis.**—The intimate relation of the hypophysis to glycosuria and diabetes has been emphasized by Cushing and is described in detail by him.[2] I have encountered but 4 instances, Cases Nos. 1155, 3620, 5457 and 5520.

10. **Liver.**—The connection between diseases of the liver and diabetes has been frequently pointed out. Such an association is only demonstrable in my cases with gall stones. Out of 609 deaths there have been only 6 who have died in which cirrhosis of the liver appeared to figure as a cause of death and but 3 of cancer of the liver. The 199 cases (Table 207, p. 542) in which gall stones have been a factor perhaps should be credited etiologically to the pancreas.

The liver is assuming more and more the prominent role which it played in diabetes in the time of Claude Bernard. Its influence for good or evil, perhaps measured by the amount of glycogen which it stores, is more and more acknowledged. Perhaps the great "factor of safety" which the liver possesses because of its size, hides its importance in the etiology of diabetes. The development of hypoglycemia, following metastases to the liver of a cancer which originated in the islands of Langerhans, as reported by Wilder,[3] is unique. Klein[4] observed an accentuation of the hypoglycemic action of insulin in diffuse, marked liver affections and in chronically decompensated heart cases. On the other hand in jaundice diabetes may become milder, but possibly because less food is assimilated. Case No. 6068.

All our ideas relating to the liver in diabetes may need to be revised in consequence of Loewi's discovery of glycemin which he considers to be the cause of diabetes. (See p. 105.)

11. **Thyroid.**—The thyroid gland is intimately concerned with sugar metabolism by physiological experiment, by pathological investigation, and by clinical experience. Hyperthyroidism precedes diabetes so much more frequently than diabetes precedes it that its place in diabetic etiology is assured.

To avoid repetition the subject of the thyroid and diabetes and the treatment, both medical and surgical, of the diseases when combined are discussed in one chapter. (See p. 878.)

[1] Konjetzuy and Weiland: Jour. Am. Med. Assn., 1915, **65**, 2264.
[2] Cushing: The Pituitary Body and its Disorders, Philadelphia, 1912, Lippincott.
[3] Wilder: Mayo Foundation, Proceed. Staff Meetings, 1927, **2**, 88.
[4] Klein: Med. Klin., 1927, **23**, 312.

12. **The Sex Glands.**—Diabetes reaches a peak in childhood at twelve years, puberty, and in adults another peak at forty-nine years, the menopause. With the general prolongation of life of men and women above the age of forty-five years, the incidence of sex in diabetes has been reversed and today universal astonishment

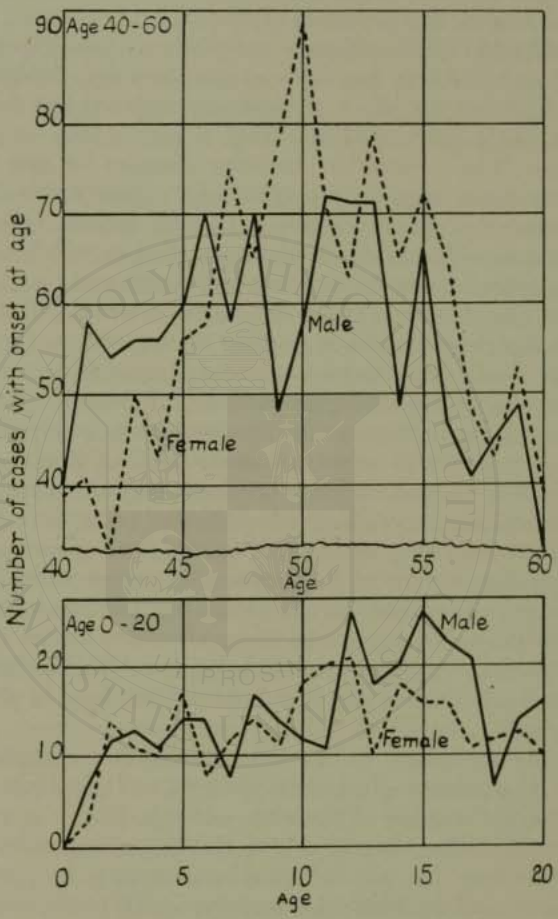


FIG. 19.—Sex and the onset of diabetes in youth and middle life.

is manifested that more women than men have the disease as well as die of it. May this not be related to the cessation of sexual activity in women?

The age at onset of diabetes is of more significance in etiological discussions than the age at its end. In Fig. 19 are recorded the curves of onset by years of all males and females in my series between

the ages of one and twenty years, as well as between forty and sixty years. The sudden rise and fall of incidence is shown for both sexes, but it is both more abrupt and reaches greater heights for females.

Puberty begins for girls at an earlier age than for boys. It might be expected that here again the incidence of diabetes would vary with sexual disarrangement. Such, however, did not occur in our series, the "peak" ages at onset of diabetes in boys being twelve and fifteen years and in girls twelve years.

Directly or more likely indirectly changes in the functions of the organs of sex are related to the onset of diabetes.

13. **Gout.**—Gout is frequently mentioned as a precursor or companion of diabetes. So seldom has this occurred in my experience that I cannot attach much importance to it. Dr. J. H. Pratt, of Boston, who has seen an unusually large number of cases of gout, assures me that in but one instance was sugar found in the urine of his patients.

Seckel[1] writing upon the basis of the cases in Umber's Clinic in Berlin believes the relationship of the trilogy diabetes, obesity, and gout still stands. Rabinowitch writes me that one of his diabetics has gout, and though he is severe enough to require insulin, its use precipitates an attack.

14. **Epstein's[2] Theory.**—The causal mechanism of diabetes is conceived by Epstein to be as follows: Changes in the permeability of the capillary vessels can result in the passage of trypsin into the blood stream, and its ultimate entry into the liver via the portal circulation. The first effect of the mobilization of trypsin is a glycogenolysis with a consequent hyperglycemia and glycosuria; the second is the neutralization of insulin secreted into the blood stream, thereby causing a deficiency of active insulin.

G. IMPROVEMENT IN TREATMENT STATISTICALLY PROVED.

When I began the treatment of diabetic patients I actually recorded the duration of their lives in days and even as late as 1916 in my book of tabulations the duration was recorded in months; then it changed to years; but now it is safe to say the average diabetic will not die during the decade in which he is born. It was a wonderful advance toward the close of the Allen Epoch in 1922 to register an increase of 25 per cent in the duration of diabetic lives, bringing this up to six years from the 4.8 years of the Naunyn Era. Since the commencement of the Banting Era it has progressed again and is now between seven and eight years. And what shall we say of

[1] Seckel: Ztschr. f. klin. Med., 1925, **102**, 195.
[2] Epstein: Jour. Am. Med. Assn., 1925, **85**, 29.

those children who have already reversed the old diabetic law that "the older a diabetic, the longer he lives" to the natural law of life!

For the successful treatment of a chronic disease it is essential that the physician be convinced that his methods of treatment are improving. In diabetes mellitus there has been no doubt about this improvement. Various factors have contributed to to bring about this result and of these an earlier diagnosis, a more general knowledge of the diet, a clearer understanding of the disease, including the prevention of coma, the far better treatment of surgical complications, and insulin are responsible.

Success in the treatment of diabetes as well as of tuberculosis depends on an early diagnosis. Naunyn urged the importance and good results of early treatment. All will agree, we are in a much more favorable position to make early diagnoses now than were the physicians of a former generation. Yearly urinary examinations and life insurance examinations help much. When a routine urinary examination is neglected, the damage done to the patient is considerable, but to the physician's reputation it is extreme. *The physician is never forgiven.*

For comparative purposes the duration of life of diabetic patients for four periods at the Massachusetts General Hospital are of especial value and are shown in Table 72. The first period includes all cases from the beginning of the records of the hospital in 1824 to 1898, the second from 1898–1913. The third period (1913–1916) represents the transition to the period of treatment by undernutrition as introduced by Allen, and the fourth brings the data up to date. For the data of the first period I am responsible,[1] for the next two periods my former secretary, Miss Helen Leonard and my former assistant, Dr. F. Gorham Brigham, and for the last as well as for the privilege of using all the data I am indebted to the Superintendent, Dr. Frederic A. Washburn, and the Chief of the Medical Staff, Professor James H. Means.

During the first seventy-four years subsequent to the founding of the Massachusetts General Hospital 172 diabetic patients were treated and 47 or *27 per cent* died within the hospital walls. Of the total number of 280 diabetic patients treated during the second period, 1898–1913, 79 or *28 per cent* died. This is approximately the same percentage, 25.8 per cent, which Seckel[2] records for the 430 cases in Umber's Clinic at the City Hospital in Berlin for the years 1912–1924, but since 1922 at the Massachusetts General the mortality has dropped to 10 per cent of the cases treated. The

[1] Fitz and Joslin: Diabetes Mellitus at the Massachusetts General Hospital, 1824–1898, Jour. Am. Med. Assn., 1898, **31**, 139.

[2] Seckel: Ztschr. f. klin. Med., 1925, **102**, 195.

fall in mortality in the first year from 32.7 per cent to 9.1 per cent is notable in Seckel's statistics, and at the Massachusetts General it has dropped from 67.5 to 17.8 per cent. The first year of diabetes is still the "danger zone" in a large hospital and city, although this is no longer true in a private series. Since 1898 the duration of the disease in fatal cases of diabetes at the Massachusetts General Hospital has risen from 1.2 to 5.1 years, and best of all this increase in duration has been progressive.

TABLE 72.—DURATION OF LIFE OF DIABETICS WHO DIED AT THE MASSACHUSETTS GENERAL HOSPITAL BETWEEN 1824 TO 1917 AND 1922 TO 1926.

Duration, years.	1824–1898.		1898–1913.		1913–1917.		1922–1926.	
	No. of cases.	Per cent.	No. of cases.	Per cent.	No. of cases.	Per cent.	No. of cases.	Per cent.
0– 1	27	67.5	28	40.6	10	47.6	8	17.8
1– 2	7	17.5	13	18.8	1	4.8	6	13.3
2– 3	3	7.5	6	8.7	2	9.5	2	4.4
3– 4	1	2.5	6	8.7	..	..	9	20.0
4– 5	..	..	2	2.9	3	14.3	3	6.7
5– 6	1	2.5	5	7.2	2	9.5		
6– 7	1	2.5	1	1.4	1	4.8	1	2.2
7– 8	..	..	2	2.8	..	..	6	13.3
8– 9	..	..	..	..	..	..	2	4.4
9–10	..	..	1	1.4				
10–11	..	..	1	1.4	1	4.8	4	9.1
12–13	..	..	..	..	..	..	2	4.4
15–16	..	..	1	1.4	1	4.8	1	2.2
16–17	..	..	2	2.9				
20–21	..	..	1	1.4	..	..	1	2.2
Unknown because of lack of past history	7		10		6		10	
Total deaths	47		79		27		55	
Percentage of diabetics treated	27		28		11		10	
Average duration, years	1.2		3.1		3.3		5.1	

The fall in mortality during the first year, namely, from 67.5 to 17.8 per cent, is a striking commentary on the improvement in diabetes in a large hospital. During the third period 243 cases of diabetes were treated at the hospital and the number of deaths was 27 and the percentage mortality was *11*. In the insulin period the number of cases treated has been greatly augmented and in general their severity has increased, because they have been selected on this account from the immense number of diabetic patients who visit the Out-Patient Department. The average duration of the disease has risen to 5.1 years from the 1.2 years prior to 1898.

The duration of life of the fatal cases of diabetes occurring in Boston for the period 1895–1913, for 1915, and for 1925 are given in Table 74. Between 1895–1913 in Boston the average duration of the disease was 3.3 years, for 1915 it was 4.3 years, but in 1925 it was 5.1 years.

Heiberg has published a table which gives the duration of life of fatal cases of diabetes in Denmark. This table does not give comparative figures for different years but shows the duration for different age groups. Thus between the ages of fifteen and thirty years 25 per cent of the cases were dead at the end of six months and 100 per cent dead in fifteen years.

TABLE 73.—THE DURATION OF LIFE IN FATAL CASES OF DIABETES. (HEIBERG.[1])

Sex	Age.	25 per cent, years.	50 per cent, years.	75 per cent, years.	100 per cent, years.
Males	15–30	½	1½	2½	15
	31–50	1½	3	4½	20
	51 and over	1¾	4¼	9	20
Females	15–30	¾	1½	2½	10
	31–50	1	2	3¾	15
	51 and over	1½	3½	7½	20

Von Noorden[2] writing in 1917, and unfortunately no additional statistics from his clinic are reported by von Noorden and Isaac, says that diabetes in children under ten years of age seldom lasts more than for one and a half or two years; in the second decade it seldom exceeds two to four years; in the third decade four to six years, occasionally even ten years, but seldom longer. People who acquire the disease after the thirtieth year have a considerably greater length of life, and with favorable conditions the disease may last from ten to fifteen years or even longer. The first half of the fifth decade, however, is a more critical period, but when this corner is passed the tendency of the disease is to remain mild, provided doctor and patient are free from blame themselves. Such patients may live fifteen, twenty or even thirty years. Still, a length of life of more than twenty years is exceptional.

Before recording my own data I wish to acknowledge the aid received from numberless doctors and patients and many ingenious secretaries and medical students who at least pretended to fall in love with the task, Registrars of Boards of Health, and the War Department, who have helped me trace 95 per cent of the 4973 patients who consulted me on account of diabetes up to July 1, 1926. Upon page 548, in the discussion of the classification of diabetes, will be found the dates when these patients were first seen,

[1] Heiberg, K. A.: Ztschr. f. klin. Med., 1921, **92**, 76.
[2] Von Noorden: Die Zuckerkrankheit, Berlin, 1917, 7th ed., p. 342.

the numbers and percentages of each group, true diabetics, potential diabetics, renal glycosurics, and unclassified cases, and for each group the number traced to death or to July 1, 1926. All of the 395 children were found—the last, Ettie G., Case No. 2124, in Los Angeles.

TABLE 74.—DURATION OF LIFE OF 1144 FATAL CASES OF DIABETES IN BOSTON DURING 1895 TO 1913, AND IN 1915 AND 1925.

Duration, years.	1895–1913.[1]		1915.		1925.	
	No. of cases.	Per cent.	No. of cases.	Per cent.	No. of cases.	Per cent.
0– 1	309	32.7	32	27.3	15	17.2
1– 2	207	21.9	16	13.6	12	13.7
2– 3	102	10.8	18	15.3	11	12.6
3– 4	56	5.9	5	4.2	10	11.4
4– 5	71	7.5	8	6.8	5	5.7
5– 6	26	2.6	14	11.9	7	8.0
6– 7	24	2.5	2	1.7	1	1.0
7– 8	30	3.2	3	2.5	6	6.9
8– 9	8	0.8	3	2.5	2	2.3
9–10	59	6.3	1	0.8	1	1.0
10–11	4	0.4	4	3.4	9	10.3
11–12	8	0.8	1	0.8	1	1.0
12–13	4	0.4	3	2.5	2	2.3
14–15	17	1.8	2	1.7		
15–16	4	0.4	2	1.7	2	2.3
17–18	3	0.3	1	0.8	2	2.3
18–19	..	..	..	..	1	1.0
20–30	8	0.8	2	1.6		
	940		117		87	
Duration long, but uncertain	207		20		21	
Unknown	567		54		46	
Diabetic gangrene	50	0.3	4	2.1	10	6.9
Total deaths	1764		195		164	
Average duration (years)	3.3		4.3		5.1	

Expense in the collection of private diabetic records I hope is justified, because only in this way are complete data about diabetics available. They will become increasingly valuable as time goes on because more and more will diabetics die after long duration and growing mildness of the disease under diagnoses which will hide the original disease. Such collections are valuable most of all to the one who treats the patients and to the patients themselves.

[1] Morrison: Boston Med. and Surg. Jour., 1916, **175**, 54.

TABLE 75.—DURATION OF LIFE IN FATAL CASES OF DIABETES ARRANGED IN DECADES.

Decades of onset, years.	Before June, 1914.		June, 1914, to March 16, 1922.		March 16, 1922 to July 1, 1926.	
	No. of cases.	Duration, years.	No. of cases.	Duration, years.	No. of cases.	Duration, years.
0– 9	25	1.2	47	2.7	16	2.7
10–19	39	2.9	69	3.3	48	2.9
20–30	80	3.9	162	5.3	114	6.9
40–59	137	6.9	216	8.1	344	8.4
60–89	50	4.5	103	6.1	134[1]	5.4
Total	331	4.8	597	6.0	656	7.0

The average increase in duration of life of the diabetic today over that of the Naunyn era is 2.2 years, or 45 per cent. But this does not represent the true change in longevity, because it is the old, not the young, diabetic who is dying. The proportionate number of deaths in the early decades has greatly decreased. In the Naunyn epoch the deaths of those with onset in the first decade constituted 7.5 per cent of the total number; in the present epoch they constitute only 2.5 per cent. In the Naunyn epoch the deaths of those with onset at over forty years were 57 per cent, they are now 73 per cent. In the Naunyn epoch the average age at death was 44.8 years, but in the Banting era 54.2 years. The average age of the 60 patients who died from among the 1138 treated during the year ending July 1, 1926, was fifty-nine years.[2] This is ten years above the average age at death of the citizens of Massachusetts and a year above that of the expectation of life of the new-born child.

It is interesting to compare this advancing age at death with the figures of the Metropolitan Life Insurance Company for their industrial policyholders. Their life expectancy has risen nine years in the past thirteen years; that of my diabetics has risen 16 years in about the same period. The median age at death from diabetes in the registration area of the United States was 57.1 years in 1900 and 60.6 years in 1920. The corresponding figures

[1] One case duration unknown, making total deaths, 657.

FOOTNOTE:—The figures in Tables 75, 76 and 79 differ slightly, first because in the compilation of statistics new reports of old cases would be received after a table was completed, dates of periods were sometimes changed from March to June, July, or August for special reasons and finally in Table 79 for the first time in calculating durations of life the midyear was employed rather than the actual number of years and months. Thus in the Naunyn Epoch there were 61 cases who lived less than a year and their average duration was estimated as 0.5 year.

[2] 60.9 years for the fatal cases during the year ending July, 1927.

for male diabetics were 57.4 and 59.5 years and for female diabetics 56.9 and 61.3 years respectively.[1]

In Table 76 the deaths and durations of the fatal cases in the Banting era are given in detail by decades. The interval covered by the deaths of the patients is slightly different from the Banting group in Table 79. The table comprises 600 cases in contrast to 656 in Table 75. First of all one is struck by the small number of

TABLE 76.—DURATION OF LIFE OF 600 FATAL CASES, AUGUST, 1922 TO AUGUST, 1926.

Decade.	No. of cases.	Duration, years.
0– 9	14	2.5
10–19	38	3.3
20–29	49	4.5
30–39	57	9.3
40–49	152	9.8
50–59	163	8.1
60–69	100	5.8
70–79	27	4.0
Total	600	7.4

TABLE 77.—DECREASE IN DEATHS DURING FIRST YEAR OF THE DISEASE.

Massachusetts General Hospital.	Total deaths.[2]	Deaths, first year, per cent.
1824 to 1898	...	68
1898 to 1913	21	41
1913 to 1917	...	48
1922 to 1926	...	..
Boston.		
1895 to 1913	...	33
1913 to 1915	...	27
1915 to 1925	...	9
Author's series.		
1898 to 1914	338	18
1914 to 1922	806	9
1922 to 1926	600	5

cases in the early decades as compared with former periods. It is misleading in this regard. It simply shows that the youthful diabetic is living not dying. If the living cases for the first decade could be included the duration would almost double. The peak of duration 9.8 years is reached in the fifth decade and this is the highest duration yet achieved by the average patient in any decade of any series thus far.

A better idea of the future duration of the diabetics' life is shown by the living children. Among 435 cases there are 12 or 2.3 per cent, 3 dead and 9 living, who have survived diabetes more than a decade

[1] U. S. Census Mortality Rates, 1910–1920, p. 139.

[2] In the series of the Massachusetts General Hospital and City of Boston, the duration of many cases was unknown, hence the comparatively small number.

and no doubt exists about the accuracy of the diagnosis of 10 of these cases. The statment, therefore, is justified that with children even with old methods there were between 1 and 2 per cent who lived more than ten years. It so happens that this is about one-half the percentage of adults who have lived over twenty years, namely, 161 cases in the first 5086 true diabetics (see p. 896) coming to me for treatment. But the increase in duration of life of the child is progressing far more rapidly than in the adult. Diabetes begins so late in life that it is clear the old conceptions of its relations will be reversed. Today the young diabetic will be the long-lived diabetic, and the old diabetic will have the shorter duration.

The prolongation of life in my own series of cases is manifest just as in the Boston series. Prior to June, 1914, my Naunyn epoch, the average duration of life of 338 of my fatal cases was 4.7 years; between June, 1914 and August, 1922, the Allen epoch, for 806 fatal cases it was 5.4 years; and from August, 1922, to July 1, 1926, the Banting epoch, for 656 fatal cases it has been 7.0 years.

The number of diabetic individuals who have lived in excess of the space of years attained by my entire group of fatal cases is considerable. Thus in seeking material for investigation of the subject of arteriosclerosis in diabetics 934 cases, living or dead, were found who had had the disease ten years or more up to July 1, 1926. (See p. 675.)

As a matter of historical interest Table 78, compiled in 1916, is inserted, and, though not exactly comparable, somewhat similar data compiled in 1926 are added to it. The new compilation is made up of true diabetics, whereas in 1916, 10 per cent of the cases may have been potential diabetics, renal glycosurics, and unclassified glycosurics.

FIG. 78.—VITAL STATISTICS OF DIABETIC PATIENTS ARRANGED ACCORDING TO PERIODS WHEN FIRST OBSERVED, IRRESPECTIVE OF PREVIOUS DURATION. DATA COMPILED IN 1916 AND 1926.

Period first observed.	1916.[1] Total cases traced.	Alive.	Per cent.	1926.[2] Total cases traced	Alive.	Per cent.
1893–1900	17	1	6	17	0	0
1901–1905	86	12	14	79	3	4
1906–1910	263	82	31	237	32	14
1911–1915	551	329	60	495	96	19
1915–1916[3]	239	216	90			
1916–1920	...	...	..	878	331	38
1921–1925	...	...	..	2394	1797	75
1925–1926[3]	...	...	..	570	531	93
Total	917	424	46	4100	2259	55

[1] Case Nos. 1 to 1208, of whom 1090, 90 per cent, were true diabetics.

[2] Case Nos. 1 to 5726, of whom 4869, 85 per cent, were true diabetics, and only these true diabetics are included in this series.

[3] Not included in final average.

TABLE 79.—THE INCREASING DURATION OF LIFE IN DIABETES, BASED UPON FATAL CASES AT DIFFERENT PERIODS.

Duration.	Naunyn.		Allen.		Banting.	
	Cases.	Per cent.	Cases.	Per cent.	Cases.	Per cent.
0– 1	61	18.1	70	8.7	32	5.3
1– 2	51	15.1	105	13.0	61	10.2
2– 3	54	15.9	110	13.6	60	10.0
3– 4	31	9.2	92	11.4	60	10.0
4– 5	22	6.5	70	8.7	55	9.0
5– 6	21	6.2	49	6.1	31	5.0
6– 7	12	3.6	41	5.1	23	3.8
7– 8	10	2.9	48	6.0	34	5.7
8– 9	12	3.5	42	5.2	28	4.7
9–10	13	3.8	22	2.7	28	4.7
10–11	8	2.4	24	3.0	26	4.3
11–12	12	3.5	18	2.2	29	4.8
12–13	9	2.7	26	3.2	22	3.7
13–14	5	1.5	12	1.5	19	3.2
14–15	1	0.3	12	1.5	17	2.8
15–16	6	1.8	12	1.5	16	2.7
16–17	2	0.6	16	2.0	13	2.2
17–18	2	0.6	2	0.2	13	2.2
18–19	2	0.6	3	0.4	7	1.2
19–20	..	...	6	0.8	5	0.8
20 on	4	1.2	26	3.2	22	3.7
Totals	338		806		600	
Average duration (years)	4.7		5.4		7.7	
Average age at death,	339 cases, 44.8				607 cases, 54.2.	

The detailed duration of life of my 1744 fatal cases arranged in successive periods is shown in Table 79. The decrease in mortality during the first, second and third years of the disease of these cases for successive epochs is definite. Particularly encouraging is the fall in mortality in the first year from 18.1 per cent in the Naunyn epoch to 5.3 per cent in the Banting epoch. But the table discloses the grim fact that even since the introduction of insulin every other diabetic has died before the fifth year of his disease was completed. However, 12.8 per cent live over fifteen years in contrast to 4.8 per cent in the Naunyn period. Finally the table teaches that today's problem is to learn to treat the diabetic who has already lived for more than five years.

The treatment of diabetes in the past has been largely concerned with the problem of diabetes, but more and more in the future the physician will have the privilege of dealing with a highly trained patient anxious to avoid not only the unpleasant sequelæ of his disease but all the ills to which flesh is heir. Diabetes is a good disease and the treatment of it is broadening for the physician.

H. THE CURABILITY OF DIABETES.

The course of diabetes occasionally ceases during the lifetime of an individual. Both Naunyn and von Noorden believe that a diabetic patient may recover. I am unwilling to state that any of my patients have been cured. Harrison[1] is fully as conservative and even goes so far as to deny even a partial remission of the disease, but with this I cannot agree. Many patients, 50 or more of my series, say they are cured, but by that they mean they are in good health. They forget they are living on a partially restricted diet. It will be desirable after investigation to report such cases, because there are already a large number. One must remember that diabetes is at times temporarily latent. The term "arrested" instead of "cured" has found general acceptance in the literature of tuberculosis, and it is equally appropriate in diabetes. It is better for the present to take the conservative standpoint and be very slow to report cured or even arrested cases. One is constantly being told of patients who have been "cured," of which proof does not exist. It should be remembered that a sugar-free urine and a normal blood sugar do not constitute a cure; both should be normal for years.

One of my friends, who reported the disappearance of diabetes in certain cases, will publish a sequel to his former article in order "to show how little one can bank on a temporary condition. 'Once a diabetic, always a diabetic,' I believe is the best rule to stick to no matter how much improvement."

Carrasco Formiguera[2] mentions the son of a diabetic who showed sugar during an infection with a furunculosis. Under scrupulous treatment and a free diet, save actual sugar, he remained free from hyperglycemia or glycosuria. My fat carbuncle patient, Case No. 5872, has done almost as well. This is the type of case which should be watched for a decade. Why should we not demand, as in cancer, a ten-year period of freedom from symptoms before we say "cured?"

The duration of the disease was fifteen or more years in 1917 with 62 cases, or 6 per cent of the then total number, and now in 1927 there are 51 patients, or 1.0 per cent of the total, who have lived over twenty-five years. Yet few, if any, of these long living diabetics are cured, though perhaps 39.6 per cent, according to A. A. Hornor who has studied the protocols for me, may be considered controlled. Even if the disease has subsided so far as glycosuria

[1] Harrison: Quart. Jour. Med., 1926, **19**, 223.

[2] Carrasco Formiguera: Footnote, Joslin: Tratamiento de la Diabetes Sacarina, Montaner y Simon, Barcelona, 1925, p. 154.

and hyperglycemia are concerned, its complications remain in most instances. I was disappointed to find no actual cure among the 75 cases of hyperthyroidism associated with diabetes.

Innocent Diabetes.—Brugsch,[1] and more recently Holst,[2] have described benign glycosuria in diabetic families. Holst means by this term, alimentary glycosuria and renal glycosuria. This is in a way depressing, because it implies that the benign and malign glycosurias are branches of the same tree. I have always suspected this, indeed feared it for my own patients whom I have described as "unclassified" glycosurias, potential diabetics, and renal glycosurics, but as yet have not proved it. Time will tell, but at present my data only allow the statements recorded on pages 549, 551 and 552. Holst is to be congratulated upon the length of time his cases of benign glycosuria were under observation before he reported them as such.

Campbell[3] reports cases of so-called innocent diabetes. I take it that this group corresponds closely with the group which I call for safety's sake potential diabetes. John[4] has also written upon the spontaneous disappearance of diabetes. Von Noorden[5] says: "Almost every diabetes starts as alimentary glycosuria. Alimentary glycosuria is always a sign of real diabetes." I do not consider any diabetes innocent.

Many of these I suppose resemble my Case No. 1686, who between August, 1921, and March, 1926, was free from glycosuria upon 19 examinations, and none of the 19 blood-sugar tests rose above 0.15 per cent, usually being considerably lower. Diet was then relaxed and glycosuria returned to the extent of 0.1 and 0.5 per cent with hyperglycemia of 0.22 and 0.24 per cent at one hour and one and a half hour after meals, respectively.

Recovery is possible in three types of cases as described by Allen:

1. **Acute Diabetes Arising from Curable Causes.**—It is quite possible that diabetes which has followed trauma might subside, either with or without operation. Recognizing the hyperglycemia which occurs in the course of infectious diseases, it is easy to understand that in a few cases glycosuria may develop, last several days, and after recovery from the infectious disease may disappear. Schmitz's remarkable case, already described on p. 146, might come under this heading and I hope Case No. 203, p. 188, will prove to be of this type. See also Case No. 1139, p. 165, who resembles very closely the patient of Schmitz. I consider Case

[1] Brugsch: Ztschr. f. artzl. Fortbildung, 1924, **21**, 586.
[2] Holst: Arch. Int. Med., 1926, **38**, 279.
[3] Campbell: Jour. Am. Med. Assn., 1924, **82**, 1990.
[4] John: Jour. Am. Med. Assn., 1925, **85**, 1629; Med. Jour. and Rec., 1925, **122** (Supp.), 739.
[5] Von Noorden: Jour. Am. Med. Assn., 1923, **80**, 968.

No. 1139 about the best case of this type which I have seen. Undoubtedly more cases of this nature will appear as time goes on because of the frequency of urinary examinations during the infectious diseases of childhood. In fact so many of these began to appear in my records that it necessitated the reclassification of the entire number for this fourth edition.

Local infections in the neighborhood of the pancreatic gland, for instance those accompanying pancreatitis and gall stones, might give rise to a temporary diabetes. Thus Case No. 18, first seen by me in 1900, was treated for diabetes for years by my friend, Dr. Pfaff, and lived conscientiously upon a diet. After an interval of fifteen years, I saw her again and found the urine free from sugar, and it remained so until her death in 1922, save when her gall stones were removed in 1919.

Syphilis might be expected to furnish cases of diabetes with recovery, but no clear-cut case of this kind has developed in my series. (See p. 753.)

2. **Exceptional Cases in Childhood.**—A considerable number of cases of mild or temporary diabetes in children is beginning to appear in the literature, just as in my records. It is not easy to decide whether diabetes originally existed. (See Riesman, already cited, p. 146.) Case No. 203 of my series is instructive. This little boy first showed sugar at the age of seven, in 1908, although symptoms were present the preceding year. His mother has diabetes and is Case No. 155 having come for consultation in 1907. He was promptly put upon a careful diet by his mother and physician, Dr. Warren White, of Roxbury, Massachusetts, and has remained sugar-free during the subsequent nineteen years. He was very faithful to his diet and remains in good condition. By advice he is purposely keeping a trifle underweight, eating a normal diet save for less sugar. When his mother had had diabetes sixteen years, she "would not touch sugar any more than she would poison." Due to her faithfulness she is still living happily in 1927.

Von Noorden reports a striking case of a boy, aged seven years, who, on a strict diet, constantly excreted 20 to 30 grams of sugar and considerable quantities of acetone bodies. He became sugar-free only with the help of oatmeal and vegetable days. He remained on this restricted diet for some years and at the age of twelve years was again seen by von Noorden, when he was in perfect health, eating an ordinary diet without a trace of glycosuria.

3. **Diabetes Associated With Organic Diseases.**—This group is subdivided by Allen into (1) those cases with nervous disorders, such as the cases described by Naunyn in association with tabes; (2) cancer involving the pancreas which may be followed by the disappearance of sugar. No instance of this kind has occurred

in my practice, though it is readily understood through the development of undernutrition in the patient (see p. 751); (3) neither has cirrhosis of the liver been observed to replace diabetes, such as Claude Bernard and Lepine describe;[1] (4) on the other hand, with the development of severe nephritis, diabetes has ceased in a few cases, notably Case No. 354. In Cases Nos. 457 and 872 it developed; (5) the fifth group mentioned by Allen is tuberculosis. Naunyn and many other writers have observed the subsidence and disappearance of the disease following tuberculous infection. In Case No. 344 of my series (see p. 748) the severest degree of diabetes, as shown by the urinary analyses for December 25–26, 1911, changed its character entirely, as proved by the urinary reports of March 17–18, 1912. During the interval pulmonary tuberculosis broke out and advanced rapidly. Weight decreased from 147 pounds to the neighborhood of 80 pounds, and the patient died without acidosis. Many diabetics are cachectic at the time of death, but this condition has by no means modified the disease. On the other hand, when cachexia, due to a cause other than diabetes, occurs in a diabetic, it may be responsible for improvement in the diabetes.

[1] See a forthcoming article by Dr. James Bordley upon this question.

SECTION IV.

PHYSIOLOGY AND PATHOLOGY.

A. BLOOD SUGAR.

1. **The Blood Sugar in Health and Diabetes.**—The blood sugar of normal individuals fasting, *i. e.*, before breakfast, is most frequently 0.10 per cent. It varies from about 0.08 per cent to 0.11 per cent and it may vary in the same individual at different times.[1] Reports upon percentages of sugar in the blood also vary in accordance with the method employed. The Folin-Wu method gives results which are lower than the Benedict method, which in turn is higher than the Bang or Hagedorn methods.

Normal values for the blood sugar according to various methods are shown in Table 80, and in Table 81 are recorded estimations of the percentage of sugar in three specimens of blood by four different methods.

TABLE 80.—THE BLOOD SUGAR. NORMAL VALUES ACCORDING TO DIFFERENT METHODS.

	Per cent.
Bertrand method	0.07 –0.11
Hagerdorn and Jensen	0.09 –0.11
Bang-Hatlehol	0.09 –0.11
Folin-Wu	0.085–0.111[2]
Shaffer-Hartman	0.09 –0.11
Lewis-Benedict	0.096–0.125[2]
Myers-Bailey	0.083–0.122[2]

TABLE 81.—COMPARATIVE PERCENTAGES OF SUGAR IN THE BLOOD ACCORDING TO METHOD OF ANALYSIS.[3]

Method.		Per cent glucose. 1	2	3
Titrimetric	Bang	0.097	0.118	0.145
	Hagedorn	0.091	0.124	0.159
Colorimetric	Benedict	0.118	0.151	0.198
	Folin	0.105	0.121	0.188

[1] Stammers: Phys. Reviews, 1926, **6**, 630.
[2] Byrd: Jour. Lab. and Clin. Med., 1927, **12**, 609.
[3] Höst and Hatlehol: Jour. Biol. Chem., 1920, **42**, 347.

On account of these differences in percentage of the blood sugar with various methods I believe it unwise to cumber clinical statistics with records to the third decimal place.

Blood-sugar values as reported by European observers are quite generally lower than the values obtained by the usual methods employed in the United States. The original Benedict picric acid method is now seldom employed. It gives the highest results and pure picric acid is difficult to obtain, although Dr. Benedict writes me that dependable results can be obtained if the acidity of the precipitating solution is carefully adjusted. It is generally conceded that nearly all the methods routinely used for blood-sugar determinations yield figures which are definitely too high for the true glucose content of the blood. The new Folin[1] copper method is probably the most accurate so far available as indicating true glucose content but it is as yet not simple enough for routine use.

Agreement has not been reached as to the nature of the sugar in the blood. Folin and Svedberg[2] have recently produced evidence to show that the blood contains a fermentable sugar in addition to glucose. It is most abundant in diabetics with high blood sugar. The existence of sugar in the blood in the form of γ-glucose[3] has not received general support, and neo-glucose has had the same fate.[4]

In diabetes the percentage of sugar in the blood is increased. Adequate data for the fasting blood sugar in diabetics are not available, because nearly all patients have undergone more or less treatment when they come for examination. With 722 diabetics examined in my office or at the hospital, the average percentage of sugar in the blood fasting was 0.21 per cent, and with 619 diabetics at varying times of the day, not fasting, the average was 0.19 per cent.[5] Under treatment the blood sugar may fall to below normal,[6] reaching as low a value as 0.017 per cent (Herman[7]) shortly before death. During an insulin reaction in a child Millard Smith[8] noted the complete disappearance of sugar from the blood and yet recovery took place. He states that all precautions were taken to check the Folin-Wu reagents employed. In a few cases fasting values are obtained above 0.40 per cent. There were 6 such in my series among 694 successive diabetics upon first coming for treatment.

[1] Folin: Jour. Biol. Chem., 1926, **67**, 357.
[2] Folin and Svedberg: Jour. Biol. Chem., 1926, **70**, 405.
[3] Winter and Smith: Jour. Physiol., 1923, **57**, 100.
[4] Krogh: Jour. Biol. Chem., 1927, **74**, 393.
[5] Gray: Med. Clin. of North America, 1923, **7**, 675.
[6] Joslin: Med. Clin. of North America, 1921, **4**, 1723.
[7] Herman: Personal communication. See p. 219.
[8] Smith: Boston Med. and Surg. Jour., 1926, **195**, 663.

As a rule, such cases are on the verge of coma, complicated with nephritis, or, as in Case No. 1015, associated with suppression of urine. (See p. 213.) Argy reports a value of 1.71 per cent in coma (see p. 651) while those of my Cases No. 1015, fatal, and 4099, recovery, were 1.49 per cent and 1.62 per cent respectively. Rabinowitch writes me he has just had a case with blood sugar 1.42 per cent. John in a series of 1000 cases of diabetes found the highest percentage of blood sugar upon admission to the hospital to be 0.908 per cent. These are the highest values I have seen either in my own cases or in the literature. I cannot agree with Petrén who considers the case severe when the percentage of sugar in the blood is above 0.24 per cent. Thus, in an analysis of 2000 cases of diabetes on admission to treatment, John[1] found 55 per cent of the patients with a blood sugar of 0.25 per cent or over, and in my series of 694 consecutive cases there were 50 per cent above 0.20 per cent. (See p. 224.)

A high blood-sugar value does not necessarily mean that the patient will be better off if it is reduced promptly to normal. Such a procedure might be as undesirable as to lower a blood-pressure of 200 or over to normal in the same space of time. Who would really wish to attempt it? The depancreatized dogs live very comfortably with a high blood sugar.[2]

The plasma gives slightly higher figures than the whole blood. Thus far all of our analyses have been with the whole blood.

It is easier to state what constitutes a normal blood sugar than to specify how abnormal a blood sugar must be to prove the presence of diabetes. My personal classification of diabetes in so far as it is dependent upon the blood sugar is based upon a fasting blood sugar of 0.14 per cent or over and a blood sugar of 0.17 per cent or over after food. A potential diabetic would find a place between these and the normal values. In the diagnosis of diabetes and thyroid disease I raised the values, in order to exclude a multitude of cases, to 0.17 per cent fasting and 0.20 per cent after operation. With such boundary lines there are enough diabetics to treat.

(*a*) **Sugar in Plasma and Corpuscles.**—It is only recently that a decided difference has been found between the amount of sugar in the plasma and corpuscles. As late as 1922 Folin and Berglund[3] wrote that "no serious error is involved in the use of the whole blood for analysis" and Hansen[4] found the percentage the same in 93 per cent of normal individuals. Högler and Ueberrack,[5] however, were

[1] See John: Arch. Int. Med., 1927, **39**, 67, but the figures in the text are from a later personal communication.

[2] Macleod: Carbohydrate Metabolism and Insulin, Longmans, Green & Co., Ltd., New York, 1926, p. 88.

[3] Folin and Berglund: Jour. Biol. Chem., 1922, **51**, 213.

[4] Hansen: Acta. Med. Scand., Suppl., 1923, **4**, 1.

[5] Högler and Ueberrack: Bioch. Ztschr., 1925, **155**, 123.

convinced that the sugar in the plasma was always higher than in the whole blood and in consequence the sugar of the corpuscles must be less.

When changes are taking place in the blood sugar the plasma responds more quickly than the corpuscles, so that if the whole blood sugar is increasing there is a lag in the diffusion of glucose into the cells and as a result the major portion of the glucose is in the plasma, and when the whole blood sugar is decreasing the plasma contains less sugar than the cells. The action of insulin affords an opportunity to observe rapid changes in the blood sugar and Foshay[1] was able not only to demonstrate the above phenomenon, but also to show that insulin causes a reduction in the quantity of glucose in the erythrocytes of the dog and man which is disproportionate to the reduction in the whole blood, He ascribes this as the reason why insulin reactions have been observed with a normal or increased percentage of blood sugar, such as John[2] has described. Foshay ascribes an insulin reaction not to hypoglycemia *per se*, but to a cytoglycopenia—a status of glucose impoverishment within the cell.

In a case published by Dr. Foshay an insulin reaction was predicted when the whole blood sugar was 0.197 per cent, the plasma sugar 0.220 per cent, *but the blood sugar in the cells 0.036 per cent.* The reaction really took place six hours later, but by that time the whole blood sugar had fallen below normal. Foshay's results have not been confirmed by Trimble and Maddock[3] working in Folin's laboratory.

(*b*) **Sugar in Tissues.**—Insulin has promoted a study of sugar in the tissues. Following an injection of insulin into an animal, Eadie, Macleod, and Noble[4] observed a disappearance of glucose from the fixed tissue cells. A new difficulty, however, has arisen in the interpretation of analyses of sugar in the blood and tissues owing to the refinement of methods. The new reagents for sugar in the blood are more specific for glucose and give lower values for sugar in the blood, but these reagents are especially sensitive to interfering substances. These newer methods for sugar in the blood may lead to the revision downward of the values for sugar in the tissues which Palmer[5] found. Sugar and inorganic phosphate curves vary more or less together in blood under the effect of insulin, but less importance is attached to this phenomenon than formerly[6].

Through the courtesy of Dr. H. C. Trimble of the Harvard Medical School I am enabled to give a series of analyses made simul-

[1] Foshay: Am. Jour. Physiol., 1925, **73**, 470; Arch. Int. Med., 1927, **40**, 661.
[2] John: Jour. Lab. and Clin. Med., 1926, **11**, 548.
[3] Personal communication, March, 1928.
[4] Eadie, Macleod, and Noble: Am. Jour. Physiol., 1925, **72**, 614.
[5] Palmer: Jour. Biol. Chem., 1917, **30**, 79.
[6] Best, Hoet, and Marks: Proc. Royal Soc., 1926, B, **100**, 32.

taneously of the sugar in the blood, skin, and muscle of a dog before and one-half hour after intravenous injection of glucose.

TABLE 82.—SUGAR VALUES BEFORE AND ONE-HALF HOUR AFTER INTRAVENOUS INJECTION OF GLUCOSE INTO A DOG. (H. C. TRIMBLE.)

Blood per 100 cc.		Skin, free sugar per 100 cc.		Muscle, free sugar per 100 gm.		
Before injection.	After injection.	Before.	After.	Before.	After.	
78	412	54	390	72	154	3 gm. glucose per kilo.
101	464	94	401	54	99	
95	360	69	274	55	89	2 gm. glucose per kilo.

Sugar in the blood, according to Dr. Trimble's analyses is invariably higher than in the skin or muscles irrespective of whether the percentage in the blood is as low as 95 mg. per 100 cc., or as high as 464 mg. Before the injection of glucose with one exception the sugar in the skin was higher than in the muscle, and it was invariably higher after the injections. The sugar in the skin, therefore, corresponds far more closely to that in the blood than does that in the muscles. Some very recent work by Mendel and Arnold[1] at Yale shows that the blood serum and the lymph serum under normal conditions have almost the same concentration of sugar (as well as of phosphorus, calcium, chlorides, etc.). Under such abnormalities as administration of insulin and of glucose given intraperitoneally, the lymph has a slightly higher sugar concentration than the blood serum. Sugar was estimated by the Lewis and Benedict method and the results may be higher than the truth in either or both fluids. But as it stands it supports the idea of ready and rapid passage of diffusible substances between blood and lymph and probably the tissues.

If the sugar is increased in the skin of diabetics, this may be one reason why complications are common in the skin in contrast to their relative absence in the deeper tissues, which appear to have better and indeed excellent recuperative power.

Gratefully also I acknowledge the kindness of Dr. W. Thalhimer who has allowed me to record his analyses of the sugar in the blood and muscle of rabbits. They, too, show the lower percentage of sugar in the tissues than in the blood.

Sugar in the sweat has been investigated by Usher and Rabinowitch[2] and found demonstrable in healthy individuals and increased in patients with eczema.

[1] Mendel and Arnold: Jour. Biol. Chem., 1927, **72**, 189.
[2] Usher and Rabinowitch: Arch. Dermat. and Syphilol., 1927, **16**, 706.

(*c*) **Sugar in Venous and Arterial Blood.**—Normally the blood sugar is higher in arterial blood than in venous blood and this indicates utilization of carbohydrates by the tissues. Rabinowitch[1] feels that severe diabetes is indicated when the fasting blood sugar in venous blood is higher than that in the arteries. Frank, Nothmann, and Wagner[2] found that insulin caused sugar in the vein to sink below that in the artery. Rabinowitch[3] has studied the blood sugar in arterial and venous blood under insulin and finds, too, that insulin lowers the venous blood sugar. His variations, however, are so slight that it is hard to consider them convincing.

TABLE 83.—THE PERCENTAGE OF SUGAR IN THE BLOOD AND MUSCLE OF A RABBIT. W. THALHIMER.

Rabbit	Time from death to removal muscle.	Sugar determinations, per cent		Insulin.
		Folin.	Benedict.	
Blood	....	0.1550		
Left leg	5 minutes	0.0766	0.0727	
Right leg	8 "	0.0660	0.0714	
Blood	....	0.1176		
Left leg	4 minutes	0.0571	0.0526	
Blood	....	0.1333		
Left leg	5 minutes	0.0570	0.0573	
Left leg	5 "	0.0690	0.0650	
Right leg	9 "	0.0670	0.0650	
Blood	....	0.1315		
Blood	....	0.1522		
Left leg	4 minutes	0.0686		
Blood	....	0.1694	.....	2 units.
" 0.5 hour	....	0.1015	.....	3 units.
" 1.5 "	....	0.0833	.....	5 units.
" 2.5 "	....	0.0619		
" 3.5 "	....	0.0537		
" 4.5 "	....	0.1000	.....	10 units.
" 5.5 "	....	0.0452		
" 6 "	....	0.0409	.....	Killed.
Left leg	5 minutes	0.0760	0.0662	
Right leg	7 "	0.0695	0.0540	

2. **Sugar Absorption and Glycogen Formation.**—In health the sugar in the blood rises slightly after a meal, but soon returns to the normal level. It has been known for years that with the disappearance of the excess of sugar from the blood the glycogen in the liver increased, but although long suspected it has only recently been proved that the glycogen in the muscles increased as well. Best[4] showed that in a perfused muscle all the sugar which disappeared from the blood was either stored as glycogen or oxidized. Likewise, Cori and Cori[5] demonstrated that 90 per cent of the sugar

[1] Rabinowitch: Brit. Jour. Exp. Path., 1927, **8**, 76.
[2] Frank, Nothmann and Wagner: Klin. Wchnschr., 1924, **3**, 581, 1404. Frank: Prac. Therapie des Diabetes Mellitus, Leipsig, 1927.
[3] Rabinowitch: Brit. Jour. Exp. Path., 1927, **8**, 302.
[4] Best: Ann. Clin. Med., 1927, **5**, 1081.
[5] Cori and Cori: Jour. Biol. Chem., 1926, **70**, 557.

which disappeared could be accounted for by glucose oxidation and by deposition of glycogen in the liver and muscles. In normal animals for 100 parts sugar, 38 parts were oxidized, 36 deposited as glycogen in the muscles, and 16 in the liver as glycogen. In insulinized animals 50 parts were oxidized, 38 parts deposited as glycogen in the muscles and 4 parts in the liver. Carbohydrate also exists in the muscles as sugar, but this can be looked upon more as active carbohydrate than as the more permanent, passive carbohydrate, glycogen.

Rabinowitch[1] has been able to find evidence to support the view that the first effect of insulin is to enable storage or conversion of glucose into glycogen and that glycogen formation is a necessary preliminary to oxidation of carbohydrates.

Burn and Dale demonstrated in 1924 that "during a period of forty minutes before insulin, the rate of disappearance of sugar in milligrams per hour was 369, whereas during four consecutive twenty-minute periods following it, the figures were 1704, 1026, 1392, 1452 respectively."[2]

Cori, Pucher, and Bowen[3] proved that insulin increases the intake of sugar by the muscles by measuring the sugar in the arterial and venous blood. It is now demonstrated that insulin accelerates the rate at which the muscles absorb the sugar from the blood stream, and this has also been demonstrated for the organs as well. Lactic acid does not increase sufficiently after the use of insulin to explain the disappearance of the sugar.

When the blood sugar has been lowered by insulin, its percentage is scarcely changed when large quantities of glucose (2 grams per kilogram body weight) are injected into rabbits, although in normal rabbits marked hyperglycemia would have been caused.

Levulose in diabetic animals forms glycogen and is metabolized more readily than is glucose and also raises the respiratory quotient which glucose does not.

An explanation of the overflow of sugar from the blood into the urine was given by Folin and Berglund.[4] "The kidneys receive their quota of sugar just as do the other tissues, and this increase of sugar does not involve the slightest degree of strain. The strain comes only when the holding capacity for free sugar is reached and when the glycogen formation must come into play to keep the sugar concentration within normal limits. The speed of glycogen formation is of a much lower order than is the earlier process of merely absorbing the sugar from the blood. At this stage, therefore, the sugar backs up in the blood and the holding capacity of some tissues including the kid-

[1] Rabinowitch: Brit. Jour. Exp. Path., 1927, **8**, 302.
[2] Macleod: Loc. cit., p. 301.
[3] Cori, Pucher, and Bowen: Proc. Soc. Expt. Biol. and Med., 1923, **21**, 122.
[4] Folin and Berglund: Jour. Biol. Chem., 1922, **51**, 213

neys is exceeded. As a result of the strain thus produced the kidneys are finally compelled to make use of a more efficient process than the glycogen formation for reducing the sugar concentration in the kidney cells, and the elimination of sugar suddenly begins. That a real local strain has preceded the escape of the sugar is indicated by the fact that the sugar excretion once begun does not stop as soon as the blood sugar has fallen below the threshold, but, in fact, continues until the level of the blood sugar has gone away down, even to subfasting values (hypoglycemia).[1]

"Normally there is neither fructose nor galactose in the tissues, and within this enormous empty reservoir the galactose disappears as readily as does fructose and more readily than glucose. With respect to absorption and distribution galactose and fructose are alike. As far as excretion is concerned, the difference between the two is not even of a quantitative character. One is, the other is not excreted. Such a qualitative difference in the matter of excretion cannot very well depend on quantitative differences in the speed with which the two sugars are transformed into glycogen. The sugar excretion observed after very small doses of galactose clearly points to the absence of a renal threshold for galactose. In the absence of such a threshold galactose will continue to be excreted as long as there is any galactose in the tissues, for a little of it will constantly leak back into the blood. The excretion would be like that of absorbed dextrin except for the fact that even galactose is gradually converted into glycogen thus diminishing and finally exhausting the supply of galactose."

3. **The Glucose Threshold.**—The glucose threshold, or renal threshold, that is the percentage level of sugar in the blood above which sugar appears in the urine, has been carefully studied. Reliance should never be placed on a single examination, because of the transient hyperglycemia caused by emotion,[2] and because of the possible influence of the previous diet. The normal glucose threshold level lies between 0.16 and 0.18 per cent sugar for whole blood and somewhat higher, about 0.19 per cent, for the plasma. These figures correspond to the highest normal level for the glucose threshold, because lower levels are frequently obtained and these lower levels eventually verge into renal glycosuria.[3] It also makes a difference in such determinations as to whether the threshold is determined on the basis of a rising or a descending curve of sugar concentration in the blood. The two may be quite different. Thus, Goto and Kuno,[4] and also Hatlehol[5] observed that the sugar

[1] Folin and Berglund: Loc. cit., p. 213.
[2] Feinblatt: Jour. Lab. Clin. Med., 1923, **8**, 500.
[3] Folin and Berglund: Jour. Biol. Chem., 1922, **51**, 213.
[4] Goto and Kuno: Arch. Int. med., 1921, **27**, 224.
[5] Hatlehol: Acta Med. Scand., 1924, supplement **8**, 1.

elimination began at 0.15 per cent of sugar in the plasma but continued until the sugar in the plasma dropped to 0.06 per cent. Also the level of the blood sugar is not the same in venous and arterial blood, according to Henriques and Ege,[1] though the blood sugar in venous and capillary blood are said to be the same. The threshold is characteristic for the individual according to John[2] and may be low or high and in untreated diabetics changes. In a personal communication John cites in support of this view the independence of insulin reactions to the blood sugar percentage. Hatlehol[3] claims the threshold does not rise with the age of the patient or with the duration of the disease. My cases show little change of percentage of blood sugar, but I cannot speak for the threshold.

A levulose threshold, similar to the glucose threshold, appears probable from the researches of Folin and Berglund,[4] but for galactose or lactose they find no such threshold exists.

"The tissues of the diabetic person should contain much higher concentrations of glucose than tissues of normal persons, and this is the immediate reason why the blood sugar rises so high after the intake of glucose in any form. The high concentration of glucose in the tissues would probably have little or no effect on their absorption of fructose. From the giving of fructose we should, therefore, get a much higher concentration of total sugar (glucose plus fructose) in the tissues without any material increase in the sugar of the blood."[5]

The concept comprised in the term "glucose threshold" is not only approximately true, but absolutely correct, however uncertain the exact figures given for the threshold may be. This appears proved, because even as much as 200 grams of glucose failed to yield a trace of sugar in the urines of normal individuals studied by Folin and Berglund, and was also without effect on the sugar excretion comprised in the term glycuresis. "Hyperglycemia definitely below the threshold does not normally produce the slightest leakage of glucose through the kidneys and normally not a trace of absorbed and circulating glucose is lost." To this conclusion Benedict and Osterberg[6] do not agree, basing their opinion largely on a different interpretation of the experiments of the writers quoted.

4. **Alimentary Glycosuria and Hyperglycemia.**—From the preceding paragraph it is evident that the views of the leaders in the

[1] Henriques and Ege: Biochem. Ztschr., 1921, **119**, 121.
[2] John: Jour. Metab. Research, 1922, **1**, 1.
[4] Hatlehol: Acta Med. Scand., 1924, supplement **8**, 1.
[3] Folin and Berglund: Jour. Biol. Chem., 1922, **51**, 213.
[5] Folin and Berglund: Loc. cit., p. 213.
[6] Benedict and Osterberg: Jour. Biol. Chem., 1923 **55**, 769.

chemistry of the blood sugar are at variance upon this topic. If it exists at all it is of so slight a degree as not to lead to confusion with actual diabetes. "The term alimentary glycosuria has been used to express the fact that some apparently normal persons eliminate moderate quantities of sugar after the ingestion of cane-sugar, glucose, or even after starch." The term alimentary glycosuria is a misnomer, according to Folin and Berglund. "The sugar is excreted either because the level of the blood sugar has risen above the normal threshold or because the threshold itself is below the normal, as in renal glycosuria. There can be no doubt as to the existence of some mechanism by which the excretion of glucose is normally absolutely prevented."[1] However, the fact remains that Holst[2] found glycosuria developed after carbohydrate meals in 31 of 159 individuals. He used the Benedict test.

Alimentary Hyperglycemia.—Alimentary hyperglycemia occurs one-half hour after a meal and frequently does not return to the normal in two hours.[3] Brill[4] found a fall in the blood sugar one and a half hours after breakfast, but after lunch there was a rise. A meal of fat and protein only may produce a rise in blood sugar.[5]

5. **Food Tolerance Tests.**—Food tolerance tests and particularly glucose tolerance tests are often fallacious. They are being more and more employed as a rapid method for the detection and diagnosis of diabetes, but the results may be as unfair to the patient as to the doctor or insurance company. The previous diet of the subject is a definite factor. Odin found that if an individual lived upon a rigid, low-carbohydrate diet for some weeks and a liberal carbohydrate meal was then taken, hyperglycemia developed to such an extent that a diagnosis of diabetes would be warranted. For years I have been using (empirically at the commencement of treatment) test diets which contained a considerable quantity of carbohydrate with a small amount of protein and fat, because I recognized that after once lowering the carbohydrate in the diet of a patient it was difficult to raise it again. I have followed this plan especially with children and with cases seen soon after the onset of diabetes. Scientifically now there is justification for such a course, because it is recognized that if carbohydrate is withheld long the insulin secreting function of the pancreas falls in abeyance. Hence the diabetic insurance applicant who thinks he will elude the company's doctor by living on a restricted carbohydrate but liberal protein-fat diet is defeating his own ends. Clinically I have always found it easier

[1] Folin and Berglund: Loc. cit., p. 164.
[2] Holst: Ztschr. f. Klin. Med., 1922, **95**, 394.
[3] Sakaguchi, Matsuyama, and Watanabe: Jour. Biol. Chem., Tokyo, 1922, **1**, 371.
[4] Brill: Jour. Lab. Clin. Med., 1923, **8**, 727.
[5] Petrén: Arch. Exp. Path. u. Pharm., 1923, **99**, 52.

to get good results with an untreated diabetic than with one who has been rigidly dieted. This phenomenon is by no means new, but it has recently been emphasized by Odin,[1] Malmros,[2] Stenström,[3] Adlersberg and Porges,[4] and most recently of all by Sweeney[5] who shows that glucose tolerance curves are postponed in dehydrated animals, that there is a definite decrease in tolerance after a fat diet and starvation, a slight decrease in tolerance on a protein diet, but an increase in tolerance on a carbohydrate diet.

Personally I believe the fairest way in which to determine whether a patient has diabetes is to make the examination without previous notice after a dinner of meat, potato, three slices of bread, and apple pie, with coffee and sugar. Practically every meal is a sugar-tolerance test. The urine should be free from sugar before, at one hour, and at one hour and a half or two hours after the meal. It can be tested immediately, and if sugar-free the evidence is probably about 99.9 per cent correct that the patient has not diabetes, but to be 100 per cent, simultaneous tests for sugar in blood and urine should be performed, and these will disclose renal glycosurics and may disclose potential diabetics.

TABLE 84.—FOOD TEST, CASE NO. 3839, MARCH 15, 1927.

Time.	Urine sugar, per cent.	Blood sugar, per cent.
Four hours after breakfast	0.1	0.10
Lunch: Baked beans, potato, 1½ rolls, apple pie, ice cream		
One hour after lunch	trace	0.23
One and a half hours after lunch	3.0	0.27

Although glucose tolerance tests are widely used, clinicians vary greatly in their interpretations of them. Some depend most on the height of the curve secured, others on the length of it, others on both. The last attitude is undoubtedly safest if one is to rely on such tests, but even then I regard them as unsatisfactory. As Rowe and Rogers[6] point out, one must take blood samples before and at one-half, one, two and three hours after the test in order not to miss any unusual and perhaps transient peak. Personally I do not recall a single case in which the diagnosis was missed by employing an ordinary test meal as described above. John in a personal communication suggests that the blood sugar be taken two and a half to three hours after a meal as a short cut to a glucose tolerance curve. A diabetic, he considers, would not present a normal blood sugar

[1] Odin: Acta Med. Scand., 1927, Supplement 8.
[2] Malmros: Zentbl. f. inn. Med., 1927, **48**, 244.
[3] Stenström: Ibid, 244.
[4] Adlersberg and Porges: Klin. Wchnschr., 1926, **5**, 1451.
[5] Sweeney: Arch. Int. Med., 1927, **40**, 818.
[6] Rowe and Rogers: Calif. and West. Med., 1927, **26**, 64.

at this time. Hale-White and Payne[1] would only have a diagnosis of diabetes on a dextrose tolerance curve which is abnormal throughout.

With these preliminary statements the following pages with their divergent views of various authors may be more easily reconciled.

After a meal the percentage of sugar in the blood of normal individuals rises promptly, but should not exceed 0.16 per cent. Since it frequently occurs that diabetic patients under treatment have normal blood sugar fasting values, various test meals have been proposed with smaller or larger quantities of glucose either selected arbitrarily or dependent upon the weight of the patient.

The administration of 100 grams of glucose to normal individuals raises the percentage of sugar in the blood, and Jacobsen[2] has shown that this takes place within five minutes. The rise is greatest when the glucose is given fasting in the morning, being somewhat less after breakfast. The increase reaches on the average 0.14 per cent in half an hour, in one hour 0.12 per cent (300 curves), in two hours, 0.11 per cent, but in three hours the percentage drops to slightly below normal or 0.09 per cent. A peak value of over 0.16 per cent is usually considered abnormal. When the quantity of glucose given is between 150 and 200 grams, the values for the four periods are 0.16, 0.15, 0.12, and 0.10 per cent, and when the quantity is between 20 and 25 grams, 0.10, 0.12, 0.11 and 0.09 per cent. With normal individuals maximal and minimal values are obtained differing considerably from the averages above recorded, but it is probable, as with the normal fasting values, that a more careful selection of normals will eliminate the gross extremes. In the latter months of pregnancy the percentage of blood sugar may rise to as high levels or even above the threshold, but is not accompanied even then by glycosuria; the reverse is also true. See page 865.

The effect of various quantities and forms of carbohydrate and some other foods upon the blood sugar is shown in Table 85, which is compiled from two sources, first, data accumulated by Gray from the literature and, second, the experiments of Folin and Berglund. The blood-sugar values obtained by Folin and Berglund in their experiments with maltose, glucose, dextrin and starch are somewhat lower than the levels attained by other investigators. They ascribe this partially to their subjects being medical students, and with these the influence of emotion would be less. Furthermore, in these experiments the blood was drawn from the veins rather than by puncturing the fingers, which causes distinctly more pain. In support of this theory they call attention to the reports of a group of investigators[3] who have obtained substantially the same degree of

[1] Hale-White and Payne: Quar. Jour. Med., 1927, **20**, 457.
[2] Jacobsen: Biochem. Ztschr., 1913, **56**, 471.
[3] Cammidge, Forsyth and Howard: British Med. Jour., 1921, i, p. 586.

hyperglycemia from any kind of food, except fat, as they obtained from sugar or any other carbohydrates. These authors took the blood from the roots of the finger nails. Peculiar, high results from certain other laboratories using micro-methods are possibly open to suspicion for the same reason.

TABLE 85.—AVERAGE BLOOD-SUGAR CURVES IN NORMAL PERSONS (COMPILED BY GRAY).[1]

Form of test.	Amount, gm.	Blood sugar. Before.	½ hour.	1 hour.	2 hours.	3 hours.
Glucose	150–200	..	0.16	0.15	0.12	0.10
	70–100	..	0.14	0.12	0.11	0.09
	50	..	0.14	0.14	0.10	0.10
	20–25	..	0.10	0.12	0.11	0.09
Sucrose	50–100	..	0.15	0.14	0.12	0.12
Levulose	100	..	0.14	0.13	0.12	0.11
Starch	70–100	..	0.15	0.14	0.12	0.11
	50	..	0.14	0.12	0.19	
Fat	10–75	..	0.10	0.10	0.10	0.10
Mixed meal	..	..	0.13	0.12	0.11	0.11
EXPERIMENTS OF FOLIN AND BERGLUND.[2]						
Glucose	200	0.105	0.152	..	0.121	0.136
"	200	0.090	..	0.118	..	0.094[3]
Levulose	200	0.100	0.102	0.101	..	0.098
Maltose	200	0.090	0.080	0.078	0.069	
Galactose	100	0.093	0.089	0.087		
"	100	0.094	0.079	0.082		
Glucose	100	0.094	0.079	0.082		
Lactose	200	0.094	0.101	..	0.088[4]	
Dextrin	200	0.101	..	0.101	0.087	0.083
Starch, potato	175	0.093	..	0.083	0.070	0.068
Olive oil	200	0.096	..	0.070	..	0.088
Egg white	1000	0.108	..	0.102	0.101	0.098
Gelatin	135	0.097	..	0.093	0.084	0.092

They mention one subject: "A medical student, S-g., never had any sugar in his urine (qualitative tests) either before or after the day of the experiment. When the preliminary sample of blood was taken, he grew pale and very faint. When the second sample was taken, he fainted completely. The plasma of this blood contained 210 mg. of sugar, whereas the first contained only 105 mg. In the course of the next hour the sugar content sank to 111 mg., and neither at this time nor later did the taking of the blood disturb him."[5]

Levulose did not raise the blood sugar in Folin and Berglund's experiments and Holm[6] found hardly any effect, though Schätti[7] observed an increase, but less than after glucose.

[1] Gray: Arch. Int. Med., 1923, **31**, 241.
[2] Folin and Berglund: Jour. Biol. Chem., 1922, **51**, 213.
[3] Four hours.
[4] One hour, forty minutes.
[5] Folin and Berglund: Loc. cit., p. 263.
[6] Holm: Ztschr. f. d. ges. Exp. Med., 1923, **36**, 43.
[7] Schätti: Biochem. Ztschr., 1923, **143**, 201.

In a study of 713 non-diabetic cases Rabinowitch[1] found only 29 with blood sugars above 0.18 per cent, Lewis-Benedict method, after the ingestion of 100 grams of glucose before breakfast, but there were 103 cases with a percentage above 0.12. So many of the cases with a blood sugar above 0.18 per cent returned to normal in three hours and yet upon analysis were found to have some disease associated with disturbance of carbohydrate metabolism that Rabinowitch believes a blood sugar of 0.18 per cent after 100 grams glucose must be considered pathological and a normal value at the end of three hours inadequate proof of the absence of diabetes. On the other hand, Fries and Kohn[2] in a study of glucose tolerance tests report they have found many in children which do not return to the normal fasting level at the end of three hours.

A demand for refinement of the glucose tolerance test by washing out the stomach at a definite time after ingestion and allowance for the recovered glucose has been put forward by Beeler, Bryan, Cathcart and Fitz,[3] but it has been shown to be immaterial[4] even if as much as 50 grams glucose remains unabsorbed.[5]

Whether large or small amounts are given, Hansen[6] found there is an upper limit of 0.18 per cent for the rise in blood sugar.

Daily repetition of glucose tolerance tests has been carried out by John, and he has been so kind as to allow me to insert his unpublished results made upon two normals. The normal individual was given 100 grams glucose for five successive days with the surprising outcome that the height of the hyperglycemia curve fell on some of the successive days, but as John significantly points out, even on the first day when the hyperglycemia reached a peak of 0.26 per cent the return of the curve to normal was attained within a three-hour limit. Upon the fifth day the peak reached was only 0.09 per cent. These instructive experiments of John made in 1921 find their explanation today in the stimulating action of carbohydrate meals on the insulin-secreting function of the pancreas. The reverse of this situation was produced with a low carbohydrate diet by Odin and has been discussed on p. 200.

That one must be careful in interpreting blood-sugar curves is suggested by Rabinowitch[7] who demonstrated the possible fallacies in such interpretations by studies of simultaneous respiratory exchange and blood-sugar curves.

[1] Rabinowitch: Jour. Clin. Inves., 1926, **2**, 579.
[2] Fries and Kohn: Am. Jour. Med. Sci., 1925, **170**, 547.
[3] Beeler, Bryan, Cathcart, and Fitz: Jour. Metab. Research, 1922, **1**, 549.
[4] Ohler: Personal communication.
[5] Malmros: Skan. Archiv. f. Physiol., 1925, **46**, 329.
[6] Hansen: Acta Med. Scand., 1923, Suppl. 4.
[7] Rabinowitch: Jour. Clin. Invest., 1925, **2**, 143.

Lennox[1] has recently carried out experiments in which varying quantities of glucose were administered, both orally and intravenously, in duplicate dosages, at intervals from twenty minutes to two hours. In this way two "tolerance curves" were secured. Although the response in different subjects varied greatly he found that the greatest single factor was the amount of glucose ingested. After the *oral* administration of *1.5 grams* of glucose per kilogram, followed in a few minutes by a similar amount of glucose, the second curve was only one-fourth the area of the first, while with a dosage of *0.33 gram* it was approximately the same area. Following the intravenous administration, the same general rule held, though the second curves were always larger than those in which the sugar was administered orally. Following double intravenous injections of glucose, hypoglycemia as low as 48 mg. per 100 cc. of blood was reached. Lennox interprets his experiments as confirming the importance of glucose as a stimulator of the blood-sugar regulating mechanism of the body. He regards the alimentary hyperglycemia which occurs after fasting as due to a lack of stimulation of the sugar-regulating mechanism. In substantiation of this, mention should be made of the fact that Lennox[2] also found that in a majority of the non-diabetic subjects, there was progressive lowering of successive curves following ingestion and injection of glucose. Of the 25 subjects with abnormally high initial blood-sugar curves, 21 of the curves were lower on second trial. Consequently he thinks that a single blood-sugar curve test, may be without diagnostic significance, and that a lowered subsequent curve may not necessarily be due to the experimental or therapeutic procedures introduced between the first and second tests. Foster likewise noted that a second dose of glucose taken soon after the hyperglycemia of the first dose had subsided produced little or no effect on the concentration of sugar in the blood. Foster[3] believes the first dose of glucose stimulates the glucose mechanism of the organism to such activity that it is able to take care of the second without becoming hyperglycemic. He ascribes the hypoglycemia which eventually follows the ingestion of glucose as due to overactivity of the glycogen-forming mechanism. With animals in the hypoglycemia stage after insulin, large doses of sugar, 2 grams per kilogram body weight, can be injected with scarcely any change in the blood-sugar level.

Frank[4] held this same view. This might explain why the Japanese and other races with a high carbohydrate diet have a relatively low

[1] Lennox: Jour. Biol. Chem., 1927, **73**, 237.
[2] Lennox: Jour. Clin. Investigation, 1927, **4**, 331.
[3] Foster: Jour. Biol. Chem., 1923, **55**, 303.
[4] Frank: Ztschr. f. physiol. Chem., 1910–1911, **70**, 291.

level of sugar in the blood. Obviously it explains the advantage clinically of giving a little carbohydrate to a severe diabetic such as Case No. 1542 an hour before the regular meal. This patient would tolerate even more carbohydrate than usual at breakfast if she had the insulin provocative meal an hour before hand.

Repetition of tolerance curves at approximately annual intervals has been carried out by Ohler[1] in 20 patients, with results which, together with the after-history, emphasize the fact that tolerance improves with proper attention to dietary restrictions and fails with neglect. Furthermore, in this series the relationship between decrease in tolerance and increase in weight has been striking, showing the harmfulness of obesity.

A study of blood-sugar curves in 25 Jewish and 25 non-Jewish patients with no apparent glycogenic disturbance indicates that race is not a factor, even though the Jew is also endowed with a nervous or emotional temperament.[2] Apparently it may vary according to the country or rather the dietary habits of a particular country. Concepcion[3] found that in 30 Filipinos the blood sugar was 0.123 per cent, but in American residents of long standing it was 0.134 per cent and in Europeans of long residence 0.154 per cent. I think I am correct in quoting Japanese friends in stating that the blood sugar of Japanese is lower than we find it here among Americans.

To the observers cited by Gray, who have obtained satisfactory curves with smaller amounts of glucose than 100 grams or 1.5 grams per kilogram body weight may be added W. R. Ohler, whose experience in Peabody's Clinic at the Boston City Hospital has made him feel that smaller amounts give information just as valuable, and that a determination two hours after a mixed meal will often give all the information required.

A combination method for the determination of the sugar in the blood and the sugar in the urine (following the procedure used in quantitating sugar in normal urine) is employed by Lewis[4] in his method for the performance of glucose tolerance tests. He considers that a fasting blood sugar of 0.13 per cent or more is nearly always indicative of disturbed carbohydrate metabolism.

The hypoglycemia in normals observed to follow hyperglycemia in a sugar tolerance test is a regular and normal occurrence and I suppose a result of the stimulation of the secretion of insulin. It is of much practical importance. Food tests should be arranged so that the maximal and minimal values will occur within a two- or three-hour (John) period following ingestion of the test meal.

[1] Ohler: Med. Clin. of North America, 1922, **5**, 1465.
[2] Morrison and Ohler: Boston Med. and Surg. Jour., 1922, **188**, 852.
[3] Concepcion: Jour. Am. Med. Assn., 1924, **82**, 580.
[4] Lewis: Jour. Lab. and Clin. Med., 1927, **12**, 380.

A satisfactory test meal has been urged by Brill.[1] It contains approximately carbohydrate 100 grams, protein 26 grams, fat 27 grams, about 760 calories, and consists of bread, butter, cereals, eggs, sugar, coffee, and cream. For the estimation of the carbohydrate tolerance the urine and blood sugar are examined before the meal and at one hour and a half after the meal. The normal individual at an hour and a half after a meal will have a blood sugar within 10 mg. of the fasting level, but in diabetics he found that the second level was invariably considerably higher, in mild cases averaging 25 to 30 mg., in moderate cases 40 to 50 mg., and in severe cases reaching over 200 mg.

This test meal has been utilized by Wright[2] in the examination of 268 individuals. Among these 81 showed no distinct evidence of impaired carbohydrate metabolism while 187 showed an abnormal blood-sugar curve and glycosuria and were classified as positive. It should be stated that this high percentage was probably in part due to the fact that the patients were old rather than young and had come to a sanitarium for treatment. Sixty-eight of the patients had a normal fasting blood sugar but showed a hyperglycemia and glycosuria two hours after a meal. Wright emphasizes the importance of such a test in order to discover early diabetics. Escudero and Puchulu[3] have used the glucose tolerance test in another form in order to discover latent diabetes in diseases of the skin. They administered glucose, 2 grams per kilogram body weight, to patients who had gone without food for twelve hours after having determined the percentage of sugar in the blood. At the end of three hours, in their opinion, the blood sugar should reach its original level.

John[4] recommends in order to determine the exact diagnosis of a patient with glycosuria the estimation of the blood sugar and of the urine at exactly three hours after a heavy carbohydrate meal. If the individual is normal, there will be no hyperglycemia, because in a normal individual whose tolerance for carbohydrate is unimpaired the blood-sugar content will be normal or subnormal. An instructive series of blood-sugar estimations is given by John. Even if the blood sugar should rise to 0.172 per cent after the noon meal, but within three hours fall to normal, John would not classify this patient as a true diabetic. In contrast, in his table he shows the blood-sugar curve of a diabetic in whom the renal impermeability was as high as 210 mgs. per 100 cc.

A summary of the results of glucose tolerance tests and test

[1] Brill: Jour. Lab. Clin. Med., 1923, **8**, 727.
[2] Wright: New York State Jour. of Med., 1927, **27**, 122.
[3] Escudero and Puchulu: Progresos de la clinica, 1926, **34**, 513.
[4] John: Am. Jour. Med. Sci., 1925, **169**, 102.

meals with a proposed method of selecting risks from among individuals with slight glycosuria has been prepared by McCrudden.[1] According to his test the applicant swallows 100 grams glucose dissolved in 250 cc. of cold water. Two hours later a blood-sugar test is made with the Folin and Wu method. Applicants showing 0.12 per cent blood sugar or less are accepted; those showing more than 0.12 per cent are not accepted. I consider this liberal treatment toward the applicant for insurance, but on the other hand I think a liberal carbohydrate meal test with urine and blood tests before and at one and one and a half hours after the meal fairer to the patient. Indeed, most cases will be settled by the urine test alone after the meal.

Test meals given to diabetic patients raise the percentage of blood sugar higher and for a longer period than with normals, and it is the prolongation or cessation of the hyperglycemia which is of the greatest importance in the opinion both of John and Mosenthal.[2] The latter has reviewed instructively the various aspects of glucose tolerance tests. Gray found that following 100 grams of glucose, the blood sugar of 40 diabetic patients with a normal, fasting blood sugar rose to 0.18 per cent in one-half hour, 0.20 per cent in one hour, 0.15 per cent in two hours, and 0.10 per cent in three hours. With 54 diabetic patients whose fasting blood sugar was 0.12 per cent or more the values were distinctly higher. These values are compared with normal values in Table 87. When the fasting blood

TABLE 86.—GLUCOSE TOLERANCE TESTS[3] IN DIABETICS AND NORMALS COMPARED.

Individuals.	Glucose given, gm.	Blood sugar (fasting), per cent.	Diabetic blood-sugar curves.				
			Fasting.	½ hour.	1 hour.	2 hours.	3 hours.
Diabetics.							
40 . . .	100	Normal	0.09	0.18	0.20	0.15	0.10
54 . . .	100	0.12 or more	0.17	0.25	0.27	0.25	0.21
6 . . .	50	0.11 or less	0.08	0.12	0.12	0.14	0.13
Normals							
300 . . .	100	....	0.09	0.14	0.12	0.11	0.09

sugar of the diabetics was 0.11 per cent or less, fasting, as in 6 individuals and these were given 50 grams of glucose, the increase in percentage of blood sugar was not abnormal until the second and third hours. Therefore, 50 grams of glucose cannot be accepted as a routine test unless blood values for at least two hours are obtained.

[1] McCrudden: Proceedings of Assn. of Life Ins. Med. Directors of Am., 1924, **11**, 156.
[2] Mosenthal: Med. Clin. of North America, 1925, **9**, 549.
[3] Gray: Arch. Int. Med., 1923, **31**, 241.

Kern and Jonas[1] point out that in a case they regard as a mild but true diabetic, because glycosuria appeared only when the blood sugar was above 0.15 per cent, the rise of blood sugar after a test with glucose, 1.75 grams per kilogram body weight, would have been missed had not a blood-sugar test been made one-half hour after its administration. Therefore, to satisfy John and Kern and Jonas the blood is best examined at one-half and three hours after a test.

The sugar in the blood and urine of a diabetic and non-diabetic were compared by John[2] during nine hours of the day. Even in the normal the blood sugar rose to 0.17 per cent, but the method employed may account for this. (Table 87.)

TABLE 87.—ESTIMATION OF SUGAR IN THE BLOOD AND URINE COMPARED IN A DIABETIC AND NON-DIABETIC DURING NINE HOURS OF THE DAY. (JOHN.)

	A.M.				M.	P.M.			
	8	9	10	11	12	1	2	3	4
Non-diabetic.									
Blood sugar mg. per 100 cc. .	110	146	110	106	140	172	140	110	110
Urine sugar	neg.	pos.	neg.	neg.	neg.	pos.	pos.	neg.	neg.
Diabetic.									
Blood sugar mg. per 100 cc. .	120	210	248	222	156	198	259	262	210
Urine sugar	neg.	neg.	pos.	po	neg.	neg.	pos.	pos.	pos.

Myers-Benedict method was used for determining the blood sugar and Benedict method for testing the urine.

In normals the blood sugar rises less after the mid-day meal than after breakfast if the interval between is three hours. This difference is not constant in normals and still less so in diabetics. In the latter the greater the severity, the greater the advantage in separating the meals instead of approximating them.[3] Maclean[4] found that the blood-sugar curve following the administration of 50 grams of glucose to fasting diabetics might be high and prolonged. After feeding the patients for a time, though starting at the same blood-sugar level, the same amount of glucose produced a reaction which was not as high or lasted as long and to this extent indicated improvement of the patient. Sakaguchi[5] explains the above phenomena on the basis that at breakfast-time glycogen formation

[1] Kern and Jonas: Jour. Am. Med. Assn., 1923, **81**, 1439.
[2] John: Am. Jour. Med. Sci., 1925, **169**, 102.
[3] Sakaguchi and Sato: Mitt. d. med. Fakultät d. Kais. Universität su Tokyo, 1920, **23**, 373. See also Petrén: Compt. rendu de la Soc. de Biol., 1925, **93**, 380.
[4] Maclean: Modern Methods in the Diagnosis and Treatment of Glycosuria and Diabetes, Constable and Co., London, 1922.
[5] Sakaguchi: Ibid., 1918, **20**, 439.

by the liver is at a low ebb. The indication, therefore, would be not only to make the carbohydrate at breakfast less than at the other meals, but to precede breakfast with a small amount of carbohydrate. Gray's[1] experience with divided meals in my clinic is a practical confirmation of these observations.

6. **The Blood Sugar During the Day in Insulin and Non-insulin Treated Diabetics.**—Without insulin the highest blood sugar concentration, according to Jonas, Miller and Teller,[2] usually occurs one hour after breakfast and with insulin either at the same time or just before the administration of the first dose of insulin for the day. Without insulin the lowest blood sugar is before breakfast and with insulin it is just before lunch or in the mid-afternoon. Hatlehol[3] found a rise in the blood sugar during the night which was simultaneous with sleep. It occurred with the more advanced cases of diabetes and therefore was an unfavorable sign. Patients in Petrén's[4] Clinic living upon a diet restricted in carbohydrate and protein, but with fat varying between 170 and 260 grams, showed a lower blood sugar at 2 P.M. than at 8 P.M.

Diabetes can be diagnosed in the vast majority of cases without the use of a glucose tolerance test. I always use such a test with reluctance, and for two reasons: (1) I fear that my patients will not understand why it is justifiable for me to give them sugar when I say it is harmful for them to take it; (2) although I have never seen a diabetic patient whom I considered injured by a glucose tolerance test, I cannot forget Allen's statement: "In the early stage, glucose is more powerful than starch in producing diabetes, and animals which are progressing toward complete recovery on starch diet can be sent into hopeless diabetes by admixture of glucose."[5]

7. **The Blood Sugar in Other Diseases.**—Other diseases or states than diabetes are often accompanied by abnormal blood-sugar percentages. Of these hypertension, nephritis, pregnancy, hyper- and hypothyroidism, diseases of the liver, of the pituitary body and of the adrenals are the most common. Gray[6] attempted to condense all the data in the literature, and Table 88 is based upon his summaries. The test meal given was 100 grams glucose in all, except a few cases whose inclusion he thought legitimate because the curves were, in each, as high as after the usual dose.

The percentage of sugar in the blood is also increased in apoplexy, pneumonia, typhoid, tuberculosis in the presence of fever, and in some cases of cancer. There is a decided increase after ether and,

[1] Gray: Boston Med. and Surg. Jour., 1922, **186**, 763.
[2] Jonas, Miller, and Teller: Arch. Int. Med., 1925, **35**, 289.
[3] Hatlehol: Loc. cit., p. 248.
[4] Petrén: Compt. rendu de la Soc. de Biol., 1925, **93**, 380.
[5] Allen: Jour. Exp. Med., 1920, **31**, 402.
[6] Gray: Arch. Int. Med., 1923, **31**, 241.

in fact, all varieties of general anesthesia and in operations on all kinds of cases. If the ether anesthesia is less than an hour, the increase is 32 to 89 per cent, but if more than an hour, the increase is greater. Pain, fear of operation or of anesthesia exert a negligible influence upon the blood sugar.[1] Claude Bernard's piqûre is the original method for causing hyperglycemia without food. Blood sugar values in phlorizin diabetes have been recently reviewed by Nash[2] with a careful survey of the literature.

TABLE 88.—BLOOD-SUGAR STANDARDS IN CONDITIONS NEITHER NORMAL NOR DIABETIC (GRAY).

Test meal, 100 grams glucose.

Condition.	Number of curves.	Average percentage of blood sugar.				
		Fasting.	½ hr.	1 hr.	2 hrs.	3 hrs.
Hypertension without nephritis	29	0.11	0.19	0.18	0.16	0.13
Nephritis without hypertension	11	0.14	0.19	0.23	0.20	0.24
Renal glycosuria without nephritis	70	0.09	0.13	0.12	0.11	0.09
Pregnancy with blood sugar 0.11 per cent or less	51	0.09	0.14	0.14	0.12	0.13
Hypothyroidism, cretinism, myxedema	8	0.10	0.16	0.15	0.12	0.11
Hyperthyroidism:						
Blood sugar (fast.), 0.12 or more	9	0.13	0.17	0.18	0.18	0.11
Blood sugar (fast.), 0.11 or less	58	0.09	0.16	0.16	0.14	0.11
After operation	4	0.08	0.12	0.10	0.09	0.09
Hepatic disease:						
Obstructive jaundice	7	0.13	..	0.22	0.23	
Cardiac cirrhosis	6	0.14	..	0.18	0.21	
Alcoholic or syphilitic cirrhosis	28	0.10	0.15	0.17	0.17	0.18
Catarrhal jaundice	10	0.10	..	0.15		
Bailey's case	1	0.12	0.32	0.37	0.34	0.27
Hypopituitarism or dyspituitarism	4	0.11	0.17	0.17	0.14	0.12
Acromegaly or hyperpituitarism	11	0.09	0.13	0.17	0.15	0.11

Marañon, Carraxo and Soler[3] state that in Addison's disease hypoglycemia is always present and that the blood-pressure falls concurrently with the blood sugar.

Extreme lowering of the blood-pressure is associated with hypoglycemia.[4] Therefore, it is not unexpected to find it is low in Addison's disease. It is also low in hypothyroidism and hypopituitarism.

Abnormal blood-sugar curves in patients without glycosuria, and conversely normal curves in patients with glycosuria, have been studied by Ohler[5] with the following results:

[1] Epstein and Archner: Jour. Am. Med. Assn., 1916, **56**, 1927.
[2] Nash: Phys. Rev., 1927, **7**, 385.
[3] Marañon, Carraxo and Soler: Revista Sud. Am., 1925, **8**, 23.
[4] Editorial: Jour. Am. Med. Assn., 1924, **82**, 1695.
[5] Personal communication.

In a series of 160 cases who underwent glucose tolerance tests, glycosuria was absent with 103 and 57 showed only small amounts. Of the 103 cases without glycosuria, 37 gave normal glycemic reactions, 53 definitely abnormal and 12 doubtful reactions; or in other words, 60 per cent of the cases without glycosuria gave abnormal sugar tolerance reactions. An analysis of the cases in this group shows that a very large percentage of the abnormal reactions were found in the following pathological conditions (arranged in order of frequency): Gall-bladder diseases; cirrhosis of the liver; bronchial asthma; arteriosclerosis; carcinoma; obesity; endocrine disturbances; chronic nephritis; chronic arthritis.

In arthritis, Pemberton,[1] and in cases of high blood-pressure, O'Hare[2] and John[3] have recorded hyperglycemia which in O'Hare's cases has at times been sufficient to suggest the diagnosis of diabetes. In the latter instance van Slyke believes the liver plays an important role. Pemberton *et al.* found that interference, through posture, with the blood flow in the limbs of normals and arthritics favored a lowered sugar tolerance. He thus explains the benefits which accrue to such patients by measures which improve the circulation. Case No. 2435 writes me that on July 6, 1926, the per cent of sugar in the blood taken from the arm was 0.215 but from the leg was 0.230.

In Ohler's group of 57 cases in which glycosuria was found, 9 cases gave perfectly normal reactions. These 9 fulfil all the requirements of so-called renal glycosuria. The remaining 48, or 84 per cent, showed definitely abnormal reactions, despite the fact that in every instance the fasting blood sugar was perfectly normal.

Blood volume in blood-sugar estimations is of significance according to Epstein and Baehr.[4] They point out that the increase in the percentage of sugar in the blood is only indicative of a relative, that is percentile, but not of absolute hyperglycemia, and suggest the advisability of studying the blood volumes and computing thereby the total blood sugar in cases of diabetes mellitus. In a later publication Epstein[5] defines "hyperglycemia as an increase in the total amount of blood sugar over the normal, and not merely an increase in concentration or percentage. Thus, it is possible to have a hyperglycemia even when the percentage of sugar is normal or below normal." Fitz and Bock have computed the quantity of sugar in the blood. (See p. 341.)

8. **Hyperglycemia (Extreme).**—It must be remembered that a varying blood sugar is a normal blood sugar, and that it is the

[1] Pemberton, Cajori, and Crouter: Jour. Am. Med. Assn., 1925, **85**, 1793.
[2] O'Hare: Am. Jour. Med. Sci., 1920, **160**, 366.
[3] John: Annals Clin. Med., 1926, **5**, 340.
[4] Epstein and Baehr: Jour. Biol. Chem., 1914, **18**, 21.
[5] Epstein: Proc. Soc. Exper. Biol. Med., 1916, **13**, 67.

extreme in either fasting blood sugar or blood sugar after a meal which is hyperglycemia. The highest percentage of sugar in the blood, 1.7, was found in a case reported by Argy, but the highest percentage, 1.62 per cent, in a case who survived is reported by Curtis and Dixson[1] from my series. (See pp. 214, 651.) The data of a notable case were furnished me by W. H. Olmsted of St. Louis.

"H. F., aged fourteen years. Onset symptoms one year previous. Two weeks before admission sore throat; five days before admission fell down stairs. Completely comatose on admission; could not be aroused for twenty hours. Moderate acetone breath; air hunger; edema of entire body and eyelids; eyeballs soft. Blood-pressure 78/34. Blood sugar 1.40 per cent. Blood CO_2 27.7 per cent. Non-protein nitrogen 140 mg. There was found an ulcerative stomatitis (streptococcus). Complete anuria. Catheter washing showed + sugar, insufficient for ferric chloride test. Large number of white blood cells and red blood cells; no casts. Benzidine ++; acetone, no reaction (too small amount). History of strong ferric chloride before coma Treatment: Insulin and alkali. Died: Uremia."

Case No. 1015 of my series also deserves mention. Here too, anuria was a factor. A schoolmaster, aged forty-seven years, highest weight 216 pounds. Family and past history negative. Indefinite onset of diabetes in February, 1916. Sugar first discovered March 12, 1916, and three days later the urine contained 6 per cent; albumin was reported absent. The patient came under my observation for the first time on March 18, 1916. During the preceding twenty-four hours he had been fasted except for 1 ounce of whisky in 3 ounces of black coffee, which he had taken every two hours. No other liquid had been given save about a pint of water in which a tablespoonful and a half of sodium bicarbonate had been dissolved. During this period he had vomited fluid which contained blood. He was dull, but conscious, and there was no hyperpnea. No edema. He had no fever; pulse 104; arteries not sclerotic. Blood-pressure in right arm 60/—; in left arm, 80/50. The heart was little if any enlarged and there was a systolic murmur at the apex. During the twenty-four hours 30 cc. of urine were obtained by catheter, showing a slight trace of albumin, no diacetic acid, and a positive reaction for sugar. The sediment contained many coarsely and finely granular hyaline casts, pus, and 6 to 8 red blood corpuscles to a field. Death was preceded by edema of the lungs and coma, although in nowise suggesting diabetic coma. The blood sugar taken twelve hours before death contained by the Bang method, 1.15 per cent, 1.45 per cent, and 1.49 per cent of sugar, or an average of 1.37 per cent. The accuracy of the solutions used in the test was immediately controlled with a standard solution of glucose.

[1] Curtis and Dixson: Jour. Am. Med. Assn., 1928, **90**, 1115.

The highest percentage of sugar in the blood ever recorded in a patient with recovery was found in my Case No. 4099. She is a young girl, aged twenty years, with a four-year duration of diabetes who entered the hospital September 18, 1927 with a blood sugar of 1.62 per cent and a CO_2 combining capacity of 13 volumes per cent. She had been in coma eighteen hours before entering the hospital and her local doctor had given her large amounts of cold water and sodium bicarbonate. She too had almost complete anuria. In ten hours after 250 units of insulin her blood sugar was reduced to 0.13 per cent and now, weeks later her blood sugar is 0.29 per cent, her urine is sugar-free and she is discharged from the hospital with an insulin dosage of 30 units.

9. **Hypoglycemia.**—Hypoglycemia had begun to appear as a serious factor in the treatment of diabetes even before the introduction of insulin. Four cases have developed in my own series and 4 others have come to my attention in the clinics of my friends. So serious did the problem appear in 1921 and so evident the cause that I reported the first 3 cases under the caption "The Critical Period of Hypoglycemia in Undernutrition."[1] Even in non-diabetics a prolonged undernutrition may be accompanied by hypoglycemia. This occurred with L. C., whose weight and vitality were brought low by partial pyloric obstruction extending over a period of years. When he came to the hospital for operation the blood sugar three hours after his noon meal was 0.05 per cent. At first it appeared as if prolonged undernutrition was necessary to produce a threateningly low blood sugar, but now it is apparent that this state can develop in the course of a few hours, and, just as in Mann's hepatectomized dogs, be relieved in a few minutes with a few grams of glucose. Just before death a marked hypoglycemia exists. In making studies of the variations of the chemical constituents of the blood from one to forty-eight hours before death, Paul[2] found that the blood sugar rapidly falls to insignificant values.

Hypoglycemia occurs clinically (*a*) as a result of undernutrition, particularly of carbohydrate; (*b*) as a result of prolonged exercise; (*c*) in conjunction with an overdose of insulin; (*d*) in Addison's disease; (*e*) experimentally following extirpation of the liver; (*f*) in status thymicolymphaticus.[3]

Harrop in a recent discussion of the subject emphasizes the development of unconsciousness with few prodromes.

(*a*) **Undernutrition as a Cause of Hypoglycemia.**—The low diets, both as a whole and especially in carbohydrate of the Allen undernutrition era, predisposed to hypoglycemia and not long after it had

[1] Joslin: Med. Clin. of North America, 1921, **4**, 1923.
[2] Paul: Bull. Ayer Clin. Lab. Penn. Hosp., 1925, **9**, 51.
[3] MacLean and Sullivan: Proc. Soc. Exp. Biol. and Med., 1926, **23**, 425.

begun instances of this occurred among my patients. The first deaths were startling and at the time unexplained.

Inanition in diabetes was the recorded cause of death of the first patient, but it takes little imagination to infer the hypoglycemia. Case No. 1085, a frail woman of thirty-four years with a history of diabetes of seven months' duration, became sugar-free with great difficulty despite fasting and a low diet. After four months the sugar in the blood decreased from over 0.5 to 0.1 per cent coincidentally with a fall in weight from 88 to 61 pounds, of which the last 10 pounds were lost between November 3 and 10, 1916. At this time her weight represented a total loss of 95 pounds and was 56 per cent below standard. No subsequent blood-sugar determination was made, but inasmuch as a few days later, without change in treatment or in general condition, she died at her home without pain or coma, there is little doubt that hypoglycemia was present. The data upon the metabolism of this patient will bear insertion. They are remarkable in three ways. (1) The metabolism was —40 per cent which was almost as much substandard as her weight, 56 per cent; (2) the respiratory quotients were high for a diabetic, 0.81, 0.81, 0.79, and 0.81 with but a single value as low as 0.70; (3) the quotient rose after levulose to 0.86 and even 0.90. It is quite possible that the levulose may have prolonged the life of this patient. (Table No. 89.)

A man, Case No. 1831, with onset of diabetes in April, 1917, at the age of thirty-eight years, entered the hospital May 5, 1920, only seven years ago, and yet how little we appreciated then the symptoms of hypoglycemia. The details of the course of treatment with laboratory findings are shown in Table 90. Acidosis was present, sugar in the urine amounted to 2.4 per cent, and in the blood to 0.36 per cent. After four days of undernutrition, during which the total calories consumed amounted to less than 900, followed by two days of fasting, the patient failed to become sugar-free and the blood sugar remained 0.27 per cent. Upon resumption of 14 to 35 grams of protein per day and 3 to 8 grams of fat the blood sugar dropped to 0.11 per cent and on the next day to 0.05 per cent. This unusually low value was assumed to be erroneous and, unfortunately, not reported. Upon the following morning the patient became irrational, disoriented, but an hour afterward again apparently normal, and was able to sit up and even walked around. Physical examination was negative. The next morning he could not be roused, coma gradually deepened, though unassociated with acidosis, and death occurred in a few hours. The blood sugar was 0.04 per cent. No marked loss of weight during hospital stay was observed though he had lost 72 pounds in the three years before admission. Quantitative examinations of the nitrogen in

TABLE 89.—METABOLISM MINUS 40 PER CENT, WEIGHT MINUS 56 PER CENT IN A DIABETIC WITH FALL OF BLOOD SUGAR FROM 0.5 TO 0.1 PER CENT. CASE 1085.

Experimental conditions.	Case No.	Date.	Body weight, naked.	Average pulse-rate.	Carbon dioxide, per minute.	Oxygen, per minute.	Respiratory quotient.	Heat output per 24 hours.		Total heat greater (+) or less (−) than predicted (H. and B.).	NH_3.	Diacetic acid.	CO_2 in alveolar air.	Urinary nitrogen per 24 hours.		Urinary sugar per 24 hours.	Carbohydrate balance.
								Total.	Per kilogram body weight.					Preceding day.	Experimental day.		
		1916															
Postabsorptive	1085	Oct. 11–12	34.2		80	98	0.81	679	20	−40	—	0	—	—	—	0	0
		19–20	30.4	53	82	102	0.81	707	23	−35	—	0	—	15.9	8.8	2	+50
		23–24	31.5	49	85	108	0.79	749	24	−32	—	0	—	14.6	5.9	5	+45
		30–31	32.2	56	81	115	0.70	778	24	−30	1.7	—	20	9.5	6.1	15	+60
		Oct. 31–Nov. 1	31.6	53	77	96	0.81	662	21	−40	—	0	34	6.1	5.2	2	0
Levulose, 50 grams	..	Oct. 19–20	30.4	53	90	105	0.86	734	24	—	—	0	—	15.9	8.8	2	+50
				51	91	113	0.81	783	26								
				51	85	99	0.86	694	23								
				52	100	111	0.90	787	26								
			Av.	52	91	107	0.86	749	25								
Levulose, 50 grams	..	Oct. 23–24	31.5	51	89	113	0.79	778	25	—	—	0	—	14.6	5.9	5	+45
				50	97	125	0.78	864	27								
				50	96	115	0.83	801	25								
			Av.	50	94	118	0.80	816	26								
Levulose, 75 grams	..	Oct. 30–31	32.0	59	104	144	0.73	979	30	—	1.7	—	34	9.5	6.1	15	+60
				62	99	119	0.84	835	26								
				63	110	137	0.80	950	30								
			Av.	61	104	133	0.79	917	28								

TABLE 90.—THE DEVELOPMENT OF HYPOGLYCEMIA DURING UNDERNUTRITION. CASE NO. 1831.

Date.	Volume. cc.	Alb.	Diacetic acid.	Sodium chloride.	Nitrogen, gm.	Sugar in urine, reduction, per cent.	Diet in grams.				Naked weight, pounds.	Non-protein nitrogen.	Bloor's blood fat, per cent.	Blood sugar, per cent.	Alveolar air CO_2, mm. Hg.
							Carbohydrate.	Protein.	Fat.	Calories					
1920															
May 7	..	..	++	..	..	2.3	..	..	..	..	93	..	..	..	30
5- 6	1600	..	+++	..	..	2.4	23	15	3	179	93	..	..	..	30
6- 7	3000	0	+	..	..	1.8	64	33	0	388	96	26.1	..	0.36	
7- 8	2000	..	0	..	..	1.7	36	27	0	252	95				
8- 9	3300	..	0	..	..	0.7	15	5	0	80	96	..	..	..	35
9–10	3800	..	0	6.7	16.9[1]	0.4	0	0	0	0	95				
10–11	2800	..	0	6.1	16.9[1]	0.4	0	0	0	0	94	..	..	0.29	
11–12	4200	0	0	6.1[1]	16.9[1]	0.2	0	0	0	0	94				
12–13	4600	..	0	6.1[1]	16.9[1]	0.1	0	14	4	83	95				
13–14	3800	..	0	6.1[1]	16.9[1]	0	0	21	5	129	94				
14–15	1600	..	0	..	19.6[1]	0	0	35	8	212	94				
15–16	3800	..	0	..	..	0	1	43	10	246	96	..	..	0.11	
16–17	4700	..	0	..	19.6[1]	0	2	50	16	332	91				
17–18	4000	..	0	..	19.6[1]	0	4	57	22	422	90	..	..	0.05	
18–19	2700	0	0	..	19.6[1]	0	13	46	28	488	..	..	1.10		
19	..	..	..	..	..	..	..	Died	1.55 P. M.		..	..	..	0.04	

[1] Aliquot values.

the urine were made and showed an average excretion of 16.9 grams from the tenth to the sixth day before death, and an average excretion of 19.6 grams on four of the five days preceding death.

Experience with these two individuals made it possible to forestall a similar outcome with Case No. 2079. This man developed diabetes in September, 1919, at the age of twenty-nine years and came for treatment on February 5, 1921, weighing 119 pounds after a loss of 66 pounds below his maximum weight. Acidosis was severe, sugar in the urine 5.8 per cent, and blood sugar 0.27 per cent, and even after thirty days of treatment the blood sugar was 0.23 per cent. Yet two days later the patient became sugar-free, and within a week the blood sugar was 0.12 per cent, and on the forty-third day 0.09 per cent. This premonitory fall in blood-sugar being noticed, the diet was at once changed to carbohydrate 19 grams, protein 59 grams, fat 62 grams. Despite the fact that this patient had required so long to become sugar-free, steady additions of carbohydrate were made to the diet until on the forty-ninth day after admission the total carbohydrate was 68 grams, the protein 71 grams, the fat 66 grams, and the blood sugar was 0.05 per cent. Even one hour after a meal two days later, when the carbohydrate was 86 grams, the blood sugar was 0.1 per cent. The patient was then discharged with carbohydrate 82 grams, protein 74 grams, fat 66 grams, calories 1234, weight 92 pounds, in contrast to a weight of approximately 110 pounds on the first day of treatment.

Two weeks later the report came that his blood sugar was 0.1 per cent, and the newly acquired tolerance was preserved. Such a gain in tolerance from such a critical state had not before come to my attention. On November 20, 1921, he was said to have died from cardiac disease but no coma.

While on the watch for insulin reactions the fourth case of hypoglycemia was discovered in an old lady of sixty-four years, Case No. 2716, whose diabetes began one year and nine months before in October, 1920. Her loss in weight amounted to fully 100 pounds, essentially all of which had occurred since her disease began. At no time did she receive insulin. On the morning of July 18, 1922, the blood sugar was 0.33 per cent, the plasma creamy with 3.4 per cent blood fat. Three days later following a sharp restriction of diet the percentage of blood sugar was 0.03. Mrs. L. felt that she was dying and actually was too weak to feed herself. Her pulse was of small volume and rapid and only after frequent feedings with oatmeal gruel did she recover. By September, 1923, the patient required 42 units of insulin daily, and she died January, 1926, in her sixth attack of coma.

A fifth case of hypoglycemia occurred in another hospital.[1] The patient was a man who was 65 per cent overweight when he developed diabetes. Two weeks before his death two-thirds of his weight had vanished and 31 pounds of it in the preceding forty-four days. A pound of body flesh is equivalent to about 1500 calories and consequently his calorie deficit between December 9 and January 22 was 46,500 calories or roughly 1000 calories a day. His inanition had reached 36 per cent below standard weight on January 22 and in the ensuing two weeks undoubtedly fell still lower. On December 10, 1922, the blood sugar was 0.16 per cent. On January 17, 1923, the blood sugar was 0.25 per cent, on January 18, it was 0.23 per cent, and insulin which had been given intermittently in doses of 5 and 10 units daily was omitted and the diet changed to carbohydrate 10 grams, protein 20 grams, fat 40 grams. By January 22 the blood sugar was 0.1 per cent and by January 31, 0.07 per cent, although the carbohydrate was 40 grams, protein 40 grams, and fat 100 grams. Upon the following day despite a further increase in diet to carbohydrate 80 grams, protein 65 grams and fat 120 grams the blood sugar was 0.042 per cent, and he died February 5, 1923. Autopsy showed hyaline degeneration of the islands of the pancreas as the primary fatal lesion, and focal pneumonia, edema of the lungs, and slight arteriosclerosis as the secondary or terminal lesions.

Woodyatt[2] refers to a case of hypoglycemia coming to his attention, but not on his service, who died in convulsions. N. B. Herman[3] has written about a patient under his observation at the Johns Hopkins Hospital, making the eighth non-insulin case of hypoglycemia. Dr. Herman has kindly furnished me data about this case in connection with which he is planning to report later in detail. "A man, aged forty-six years, was told six years ago that he had diabetes and for four years lived on a diet prescribed by his physician. At the end of this time, still feeling rather weak, he broke diet and ate whatever the rest of the family ate. From 1917 to 1921 he lost about 25 pounds and from 1921 to November, 1922, about 35 pounds. In November, 1922, following the use of male fern for supposed tape worm, an intractable diarrhea started and continued to the time of death.

"On admission his weight was 93 pounds and his height 6 feet, 50 per cent below standard. After one day on calculated maintenance diet his blood sugar was 0.054 per cent. He was immediately

[1] Cabot, R. C., and Cabot, H.: Case Records, Massachusetts General Hospital, April 17, 1923, vol. **9** (Case 9161).

[2] Woodyatt: Jour. Metab. Research, 1922, **2**, 793.

[3] Personal communication, May 14, 1923.

put on ward diet and his blood sugar rose to 0.284 per cent. There was sugar in the urine, of course, at this time. His diet was modified and his blood sugar varied between 0.054 and 0.09 per cent. The diarrhea remained about the same and we were never able to be sure about the cause. There was no evidence of outspoken pancreatic insufficiency; the stool was lower than normal in diastase content. The patient seemed to be getting along a little better than usual when he suddenly went into coma and died, the intraveneous injection of 6½ grams of glucose having no effect. The blood sugar at the onset of coma was 0.017 per cent."

Marked loss of weight has characterized all of these cases for whom the data have been recorded. In 2 of the cases sudden decline in weight, although already low, took place shortly prior to the hypoglycemia. In 2 instances the excretion of urinary nitrogen per kilogram body weight was high, 0.216 grams, and from 0.523 to 0.165 grams. The metabolism in Case No. 1085, who presumably died of hypoglycemia a few days later, was —40 per cent. At the time I reported this first case no similar one had come to my attention.

(*b*) **Exercise as a Cause of Hypoglycemia.**—The blood sugar of the competitors in a 25-mile Marathon run was studied by Levine[1] and others and found to be moderately diminished in two runners and markedly diminished in four. A close correlation existed between the physical condition of the runners at the finish of the race and the level of the blood sugar. Those competitors who had extremely low blood sugars presented a picture of shock not unlike that produced by an overdose of insulin. Percentages as low as 0.05 and 0.049 were obtained, but when these same individuals ate candy during the run, the percentages were 0.114 and 0.092 and they finished in very good condition. Soon after the beginning of exercise there is an initial rise in blood sugar as Levine and his co-workers, as well as Rakestraw,[2] previously showed.

Accidents undoubtedly result from hypoglycemia due to overexercise. My strenuous relative of equal age, weight 100 pounds, who holds the cup for broken bones, rode to hounds, then home five miles, took her usual meagre breakfast, attended to the day's household affairs, exercised the dogs, and then went for another ride on a spirited hunter. Some time later in the forenoon she was found on the ground near a jump. She had no recollection whatsoever of taking the jump and never would have taken it in the manner disclosed by the hoof marks of the horse, if she had been in the full possession of her faculties. Therefore, I believe the evidence points

[1] Levine, Gordon, and Derick: Jour. Am. Med. Assn., 1924, **82**, 1778; Gordon, Kohn, Levine *et al.*: Jour. Am. Med. Assn., 1925, **85**, 508.

[2] Rakestraw: Jour. Biol. Chem., 1923, **56**, 121.

to hypoglycemia. Having recovered from her broken pelvis, though not a diabetic, she now carries a lump of sugar when she rides.

In their treatment of 5 epileptic but not diabetic children with a ketogenic diet Talbot *et al.*,[1] and Shaw and Moriarty[2] noted hypoglycemia upon several occasions which in 1 instance was 0.038 per cent, and the symptoms were sufficient to lead to the administration of carbohydrate.

(*c*) **Insulin as a Cause of Hypoglycemia.**—Hypoglycemia begins to develop immediately as a result of administration of insulin, and reaches a maximum in three-quarters of an hour, almost irrespective of whether the insulin is given subcutaneously or intravenously, though occurring a little faster with the intravenous administration, but producing the same result in an hour. The extent of its action depends chiefly but not entirely on the glycogen in the liver. The initial fall is not closely related to the number of units. If the sympathetic nervous system in animals is paralyzed with ergotamin or section of the splanchnics, recovery from hypoglycemia is greatly delayed. Recovery does not take place until the blood sugar reaches a low normal level. If no glycogen is available, gluco-neo-genesis is necessary. An insulin reaction varies according to the diffusion of sugar in the blood and tissues, but the recent work showing the interaction of the thyroid and adrenal glands on insulin is important. The reaction may be due as Foshay believes to the lowered sugar in the blood corpuscles even though the total blood sugar is normal, but his theory still needs confirmation as has been noted on page 194.

(*d*) **Addison's Disease.**—See Section XV, p. 873.

(*e*) **Extirpation of the Liver as a Cause of Hypoglycemia.**—In the hypoglycemia of Mann's and Magath's dogs glucose alone was specific save for maltose and mannose. Lactose, levulose, sucrose, glycerol, lactic acid, and even epinephrin and pituitrin were without effect.

(*f*) **Status Lymphaticus.**—MacLean and Sullivan[3] in studying the status thymolymphaticus have found low blood sugars, although seldom if ever low enough to provoke symptoms.

(*g*) **Cancer of the Islands of Langerhans.**—In a case reported by Wilder[4] metastases in the liver developed and from these potent insulin was obtained. Severe hypoglycemia kept recurring over a period of months, and for the last few weeks of his life was so severe as to necessitate his taking 1000 grams of cane-sugar daily.

(*h*) **Progressive Muscular Dystrophy.**—McCrudden and Sargent[5] found the blood sugar 0.064 per cent in a case of progressive muscular

[1] Talbot *et al.*: Boston Med. and Surg. Jour., 1927, **33**, 218.
[2] Shaw and Moriarty: Am. Jour. Dis. Child., 1924, **28**, 553.
[3] MacLean and Sullivan: Proc. Soc. Exp. Biol. and Med., 1926, **23**, 425.
[4] Wilder: Jour. Am. Md. Assn., 1927, **89**, 348.
[5] McCrudden and Sargent: Arch Int. Med., 1916, **17**, 465.

dystrophy. When the blood-sugar concentration was raised with carbohydrate an increase in health, strength, and weight ensued.

(*i*) **Postoperative Thyroidectomy.**—After thyroidectomy hypoglycemia may occur in dogs[1] and in humans.[2]

Parsons[3] reports a case of benign diabetes of nine years' duration discovered during pregnancy. A not dissimilar case is that of Shapland's whose renal threshold was low and a disabled gall-bladder apparently the inciting factor. My patient, Case No. 2296, has survived his diabetes 14.8 years. He develops reactions readily and some of them seem to occur when the blood sugar is comparatively high.

10. **The Blood Sugar in Relation to Clinical Aspects of the Disease.**—The diagnosis of diabetes is aided greatly by a knowledge of the percentage of the blood sugar. When the fasting blood sugar percentage is above 0.13, the test should be repeated, and if constantly elevated, it indicates diabetes. The same is true for a blood-sugar percentage of 0.18 per cent after a meal, and a value of 0.17 per cent is suspicious. The demonstration of a normal blood-sugar percentage coincidently with the presence of glycosuria is reassuring and suggests renal glycosuria. For exceptions, see Table 88. According to Petrén the twenty-four hour blood-sugar curve in diabetic patients during a fasting day showed as a rule that the drop in the blood sugar is greatest during the first six hours, a smaller decrease during the next six hours, while during the last twelve hours a very slight drop or even an increase may occur.

Estimations of the blood sugar are of great value in the treatment of diabetes. An increase in the percentage of blood sugar almost invariably precedes the appearance of glycosuria. It thus enables earlier measures to be undertaken to eradicate the cause. Though valuable, it is certain that such tests will be made in but a very small proportion of the diabetics who need treatment for some years to come. The preceding sentence was written in 1923. Writing in 1927 I believe it to be the exception for a patient to die of diabetes in Massachusetts without a blood-sugar estimation having been made. This is partly because so many diabetics die in hospitals. In 1925, 51 per cent of the diabetics dying in Boston died in hospitals.

Cases can be treated very satisfactorily without such estimations or with infrequent estimations, and in proof Table 91 is submitted, showing the course of the disease in 10 children in the first decade of life, untreated with insulin, and 8 similar children treated without any estimations of the blood sugar.

Time and insulin unravel many queer conceptions. In the third

[1] Janney and Isaacson: Arch. Int. Med., 1918, **22**, 160.
[2] Holman: Bull. Johns. Hop. Hosp., 1923, **34**, 69.
[3] Parsons: Boston Med. and Surg. Jour., 1926, **195**, 660

edition Table 91 was printed to show that even without blood-sugar tests patients lived long. Since classification of the diabetics last year, this table becomes explainable. I reprint the table exactly as before, but in italics insert classification, placing in heavy type alone the two remaining cases whose blood sugar has not yet been done but should be done when the opportunity is available. I am all the more ready to print this table again because not one of the living diabetic children in 1923 recorded in the table has since died. I believe that case numbers should be given by those who promulgate any types of treatment so that, after a series of years, their records stand disclosed.

TABLE 91.—THE COURSE OF DIABETES IN CHILDREN WITH INFREQUENT BLOOD SUGAR TESTS.[1]

With blood sugar tests.			Without blood-sugar tests.			
Classification.[2]	Case No.	Age at onset.	Duration years.	Classification.[2]	Case No.	Age at onset.	Duration years.
			Living				
P. D.	1162	5.0	12.1	*Unc.*	**1035**	**8.0**	**11.3**
D. M.	1484	9.9	10.3	*P. D.*	**1139**	**2.0**	**11.1**
D. M.	1568	8.1	9.5				
R. G.	1612	10.6	10.2				
D. M.	1707	6.2	9.6	*D. M.*	2084	3.0	8.1
D. M.	1753	8.8	11.5	*D. M.*	2997	5.0	12.3
			Fatal				
D. M.	894	1.6	8.0	*D. M.*	534	9.0	6.6
D. M.	949	7.3	7.0	*D. M.*	620	4.0	5.8
D. M.	1151	3.6	8.2	*D. M.*	750	10.0	5.2
D. M.	1231	9.5	6.0	*D. M.*	1202	2.0	5.8
R. G.	1266	5.4	6.5				

Table 91 is inserted here not to discredit blood-sugar estimations, but to show that there is no excuse for a case to be neglected because such laboratory facilities are not available. Children will live a considerable number of years without them, but Carrasco Formiguera[3] very properly points out that with adults a table of this sort would yield far less favorable results because of the difference in renal threshold.

11. **The Prognosis in Relation to Blood Sugar.**—The prognosis is also aided by blood-sugar tests, but, as Host[4] has said, "it is not so much the initial blood sugar as the degree to which it can be lowered by treatment." Gray,[5] analyzing the records of 210 of my fatal

[1] Durations compiled to July 1, 1927.

[2] *D. M.* = Diabetic; *P. D.* = Potential diabetic; *R. G.* = Renal glycosuria; *Unc.* = Unclassified.

[3] Carrasco Formiguera: Joslin, Tratamienta de la Diabetes Sacarina, Montaner y Simon, Barcelona, 1925, p. 177.

[4] Host: Jour. Am. Med. Assn., 1924, **82**, 430.

[5] Gray: Med. Clinic of North America, 1923, **7**, 675.

TABLE 92.—RELATION OF BLOOD SUGAR (FASTING, FOLIN AND WU) TO PROGNOSIS. (GRAY.)

Blood sugar, per cent.	No. of patients.	Duration after blood sugar to death, years (average)	Fatal.[1]		Living.[2]		Total.[3]	
			No. of cases.	Duration after blood sugar, years.	No. of cases.	Duration after blood sugar, years.	No. of cases.	Duration after blood sugar, years.
0.40–0.57	10	0.66	3	1.3	3	3.7	6	2.5
0.30–0.39	48	1.13	30	1.9	41	4.1	71	3.1
0.20–0.29	90	1.23	91	2.1	180	4.1	271	3.5
0.19 or less	62	1.81	76	2.9	270	4.3	346	3.9

cases, has tabulated the percentage of blood sugar when first seen in connection with the date of death. The table shows quite clearly that the higher the percentage of sugar in the blood when the patients come for treatment, the shorter the duration of the disease. Thus, the 10 patients who showed a blood sugar of 0.4 per cent or above succumbed within two-thirds of a year, whereas those with a blood sugar percentage between 0.3 and 0.39 lived 1.13 years, those with a blood sugar 0.2 to 0.29 per cent, 1.23 years, while those whose blood sugar was less, 0.19 per cent, lived 1.81 years. Of course, it must be emphasized that these values relate purely to fatal cases of diabetes and that the causes of death in these cases may have not been directly dependent upon the diabetes but upon other factors. Gray's table, however, does indicate that the higher the blood sugar, the more serious the diabetes. It has now been amplified by adding to it 200 consecutive fatal cases of diabetes whose deaths occurred subsequent to the introduction of insulin, though by no means all of these cases had insulin, because they lived all over the country. Only those fatal cases were taken who first came for treatment between April 1, 1919, and September, 1923. At a glance one can see that a blood sugar of 0.40 per cent or above is serious, although even such cases live twice as long as formerly. The table also shows how rare such a blood-sugar percentage is when a patient is first seen. The dependence of prognosis upon the sugar percentage is shown by the remaining figures. For comparison the data for 494 consecutive cases have been added who were living July 1, 1926, and also seen first between April, 1919, and September, 1923. These figures illustrate far less than the fatal cases the prog-

[1] Compiled from 200 consecutive fatal cases who died between August, 1922, and July 1, 1926, and who were first seen between April, 1919, and September, 1923.

[2] Compiled from 494 consecutive living cases who were first seen between April, 1919, and September, 1923, and who were living July 1, 1926.

[3] Compiled from the 200 fatal and 494 living cases.

nostic value of the blood sugar, but the small number of cases alive with a blood sugar above 0.40 per cent compared with those whose blood sugar was 0.19 per cent or less tells the story. Perhaps the fairest idea of the prognostic value of the blood sugar is shown by the right hand column of the table, which gives the average values for both living and dead.

Patients in coma have high values for the sugar in the blood, yet many live for years upon recovery. In Table 93 the figures for the blood sugar in coma and its relation to prognosis are collected. The table has the defect that in 8 cases insulin had preceded the taking of the blood for analysis. It is quite evident from the per cent of

TABLE 93.—BLOOD SUGAR IN COMA AND ITS RELATION TO PROGNOSIS.[1]

Blood sugar, per cent.	Fatal cases. No.	Fatal cases. Duration days.	Living cases. No.	Living cases. Duration years.
0.70–0.83	2	**1**	5	**0.6–1.5**
0.60–0.69	2	**7–8**	3	**0.7–2.0**
0.50–0.59	2	**21–600**	4	**0.5–3.0**
0.40–0.49	3	**1–6**	7	**1.0–2.3**
0.30–0.39	2	**2–7**	8	**0.1–3.4**
0.20–0.29	..	.....	3	**0.8–3.1**
0.19 or less	..	.....	2	**2.0**

sugar in the blood in coma that a close relation to prognosis does not exist.

Petrén has regarded a percentage of blood sugar of 0.24 as of serious import. His own data have been collected and discussed by himself[2] and Malmros.[3] It is a cautionary signal to all who use insulin and thereby allow the percentage of blood sugar to rise, because of the increased diets permitted.

The method of Ivar Bang was employed in the earlier analyses, the Lewis-Benedict method in 1916 and 1917, and the Folin-Wu method from April, 1919, to date.

TABLE 94.—THE INFLUENCE OF AGE UPON THE BLOOD SUGAR (FASTING) IN TRUE DIABETES.

Age, years.	1916 Cases No.	1916 Blood sugar, per cent, average.	1922–1923 Cases No.	1922–1923 Blood sugar, per cent, average.	1926 Cases No.	1926 Blood sugar, per cent, average.
0–10	11	0.19	20	0.19	20	0.18
11–20	23	0.21	..	....	20	0.18
21–30	27	0.24	20	0.19	20	0.19
31–40	28	0.23	..	....	20	0.24
41–50	18	0.22	20	0.22	20	0.21
51–60	35	0.20	..	....	20	0.21
61–70	18	0.21	20	0.24	20	0.23
71 on	2	0.27	20	0.22	20	0.19

[1] The first case occurred on April 23, 1923, the last case on August 8, 1926, and the table is compiled to September, 1926. In heavy type are the extremes of duration.

[2] Petrén: Compt. rendu de la Soc. de Biol., 1925, **93**, 380.

[3] Malmros: Acta Med. Scand., 1925, **62**, 294.

12. **Age.**—The influence of age upon the percentage of sugar in the blood of diabetics is negligible. Table 94. Furthermore, there appears to be no change in the blood sugar of a routine series of cases as compared with similar series either before or at the time treatment with insulin was introduced.

In general the younger the patient the lower the blood sugar, but the converse is not true, and indeed the difference between different decades is slight. Four cases, all under the age of ten years, showed 0.06, 0.04, 0.08, and 0.07 per cent of sugar within a few days of the beginning of treatment in the Allen Epoch of undernutrition. Their course in the hospital was by no means as favorable as such low percentages would imply. The total duration of the disease was 1 year in one of these cases, 2 and 3 years in another, and 6 years and 6.5 years in the third and fourth. Death resulted from coma in 3 and from accident in the other.

Normal infants, fasting, under two weeks old have a low blood sugar averaging 0.087 per cent. In ill-nourished infants lower values are found.[1] At three to five hours after nursing the amount varies in healthy infants from 0.085 per cent to 0.125 per cent.[2]

13. **Duration.**—The duration of the disease does not bear a close relation to the percentage of sugar in the blood. In general there is a tendency to a slight rise in the blood sugar, but it is so moderate as to afford little support to the theory that diabetes becomes more severe the longer it lasts. It is distinctly encouraging to see that cases with duration over ten and even fifteen years should show so little increase. One would have expected that a rising renal threshold alone would have exerted more of an influence.

TABLE 95.—THE INFLUENCE OF THE DURATION OF THE DISEASE UPON THE BLOOD SUGAR IN DIABETES.

Duration, years.	1916		1922–1923		1923–1926	
	Cases No.	Blood sugar, per cent, average.	Cases No.	Blood sugar, per cent, average.	Cases No.	Blood sugar, per cent, average.
Under 1 yr. . .	54	0.21	20	0.18	8	0.18
1– 5 . . .	81	0.22	20	0.21	22	0.23
6–10 . . .	26	0.22	20	0.26	27	0.21
11–15 . . .	12	0.23	20	0.21	52	0.19
16–29 . . .	7	0.22	20	0.23	31	0.19

The tables cited under prognosis, Tables 92 and 93, also throw light on the blood sugar in relation to the disease.

Gray writes, "A rise in blood sugar might appear if instead of tabulating averages of groups of patients with successive durations, one either considered the same patient at different periods, or in

[1] Brown: Quart. Jour. Med., 1925, **18**, 175.
[2] Stammers: Phys. Reviews, 1926, **6**, 630.

each group considered not the average, but the relative frequency of different blood thresholds at different periods from onset."

I have met this suggestion through the compilation of Table 96 which shows the changes in blood sugar of the same patient at intervals either of five years or ten years following the date of the first blood-sugar estimation. For these 50 cases the tendency of the blood sugar was to be lower rather than higher after intervals of five or ten years between tests.

TABLE 96.—THE BLOOD SUGAR IN DIABETIC PATIENTS DURING FIVE OR MORE YEARS ACCORDING TO THE AGE OF ONSET OF THE DISEASE.

Age at onset.	First observation,		Second observation, 5–9 years later.		Third observation, 10–12 years later.	
	Cases No.	Average B. S. per cent.	Cases No.	Average B. S. per cent.	Cases No.	Average B. S. per cent.
0–19	1	0.18	..	....	1	0.15
20–39	14	0.18	9	0.15	8	0.17
40–59	35	0.18	24	0.19	32	0.19

14. **Glycosuria.**—The presence of sugar in the urine (during the preceding twenty-four hours) is almost invariably accompanied by an increase of sugar in the blood. Among 207 blood-sugar analyses, there were only 5 instances in which this did not occur. On the other hand, the sugar in the blood may be as high as 0.5 per cent without glycosuria. This is most apt to occur in nephritis. John[1] found a blood sugar of 0.31 per cent to be the highest percentage without glycosuria in a series of 1000 diabetics. Major and Davis[2] observed 7 patients between the ages of eleven and thirty-five years without arteriosclerosis or sign of renal disease, who were taking insulin, whose percentages of blood sugar were between 0.425 and 0.250 without glycosuria. Rabinowitch[3] also has observed a rising renal threshold under insulin treatment in young diabetics.

In studying the question of high renal threshold in 1000 of my cases, Dr. C. T. Stone[4] felt that they afforded an unfavorable prognosis inasmuch as autopsy records appeared to show that the high renal thresholds often were associated with hyalization of the islands of Langerhans.

In Table 97 is shown the range of the percentage of blood sugar in a group of my cases and the quantity of sugar excreted in the urine

[1] John: Arch. Int. Med., 1927, **39**, 67.
[2] Major and Davis: Jour. Am. Med. Assn., 1925, **84**, 1798.
[3] Rabinowitch: Brit. Jour. Exp. Path., 1926, **7**, 352.
[4] Stone: Jour. Am. Med. Assn., 1926, **87**, 388.

in the preceding twenty-four hours. On the average the higher the quantity of sugar excreted, the higher the percentage of sugar in the blood. Exceptions are numerous and are caused by the cases with a high renal threshold or by renal glycosuria. Case No. 6181 at his first visit had a blood sugar of 0.54 per cent and I should judge the twenty-four-hour urine contained at least 150 grams glucose.

TABLE 97.—THE BLOOD SUGAR IN RELATION TO THE TOTAL QUANTITY OF GLUCOSE EXCRETED IN THE PRECEDING TWENTY-FOUR HOURS.

Excretion of glucose in preceding 24 hrs., grams.	Cases, No.	Analyses, No.	Blood sugar, per cent. Lowest.	Average.	Highest.
0	135	321	0.07	0.19	0.50
1– 5	41	62	0.11	0.24	0.50
6– 10	19	29	0.09	0.24	0.35
11– 20	27	38	0.18	0.28	0.50
21– 30	18	22	0.15	0.26	0.43
31– 50	18	25	0.19	0.24	0.45
51– 70	11	12	0.11	0.28	0.45
71–100	8	9	0.24	0.32	0.40
101–150	6	6	0.19	0.31	0.38
151–200	1	1	0.13	0.13	0.13
318	1	1	0.25	0.25	0.25

TABLE 98.—ANALYSES OF BLOOD-SUGAR FASTING MADE UPON DIABETIC PATIENTS DURING THE COURSE OF TREATMENT.

Treatment without insulin.				Treatment with insulin.			
Year.	No. of cases.	Hospital cases, blood sugar. Within 3 days of admission, per cent.	Hospital cases, blood sugar. At discharge, per cent.	Year.	No. of cases.	Hospital cases, blood sugar. Within 3 days of admission, per cent.	Hospital cases, blood sugar. At discharge, per cent.
1916	33	0.22	0.17	1922	30	0.27	0.19
1919	100	0.19	0.14	1923	100	0.22	0.17
1922	100	0.22	0.15	1927	50	0.22	0.19

The blood sugar of Case No. 564 was 0.13 per cent. He represented a severe type of diabetes in a boy aged sixteen years who, although ultimately becoming sugar-free, remained so with strict adherence to diet. He lived for ten years when he succumbed to a gastric ulcer. Case No. 706 also had a blood sugar of 0.11 per cent. He likewise represents a serious form of diabetes, but in spite of this fact he eventually became sugar-free and lived 7.7 years until February 4, 1923, when he died of perforation of peptic ulcer. These low blood-sugar percentages were simply the result of treatment by undernutrition and therefore illustrate only the results of

treatment by that method. The blood sugar indicated better than the clinical impression the true nature of the case.

No essential change has taken place in the percentage of blood sugar in patients admitted to the hospital for treatment in the years 1916, 1919 and 1922 as shown by various groups of cases collected in Table 98. On the other hand, the blood sugar at discharge is a trifle lower. It reached its lowest value in 1919 when undernutrition was more strenuously followed than now. For comparison three series of cases treated with insulin are added. The first series is the earlier and hence made up of more severe cases, the second series comprises both severe and moderately severe diabetics.

The percentage of sugar in the blood in coma is increased and may be very high at onset, remain high without glycosuria in the case of renal block, and fall nearly to normal with insulin and the low diet before the coma is over. For the blood sugar in coma see Section IX, page 650.

15. **Glycolysis in Blood.**—For many years, despite certain contradictory evidence, the impression has existed that the disappearance of sugar from unpreserved blood *in vitro* proceeds at a slower rate in diabetic blood than in normal blood. Numerous investigations have been carried out with the idea of discovering any fixed rule by which such glycolysis takes place. Since even now the subject is one of dispute and has not as yet been shown to play a significant part in carbohydrate metabolism, I dismiss it without statement of opinion by referring to the recent paper of Lemann and Liles[1] who quote the available literature and conclude that glycolysis proceeds more slowly when there is hyperglycemia, however produced, and that administration of insulin, *per se*, does not affect this behavior. They suggest that delayed glycolysis in diabetic blood may be due to the hyperglycemia *per se* and not to any essential quality of the blood characteristic of the disease.

B. BLOOD LIPIDS.

By HAZEL M. HUNT
AND
ELLIOTT P. JOSLIN.

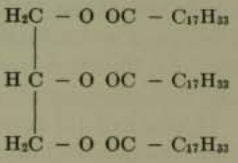
1. **Blood Lipids in Health.**—Lipids,[2] the name given to all substances closely connected with fat metabolism, are normally present in blood in four forms:

(*a*) *Triglycerides.*—Glycerides of the higher fatty acids, usually oleic, palmitic, or stearic. These glycerides are fatty acid tri-esters

[1] Lemann and Liles: Jour. Lab. Clin. Med., 1926, **11**, 339.

[2] Lipids is the new term recommended by the International Congress of Pure and Applied Chemistry.

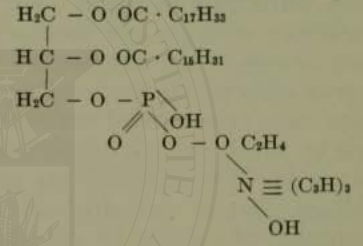
formed from glycerol and one or more of the higher fatty acids. A good example is triolein.



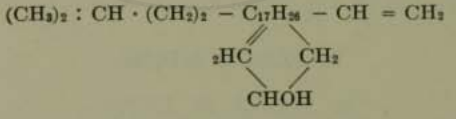
Triglycerides yield about 98 per cent of their weight of fatty acids.

(*b*) *Phosphatides.*—Glycerol esters of the higher fatty acids but containing phosphorus in the molecule. Lecithin and cephalin are the best known phosphatides and lecithin is the more important of the two. It is a glyceride containing 2 molecules of fatty acid and 1 molecule of phosphoric acid which is in turn combined with 1 molecule of cholin. The fatty acid composes about 70 per cent of the whole compound and the phosphoric acid about 12 per cent.

Oleo-palmitic lecithin contains 1 molecule of glycerin, 2 molecules of fatty acid (oleic and palmitic acids), 1 molecule of phosphoric acid, 1 molecule of cholin.



(*c*) *Cholesterol.*—A substance whose chemical formula is still being studied. It is believed to be a secondary alcohol belonging to the terpene series of compounds and probably contains two double bonds. The formula ascribed to it is as follows:



About two-thirds of the cholesterol in the plasma is combined with fatty acids, thus forming esters, but in the corpuscles all of the cholesterol is free.

(*d*) *Cholesterol Esters.*—Combinations of cholesterol with a fatty acid, ordinarily palmitic or linoleic acid. In the cholesterol esters the fatty acids constitute about 44 per cent of the whole molecule.

The total fatty acids, which comprise the fatty acids in the glycerides, the fatty acids in lecithin and the fatty acids combined with cholesterol, represent the predominant form, about 50 per cent,

in which fat appears in the blood. The average normal percentage of fatty acids is 0.37, range 0.29 to 0.42 per cent. The lecithin comes next and the average is 0.3 per cent, range 0.28 to 0.33 per cent. Cholesterol, in both free and combined forms, is least abundant, the average being 0.22 per cent, the range 0.19 to 0.25 per cent.

Analyses for the total fatty acid, lecithin, and cholesterol in the whole blood, the plasma, and the corpuscles are given in Table 99, which is based upon Bloor's figures for 19 normal individuals. The plasma affords the best index of changes in the lipids of the blood. The lipid content of the corpuscles varies but slightly in health or disease and little attention need be paid to it.

The analyses of the fat in the blood made upon my own patients have been performed upon the plasma of blood obtained in a post-absorptive condition unless otherwise stated. Usually the blood has been secured fourteen hours after the last meal. The analyses have been begun as a rule not later than two hours from the time the samples of blood were obtained.

The influence of food upon the blood fat is striking, but as yet there is no fat tolerance meal to serve as a standard. Speculation suggests that as wide a variation might exist in the blood lipids after the ingestion of fat in diabetes as takes place in the blood sugar in diabetes after the ingestion of carbohydrate. Bloor[1] used standard doses of olive oil in his study to determine the utilization of fat in diabetic dogs. Thus he found the blood fat to be 0.6 per cent twenty-four hours after a meal, but 0.73 per cent three and a quarter hours after 100 cc. olive oil, 1.2 per cent, the peak of the rise, in six and a quarter hours, and 0.87 per cent in eight hours. Surraco[2] noted that the cholesterol could be easily influenced in ascitic fluid by changes in the diet. Luden, studying the influence of diet upon cholesterol in the blood, found a very definite increase in blood cholesterol when diets rich in cholesterol were fed, as did Landau and his co-workers.[3] McClure and Huntsinger[4] report increases in blood cholesterol and fatty acids after a meal, regardless of the character of the foodstuffs. When fed in relatively large amounts there is some evidence that it or its esters may be deposited in the tissues and walls of the bloodvessels.[5]

Blaisdell and Chandler[6] have also noted an increase of cholesterol in the blood following the feeding of cholesterol and of egg yolks to dogs and rabbits.

[1] Bloor and Gilette: Proc. of Soc. Exp. Biol. and Med., 1925, **22**, 251.
[2] Surraco: Jour. Am. Med. Assn., 1918, **70**, 1269.
[3] Landau: Ann. de Méd., 1925, **18**, 143.
[4] McClure and Huntsinger: Jour. Biol. Chem., 1928, **76**, 1.
[5] MacCallum: Physiol. Rev., 1922, **2**, 70.
[6] Blaisdell and Chandler: Am. Jour. Med. Sci., 1927, **174**, 492.

TABLE 99.—LIPIDS OF NORMAL BLOOD.[1]
(Compiled from tables of W. R. Bloor, Jour. Biol. Chem., 1916, **25**, 585.)

	Total fatty acids, grams per 100 cc.			Lecithin, grams per 100 cc.			Cholesterol, grams per 100 cc.			Total lipids, calculated.
	Whole blood.	Plasma.	Corpuscles.	Whole blood.	Plasma.	Corpuscles.	Whole blood.	Plasma.	Corpuscles.	Whole blood.
Highest normal . . .	0.42	0.47	0.45	0.33	0.26	0.48	0.25	0.31	0.24	0.76
Av. (19) normals . . .	**0.37**	**0.39**	**0.34**	**0.30**	**0.21**	**0.42**	**0.22**	**0.23**	**0.20**	**0.68**
Lowest normal . . .	0.29	0.30	0.27	0.28	0.17	0.35	0.19	0.19	0.17	0.57

[1] The results of the analyses of blood lipids of both males and females have been combined in this table.

Fasting, hemorrhage and narcosis cause an increase in the blood lipids, but this is not constant, apparently depending upon the nutritional condition of the animal. In those instances without marked increase it could be obtained after a period of forcing fat food. However, in starving animals, according to Rosenfeld, the fat mobilization ordinarily produced by phosphorus poisoning in dogs was absent.

The total fatty acids of the blood are increased in nephritis, pneumonia, pregnancy and in extremely severe anemia. In these conditions acid poisoning may be a factor.

Lecithin appears to be an intermediate stage in the metabolism of fat. After passage through the intestinal wall when the fat reaches the blood or soon after, there is an increase in lecithin which is believed to have its origin in the fat and to be a stage in its metabolism. Lecithin may be increased in nephritis and high values have been observed in the blood corpuscles in leukemia, but in the cachexia of carcinoma low values are obtained. It has also been reported increased in experimental conditions in animals, such as in the anemia produced by continued bleeding, and in depancreatized dogs. Lecithin is destroyed upon standing by the action of an esterase in the corpuscles, and this may account for the low values occurring in the literature.

Cholesterol is a relatively well defined and stable chemical substance, and is the lipid which can be most readily determined. Its significance is still an unsolved problem, but that it has a very definite and important role in the fatty acid metabolism is well recognized. Professor Bloor[1] says of it: "It is universal in its occurrence wherever there are other lipids, sometimes free and sometimes in the form of esters. In the blood, when not disturbed by food absorption, it bears a constant relation to lecithin and in the plasma to its own esters. In the corpuscles it is always found free. In the blood plasma it increases as other lipids increase, and any increase of cholesterol due to overfeeding is followed by an increase in other lipids. In blood plasma it occurs both free and combined in the proportion of about 1 part free to 2 parts combined." From the work of Hürthle[2] and the more recent work of Bloor[3] the cholesterol esters are believed to be the palmitate and the linoleate. Cholesterol seems to be the main vehicle for the transfer of the unsaturated fatty acids in the blood stream. Bloor states in this regard: "The significance of this fact is not altogether clear, for while it seems to connect cholesterol closely with the intermediary metabolism of the fatty acids, the cholesterol esters are in contrast to

[1] Bloor: Jour. Metab. Res., 1923, **4**, 549.
[2] Hürthle: Ztschr. Physiol. Chem., 1895–1896, **21**, 331.
[3] Bloor: Jour. Metab. Res., 1923, **4**, 549.

lecithin, very stable compounds. It brings to mind the familiar experiments of Knoop who found on feeding phenyl derivatives of the fatty acids that fatty acid chains were reduced 2 carbons at a time to within 1 or 2 carbon atoms of the ring. It may be that cholesterol forms such an unburnable 'handle' from which the fatty acids are burned."

Sunderman and Weidman[1] investigated the blood cholesterol of various animals in relation to their normal diets and plotted the curves for each species. Their list includes both herbivorous and carnivorous animals. They conclude from their work that there is no relation between the dietary habits of animals and their blood cholesterol content.

Cholesterol is increased in narcosis, alcoholism, and pregnancy, as well as in all cases of jaundice, because of the stoppage of one of its normal paths of excretion. It is increased in nephritis, but decreased in cachexia of various origins. In the blood of natives of the tropics cholesterol is very low despite the fact that infections of the liver are common. De Langen[2] noted the rarity of gall stones in the tropics. The single case he observed among 15,000 patients was not in a native of the East Indies and no case was recognized among 40,000 out-patients.

Cholesterol and lecithin are constituents of all living cells and probably constitute most of the "built in" or invisible fat of the tissues. Both may be synthesized in the body. Lecithin probably takes an active part in fat metabolism and is the first stage through which the fats pass in their utilization by the organism. Where the vitality was low McCrudden[3] found a relation between the severity of the condition and the low values for cholesterol and blood sugar. When the patient improved under treatment, the values for both blood sugar and cholesterol increased.

The fats of the food, after digestion and absorption, reach the blood mainly by way of the lymph vessels and apparently do not pass in any appreciable amounts into the intestinal blood capillaries. Because only 60 per cent of the absorbed fat could be recovered from the thoracic duct at its point of entry into the blood stream, it was believed for some time that the other 40 per cent must be absorbed directly into the intestinal blood capillaries and thus get into the circulation. However, it does not enter directly. Even if the thoracic duct is tied, fat, according to Lee,[4] still gets into the blood by other openings which evidence indicates are lymphatic.

[1] Sunderman and Weideman: Arch. Dermat. and Syph., 1925, **12**, 679.
[2] De Langen: Jour. Am. Med. Assn., 1918, **71**, 1099.
[3] McCrudden: Jour. Am. Med. Assn., 1918, **70**, 1216.
[4] Lee: Johns Hopkins Hosp. Bull., 1922, **33**, 21.

Because of the adaptive changes made possible during the resynthesis of fats as they pass through the intestinal wall, the fat as it reaches the blood stream may have quite different properties from the food fat in which it originated.

Sugar falls but fat rises in the blood in starvation. Coincident with this change in the blood acidosis appears. From this increase in fat in the blood one might infer that the blood is mobilizing fat from its fat depots for its nutritional needs, and it is readily conceivable that in the presence of abnormal metabolism the fat of an obese subject might be more easily drawn upon and that the effect would be the same as that of ingested fat. For this reason the lipids in the blood of fat and thin people present an interesting field for study.

The power exhibited by the lungs and by the liver to destroy cholesterol is lost if the pancreas is not functioning. This power is recovered with the use of insulin. Nitzescu and Cadarin[1] believe it is possible to say with certainty that the pancreas by its endocrine secretion plays a principal role in the metabolism of cholesterol.

2. **Blood Lipids in Diabetes.**—With an excess of fat diabetes begins and from an excess of fat diabetics die, formerly of acidosis, now of arteriosclerosis. In 75 per cent of 1000 of my diabetic cases an increase of body fat preceded the onset of diabetes, and in 66 per cent of my earliest cases abnormal fat metabolism resulting in acidosis caused death, and in 47 per cent of my more recent cases arteriosclerosis caused death.

Disordered fat metabolism was first associated with diabetes when phlebotomy disclosed a milkiness of the blood of diabetic patients. Severe diabetes was, and is, the only disease in which lipemia is frequent enough to be of special significance. The milky appearance of the serum and the "cream" which rose from it on standing indicated the fat. When bleeding fell into disuse, nothing more was learned regarding the nature of this fat until in 1903 Fischer observed that the quantity of cholesterol in diabetic blood was abnormally high, and this finding was confirmed by Klemperer and Umber, who made a similar observation with regard to lecithin.

The percentage of fat reported was extreme, and in 1 case Klemperer found 26 per cent; figures of 15 to 20 per cent were not unusual. Among my cases the highest values are 13.1 per cent as found by Bloor,[2] Case No. 786, and 16.3 per cent in the same patient as found by H. Gray, but these two analyses are based actually upon a patient undergoing treatment with restriction of fat and after fasting fourteen hours. In comparison with the extreme values of Klemperer the increase of 13.1 per cent appears

[1] Nitzescu and Cadarin: Comptes Rend., 1925, **92**, 296.
[2] Bloor: Jour. Biol. Chem., 1921, **49**, 201.

only moderate, but in reality it represents an increase of twenty times the average normal value.

(*a*) **Lipemia** (cloudiness or milkiness of the plasma) does not normally appear in the postabsorption period, although the blood plasma may contain an excess of cholesterol, lecithin, and probably some fat. The introduction of more fat into the blood by feeding or mobilization from body fat generally produces a milkiness normally lasting but a few hours, but under certain conditions for considerably longer periods. If the total fat of the plasma rises above a normal value of 0.5 per cent to 0.8 per cent, lipemia usually appears, but in diabetes values above 1 per cent with clear plasma are often found. Bloor obtained a value of 4.35 per cent total lipid in my case, H, with clear plasma. Such cases of "masked" lipemia have been frequently noted. The "masking may be an unstable condition, since on standing for a time, twenty-four hours to forty-eight hours, milkiness may develop in a plasma which was clear when drawn." Professor Bloor considers this as due probably to a change only in the physical condition of the fat present. Of a series of 116 insulin treated diabetics studied at the New England Deaconess Hospital during the past year 9 cases showed a definite lipemia. Six of these cases were severely acidotic and might be termed cases of "threatened coma." They all had high plasma cholesterol values. One case of five days' duration, Case No. 6089, showed lipemia with a cholesterol plasma content of only 0.236 per cent and 2 cases of seven and nine years' duration had cholesterol values of 0.221 and 0.214 per cent, respectively. Thus it appears that a change in the physical condition of the fat in blood plasma may make normal amounts visible.

TABLE 100.—CHOLESTEROL VALUES IN LIPEMIC BLOOD PLASMA.

No. of cases.	Cholesterol, per cent.		Age in years.		Duration in years.	
	Range.	Average.	Range.	Average.	Range.	Average.
9 . .	0.214–0.955	0.484	12–39	29	5 days to 9 years	3

In one of my cases of lipemia, Case No. 786, Bloor found all the lipids increased, but as the lipemia disappeared the total fat diminished most rapidly, the lecithin less rapidly, and the cholesterol relatively slowly, "showing that the fat is the first to decrease as it was the first to increase, the lecithin next, and the cholesterol last." In one case with a clear plasma the total lipid content was over 4 per cent, the lecithin 1 per cent, and the cholesterol 1.4 per cent. Bloor believes that both the fat of the food and the fat stored in the body may be sources for the lipemia but that the former is the more important. The accumulation of fat in the blood which causes

the lipemia, he ascribes to the difficulty which the diabetic has in removing fat from the blood in contradistinction to the lipemia following hemorrhage, which can be explained by an excess of inflow of fat into the blood.

Bloor and Gilette working with dogs found that there was a much greater accumulation in the plasma and slower removal of fat from it in response to a standard fat feeding in the case of diabetic dogs than in normal dogs. These experiments indicate that these animals may not be able to utilize fat as well as normals.[1] This inability is not digestive, but shows itself in a greatly increased response of free fat in the blood plasma after a standard fat meal. Cholesterol and lecithin levels are not much affected until the diabetes produced is quite severe. The defect appears to be concerned only with the disposal of free fat as it comes into the blood from the thoracic duct. The fact that insulin will bring these animals quickly back to normal lends support to the theory advanced by Bloor that insulin may increase the permeability of body cells whose power to take up fat has been lowered by the diabetic condition. This hypothesis also fits in well with Allen's conception of the cause of lipemia in diabetes—a general cachectic condition of the whole organism which affects all the cellular functions including permeability. This conforms to the broader pathology of the pancreas in diabetes which includes the acinar tissue and its deficient secretion of pancreatic juice as observed in diabetic patients. Bloor also inclines to the belief that there is a deficiency in diabetes of a hormone whose function is to aid in the removal of fat from the blood, basing his opinion upon: (1) the lipemia which is so common with diabetics; (2) its easy production in dogs made diabetic, but the difficulty of its production in normal dogs; and (3) the high content of blood lipids in diabetics.

(*b*) **High Values in Diabetes.**—Professor Bloor in 1916 found all the lipids increased in diabetes. This is shown in Table 101 taken from Bloor, in which he compares the blood lipids of normals and 28 of my diabetic patients. It is also confirmed by Table 102, which represents analyses of 131 bloods of my cases made by H. Gray[2] in Bloor's laboratory. The increase is greatest in the plasma, the composition of the corpuscles remaining so nearly constant as to be disregarded.

Gray's series of 131 specimens of blood fat were divided into three groups, according to whether the patients were mild, moderate, or severe in degree. All of these types of diabetes were distinguished by a marked increase in lipids of the blood, and the general statement was made that the increase is progressive with the serious-

[1] Bloor and Gilette: Proc. Soc. Exp. Biol. and Med., 1925, **22**, 251.
[2] Joslin, Bloor and Gray: Jour. Am. Med. Assn., 1917, **69**, 375.

ness of the disease. Thus, the average quantity of lipids obtained by Bloor's method in the whole blood amounted to 0.59 per cent in 19 normal individuals, but was increased to 0.83 per cent in 32 mild diabetics, to 0.91 per cent in 37 moderately severe diabetics, and to 1.41 per cent in 55 severe cases of diabetes. The increase holds not alone for the lipids obtained by Bloor's method, which extracts approximately 91 per cent of the total blood lipids, but for each of the three groups of lipids.

TABLE 101.—COMPARISON OF BLOOD LIPIDS OF NORMAL AND 28 DIABETIC INDIVIDUALS.

(Compiled from table of W. R. Bloor, Jour. Biol. Chem., 1916, **26**, 424.)

	Total fatty acids, gms. in 100 c.c.			Lecithin, gms. in 100 c.c.			Cholesterol, gms. in 100 c.c.		
	Whole blood.	Plasma.	Corpuscles.	Whole blood.	Plasma.	Corpuscles.	Whole blood.	Plasma.	Corpuscles.
Diabetic extremes	.41–.76	.46–.93	.33–.62	.26–.50	.17–.48	.32–.60	.19–.44	.16–.65	.17–.24
Diabetic average	**.52**	**.59**	**.43**	**.36**	**.30**	**.46**	**.29**	**.36**	**.20**
Normal average	**.37**	**.39**	**.34**	**.30**	**.21**	**.42**	**.22**	**.23**	**.20**
Normal extremes	29–.42	.30–.47	.27–.45	.28–.33	.17–.26	.35–.48	.19–.25	.19–.31	.17–.24

The patient who showed the greatest increase of total fatty acids in the plasma—save for lipemia—was Case No. 983, who was obese and developed severe acidosis upon restriction of carbohydrate and only after eighteen days of treatment became sugar- and acid-free. (See p. 279.) Eventually she was proven to be one of the mildest of diabetics, showing that a *diabetic is mild or severe as the diet and doctor make him*. On the other hand, a clinically mild case may show considerable abnormality, due probably to diet, as in Case No. 914 (p. 424, Bloor[1]) whose increase in total fatty acids was 60 per cent. His tolerance for carbohydrate was 150 grams. Between the mild and severe cases were all degrees of gradation in the blood lipids, but in general the more severe the diabetic condition the more marked was the abnormality in the blood lipids.

(*c*) **The Relation Between the Different Lipids** in diabetics was not the same in the larger group of cases examined by Gray as contrasted with the small group first examined by Bloor. Although the quantity of total fatty acids is trebled, the cholesterol is only doubled and the lecithin increased but one-third. The increase in cholesterol is significant and suggestive and seems indeed pathognomonic of the prolonged diabetic hyperlipemia, since Bloor has found it lacking in the acute lipemia of overfeeding which is characterized by an increase in the total fatty acids alone.

[1] Bloor: Jour. Biol. Chem., 1916, **23**, 424.

TABLE 102.—LIPIDS IN DIABETES. ANALYSES BY H. GRAY.

	No. of bloods.	Fat by Bloor's method.[1]		Total fatty acids.[2]			Lecithin.			Cholesterol.			Total lipids.	Blood sugar, per cent.
		Whole blood, per cent.	Plasma, per cent.	Whole blood, per cent.	Plasma, per cent.	Corpuscles, per cent.	Whole blood, per cent.	Plasma, per cent.	Corpuscles, per cent.	Whole blood, per cent.	Plasma, per cent.	Corpuscles, per cent.	Plasma, per cent.	
Normal	23	0.50	0.62	0.37	0.39	0.34	0.30	0.21	0.42	0.22	0.23	0.20	0.68	0.10[3]
Mild diabetes	32	0.83	0.90	0.59	0.64	0.45	0.32	0.24	0.42	0.24	0.26	0.21	0.98	0.17
Moderate diabetes	37	0.91	1.06	0.65	0.76	0.48	0.33	0.28	0.40	0.26	0.30	0.20	1.16	0.26
Severe diabetes	55	1.41	1.80	1.01	1.28	0.62	0.40	0.40	0.40	0.41	0.51	0.24	1.98	0.23

[1] Represents about 90 per cent total fat.
[2] Represents fat (Bloor) minus cholesterol.
[3] Estimated, not analyzed.

The increased amounts of lecithin and cholesterol in the blood have led to the belief that the increase was due to degeneration of tissue cells, setting free their lipids, but analyses of various tissues have shown that the lipid content of the tissues in diabetes is not abnormal. The increased fat in the liver, rising to even more than 10 per cent does constitute an exception, because it represents storage. Increased mobilization of stored fat as the result of the partial starvation has also been offered as an explanation, but here again the evidence does not bear out the assumption. In the first place the stored fat contains only traces of lecithin and cholesterol; in the second place, though fat at onset, diabetics generally become thin later and have very little stored fat; also even complete starvation does not necessarily mean increased blood fat. A third interpretation considers the increase due merely to an accumulation of food fat which the organism can no longer burn, and in the light of the knowledge that in diabetes the fat-burning mechanism is probably deranged and of the recent discovery that lecithin and probably cholesterol (as ester) are steps in normal fat metabolism, this seems to be the most reasonable explanation.

Lecithin, however, except for lipemia, varies with the fatty acids in nearly all cases, but not as constantly as does the cholesterol. In Case No. 786, with lipemia, the values for lecithin were not greatly increased, as is shown by a comparison with the lecithin values in this same patient when he did not present lipemia.

Cholesterol has been found to run parallel with the total fatty acids in all cases, including lipemia. Therefore, the determination of the cholesterol alone in the plasma has been considered to give valuable information regarding the lipid content of the blood in diabetes. Whether or not this is true in insulin-treated diabetics is a question which needs further work to solve. Wishart's[1] studies revealed no especial retention of cholesterol when diabetic patients subject to lipemia were fed cholesterol or foods rich in cholesterol. This is, of course, quite the opposite of what Luden[2] found in normal individuals.

In the right hand column of Table 102 the blood sugar values corresponding to the fat values are inserted. Gray thus shows the greater reliability of blood fat in prognosis. Rabinowitch[3] also considers the quantity of cholesterol in the blood of greater prognostic value in insulin treated diabetes than the blood sugar or the clinical condition of the patient.

Williams examined the cholesterol in 89 cases of diabetes. In 52 of these it was under 0.25 per cent, in 11 between 0.25 and 0.3

[1] Wishart: Jour. Metab. Res., 1922, **2**, 199.
[2] Luden: Jour. Lab. and Clin. Med., 1917, **3**, 141.
[3] Rabinowitch: Canadian Med. Assn. Jour., 1927, **17**, 171.

per cent and in 26 it amounted to over 0.3 per cent, compared with Bloor's 0.23 per cent for normals.

The total fatty acids afford the surest indication of a change in the blood lipids. It will be seen that the normal variations for lecithin and cholesterol were so great as to overlap the variations for the lecithin and cholesterol in diabetic blood. On the other hand, the lowest figure obtainable for total fatty acids in diabetic blood was at the upper normal limit for these acids in normal blood, but this held good only for the plasma.

The mild cases of diabetes were subdivided into two groups based upon the presence or absence of nephritis. The differentiation, however, showed nothing characteristic. Indeed, the uniformity for the groups was so close that it extended to all the different lipids.

(d) **Blood-fat Values on Fasting and on High-fat Diets.**—The effect of fasting upon the blood lipids was studied by Cowie and Hoag[1] in a boy, aged seven years, with diabetes presenting acidosis. After four days without food, the total lipids increased 182 per cent. Another patient showed a 64 per cent increase during three days of fasting, and this was also accompanied by acidosis. When these patients were given a diet high in fat and low in carbohydrate and protein, the lipids decreased. This is surprising. The increase in the blood fat during starvation should be related to the insufficient combustion of carbohydrate. In fact, all our conclusions upon the utilization of fat by the body or the accumulation of fat in the blood must be restudied in the light of our present knowledge of the ketogenic-antiketogenic ratio. Blau and Nicholson[2] recognized this in their conclusions upon their studies of the blood fat in 26 cases of diabetes. They also call attention to the presence of another factor, namely, infection, which might easily complicate the problem.

The administration of fat in the form of cream to normal children was also investigated by Cowie and Hoag. They found that the maximum amount of lipids in the blood was reached from the fifth to the seventh hour after ingestion and that with 3 adults the maximum was obtained in six hours. When the fat was given together with a large amount of carbohydrate, the highest point was reached with the adults during the second hour.

"The fat absorption-utilization curve of an adult diabetic patient was studied following the ingestion of 143 grams of fat, 6 grams of carbohydrate, and 16 grams of protein in a single meal. The maximum concentration in the blood was reached at the sixth and eighth hours, showing, however, a rise of only 10 per cent over the first hour after ingestion. A boy, aged eleven years, with diabetes,

[1] Cowie and Hoag: Jour. Am. Med. Assn., 1921, **77**, 493.
[2] Blau and Nicholson: Arch. Int. Med., 1920, **26**, 738.

showed at the eighth hour a 26 per cent increase over the first hour, following ingestion of 90 grams of fat, 14 grams of protein, and 11 grams of carbohydrate. These results show no gross variation from the normal curve." One of our cases, a boy, Case No. 2878, diabetes of five years' duration, who had been on a fat diet of 186 grams with carbohydrate probably high in quantity per day for two months, showed low cholesterol values, 0.162 per cent. This is about the value we now obtain with most of the diabetic children, save adolescent girls."

Cowie and Hoag's 8 diabetics examined showed an increase of total lipids, the highest being 8.8 per cent. "When these patients were fed a minimum of carbohydrate and protein, but large amounts of fat, ranging from 100 to 200 grams daily, and furnishing an adequate caloric intake for the individual, the lipids content of the blood steadily decreased. The patient whose case is cited above had 8.18 per cent on entrance, which was reduced to 1.5 per cent before he was discharged from the hospital on a diet containing 220 grams of fat."

The high-fat, low-protein and low-carbohydrate diet led to a reduction of the lipemia likewise in the cases studied by Marsh and Waller.[1]

These results are similar to those of Newburgh and Marsh[2] in their studies of high fat feeding. It should be noted that these results were obtained coincident with a decrease in the sugar in the urine and in the blood, and the explanation is offered that the decrease in fat in the blood of their cases was not on account of the large quantity of fat in the diet, but rather on account of the improvement in the diabetes brought about by the better utilization of carbohydrate. This agrees with Allen's[3] statement that the one indispensable prerequisite for diabetic lipemia is the existence of active, severe symptoms in the form of glycosuria and that severe cases whose glycosuria has been abolished by diet never exhibit any extreme grade of lipemia, however high the fat intake. In other words, the improvement in the treatment of the patient as a whole is the important factor, irrespective of the method employed. Although the diets of Newburgh and Marsh were high in fat, it is probable from the work of DuBois and Richardson[4] as well as McCann[5] that considerable portions of this were not burned. It is all the more striking that the fat in the blood was not increased to a greater extent. If there is a defect in the metabolism of fat in diabetes apart from that dependent upon the deranged metabolism of carbohydrate, one would expect it to show more plainly.

[1] Marsh and Waller: Arch. Int. Med., 1923, **80**, 655.
[2] Newburgh and Marsh: Arch. Int. Med., 1923, **31**, 63, also 455.
[3] Allen: Jour. Metab. Research, 1922, **2**, 219.
[4] DuBois and Richardson: See p. 287.
[5] McCann: Loc. cit., p. 202.

Cases of mild and moderate diabetes were found by Blatherwick[1] to utilize satisfactorily large amounts of fat. He determined this point by demonstrating the consistency of the blood-fat level of his patients and the absence of acid bodies in the urine. His results, however, were during short periods.

(*e*) **Acidosis and Blood Fat.**—The influence of acidosis upon blood lipids deserves attention because it is from abnormalities in the fat metabolism that so great a percentage of our patients formerly died. However, data based upon groups classified according to severity of diabetes do not give consistent results. Gray in 1916 found a higher level of total lipids in cases of diabetes with acidosis than in cases without acidosis. The total lipids were not, however, proportional to the severity of the acidosis as it was found that patients classified as having moderate acidosis showed higher values than those with severe acidosis. In some instances there have been cases in extreme conditions of acidosis with blood lipid values normal or below normal. The blood of two such patients dying in coma in 1916 was examined for blood lipids one day and three days respectively before death. In neither of these cases were the lipids high. One day before death the plasma cholesterol of Case No. 1004 was 0.180 per cent, total fatty acids 0.43 per cent and lecithin 0.18 per cent. Three days before death the plasma cholesterol of Case No. 1005 was 0.300 per cent, the total fatty acids 0.56 per cent and the lecithin 0.25 per cent.

In the work[2] done recently in our laboratory on insulin-treated diabetic patients the highest cholesterol values were found in cases showing moderate to severe acidosis. The explanation possibly lies in the differentiation of the cases with an without acidosis. In 1927 we have had no cases which died in coma. The severity of the acidosis in the cases described below was determined by clinical symptoms and the CO_2 combining power of the plasma.

All three patients made good recoveries. Case No. 6159 entered the hospital with a blood-sugar value of 0.66 per cent, a plasma CO_2 combining power of 9 volumes per cent and a blood cholesterol value of 0.368 per cent. In spite of the fact that 295 units of insulin had been given the blood sugar was still increasing, the CO_2 combining power was unchanged but there was a definite gradual decrease in the cholesterol. Does this apparent lag in sugar value and apparent response in the cholesterol value when insulin is given indicate a possible direct influence of insulin on fat metabolism?

In contrast to this is Case No. 4099 in which the increased cholesterol values remained very little changed although large amounts of insulin had been given and the blood sugar had been lowered from 1.60 per cent to 0.13 per cent in twelve hours.

[1] Blatherwick: Jour. Biol. Chem., 1921, **49**, 193.
[2] To be published.

TABLE 103.—INFLUENCE OF COMA ON PLASMA CHOLESTEROL.

Date, 1927	Time.	Insulin units.	Blood sugar, per cent.	CO_2 volumes, per cent.	Cholesterol per cent.	Remarks.
			Case	No. 6159		
June 23	1.30 P.M.	295	0.66	9	0.368	Plasma very milky.
June 23	3.30 P.M.	...	0.84	9	0.313	Plasma milky.
June 24	7.30 A.M.	70	0.36	31	0.272	Slight lipemia.
June 25	7.30 A.M.	70	0.24	39	0.275	Slightly cloudy.
June 27	7.30 A.M.	60	0.26	40	0.225	Plasma clear.
			Case	No. 4099		
Sept. 18	5.30 A.M.	...	1.60	13	0.370	
Sept. 18	8.15 A.M.	...	1.38	18	0.358	
Sept. 18	10.45 A.M.	255	0.79	24	0.312	
Sept. 18	2.55 P.M.	...	0.37	37	0.452	
Sept. 18	6.10 P.M.	...	0.13	48	0.394	
			Case	No. 6356		
Oct. 10	6.00 P.M.	...	....	16	...	
Oct. 10	7.45 P.M.	...	0.37	..	1.22	Plasma creamy.
Oct. 10	10.00 P.M.	40	0.24	12	1.19	Plasma creamy.
Oct. 11	7.45 A.M.	40	0.16	14	1.12	Plasma creamy.
Oct. 12	2.00 P.M.	55	0.17	..	1.01	Plasma creamy.

Case No. 6356 shows a very marked increase of blood cholesterol in coma. The cholesterol upon admission was 1.22 per cent and the fatty acids were 3.82 per cent. The patient showed definite signs of acidosis with a CO_2 combining power of 16 volumes per cent although the sugar content was only 0.37 per cent. Very little insulin was required to lower the blood sugar and to cause the acidosis to disappear but the blood lipid values remained very high.

A suggestion that the high fat content of the blood in such cases is due to the susceptibility of the individual to hyperlipemia was made by Bang and by Allen in 1922.

(*f*) **Blood Sugar and Blood Fat.**—Cholesterol and blood-sugar values stand in fairly close relation in the milder cases of the disease, but as the disease advances in intensity the cholesterol tends more to increase than does the blood sugar although this is by no means the invariable rule. Any close parallel relationship is destroyed entirely in instances of marked metabolic disturbance as is clearly illustrated by Cases Nos. 4099 and 6356 in Table 103. Certainly there is no correlation of blood sugar and cholesterol in these two remarkable cases of diabetic coma. Case No. 4099 had the highest blood sugar ever recorded in my series of patients and the blood cholesterol figure is not remarkable.

If we chart the blood sugars on the basis of super and subnormal cholesterol values we find there is a general rise and fall of sugar values with cholesterol values. This is true of values based upon averages only. There are many exceptions as Table 104 discloses.

TABLE 104.—PLASMA CHOLESTEROL AND BLOOD-SUGAR VALUES COMPARED IN PRE-INSULIN AND INSULIN PERIODS.

Cholesterol (Normal 0.23 per cent).	Allen Epoch. (Analyses by H. Gray in 1916–1917).			Banting Epoch. (Analyses by H. Hunt in 1926–1927).		
	Total cases.	Cholesterol, per cent.	Blood sugar, per cent.	Total cases.	Cholesterol, per cent.	Blood sugar, per cent.
Below normal, range	10	0.19–0.23	0.17–0.41	60	0.11–0.23	0.05–0.40
Average		0.214	0.23		0.19	0.19
Above normal average	23	0.25–0.44	0.16–0.42	41	0.24–0.88	0.05–0.50
		0.330	0.24		0.37	0.26

(*g*) **Prognosis and Blood Fat.**—The prognosis in diabetes is definitely related to the percentage of fat in the blood of non-insulin-treated diabetics as shown by a study of 171 of my fatal cases made by H. Gray.[1]

Patients with the highest percentages of fat about the year 1916 lived on the average but a few weeks, whereas those with percentages but slightly above normal lived for three to five years. (See Table 105.) Between the extremes of the table the values vary quite uniformly. When the statistics are examined for the same number of cases but based on twice the number of analyses of the blood, including those made both at entrance and during the course of treatment, the same results are to be seen. The table therefore shows clearly that conditions which favor an increase in the fat of the blood of diabetics are inimical to a favorable prognosis, and furthermore, that even very slight increases are distinctly harmful. However it should be emphasized that these high percentages of fat are amenable to treatment and can be made innocuous. (See Case No. 983, pp. 238 and 279.)

Cholesterol in the blood is also distinctly related to the prognosis in diabetes. (See Table 106.) The higher the percentage of cholesterol the more unfavorable the prognosis. The statistics in the table vary consistently between its extremes. Here again none of the values obtained for cholesterol with the blood of diabetics were normal, and the therapeutic indication is plain—an excess of cholesterol as well as of total fat is to be combated.

Remond and Rouzaud[2] in studying the plasma-cholesterol of 189 diabetic patients found that 7 per cent had a value higher than 300 mgs. per 100 cc. and that of these cases only 1 survived two years after these findings. In my fatal cases reported by Gray in 1916, 35 per cent exceeded the cholesterol danger line, 310 mg., and

[1] Gray: Am. Jour. Med. Sci., 1924, **168**, 35.
[2] Remond and Rouzaud: Bull. de l'Acad. de Méd., 1923, **89**, 60.

31 per cent lived more than two years. However, the higher the cholesterol values the more decided was found to be the decrease in subsequent length of life. When the patient lived less than two years, the average cholesterol was 0.53 per cent *versus* 0.30 per cent when the patient lived more than two years.

TABLE 105.—RELATION OF BLOOD FAT TO PROGNOSIS.[1]
BEFORE INSULIN.

Blood fat, per cent.	Length of life in years, based upon fat in the blood.				
	Fatal: admission and later specimens consolidated, years.	Living: admission and later specimens consolidated, years.	Admission specimens: fatal and living specimens consolidated, years.	Later specimens: fatal and living specimens consolidated, years.	Grand total duration in years.
0.67 or less	(78) 1.2	(151) 2.8	(146) 2.5	(83) 1.9	(229) **2.3**
0.68 to 0.99	(135) 1.2	(296) 2.4	(278) 2.2	(153) 1.8	(431) **2.1**
1.00 to 1.49	(87) 0.9	(176) 2.1	(130) 1.7	(133) 1.6	(263) **1.7**
1.50 to 1.99	(26) 0.9	(38) 1.7	(24) 1.2	(40) 1.5	(64) **1.4**
2.00+	(4) 0.6	(27) 1.9	(12) 1.4	(19) 2.0	(31) **1.7**
3.00+	(2) 1.5	(7) 1.0	(2) 1.5	(7) 1.0	(9) **1.1**
4.00+	(7) 0.7	(2) 0.3	(3) 0.8	(6) 0.5	(9) **0.6**

Parenthesis enclose the number of specimens consolidated to obtain each average length of life.

TABLE 106.—RELATION OF BLOOD CHOLESTEROL TO PROGNOSIS.
Before June 1, 1923.

Length of life after blood analysis to death, or, if living, to June 1, 1923, years.	No. of analyses.	Cholesterol, gm. per 100 cc.			
		Whole blood, per cent.		Plasma, per cent.	
0.1 or less	6	0.38		0.48	
0.2 to 0.5	6	0.25	0.41	0.27	0.53
0.6 to 0.9	16	0.59		0.75	
1.0+	32	0.37		0.46	
2.0+	11	0.30		0.32	
3.0+	7	0.37		0.45	
4.0+	2	0.25	0.27	0.28	0.30
5.0+	4	0.20		0.22	
6.0+	30	0.25		0.28	
7.0+	1	0.21		0.25	

Overweight does not cause an increase in the blood fat of diabetes, because patients 11 per cent or more above actuarial standards showed a slightly lower percentage of blood fat than those diabetics

[1] Whole blood, Bloor's "total-fat" method. Highest value among 20 normal bloods (Bloor) was 0.67 gm. per 100 cc.

within a broad zone between +10 per cent and −10 per cent of the standard. (See Table 107.) Yet these comfortably nourished diabetics exhibited as average percentages of blood fat 0.81 per cent and 0.82 per cent which are 20 per cent above the normal blood fat—namely, 0.68 per cent. The differences in these percentages of blood fat are absolutely slight, but relatively considerable. An increase of 20 per cent in the blood fat is not to be disregarded. In the data of Newburgh and Marsh similar increases in the blood fat of their patients are recorded but are considered by them as normal and as proof that a high-fat diet does not increase the blood fat of a diabetic. Their contention is true to a greater extent than I considered possible, but one must not get the impression that their patients have a normal blood fat. When the diabetic patients showed an average weight 11 per cent or more below standard, their blood fat was increased to 1.25 per cent, which is almost twice the normal fat value. But from other tables in this section this increase can be explained as due to these diabetic patients being more severe in type rather than by an attempt to relate it to the substandard weight. However, it suggests that it would be desirable to have a series of analyses of the blood fat of non-diabetics some of whom are above and some of whom are below standard weight.

TABLE 107.—RELATION BETWEEN BLOOD FAT AND BODY WEIGHT WHEN BLOOD WAS TAKEN.

Weight of patient at time of blood expressed in per cent overweight (+) or underweight (−) compared with Medico-actuarial Insurance tables of average weight for height and age.	No. of analyses.	Blood fat, average; (Bloor's method), whole blood per cent.[1]	
+21 and over (maximum, +84)	44	0.83	0.81
+11 to 20	44	0.80	
+1 to 10	82	0.94	0.91
0 Broad normal	4	0.75	
−1 to −10	116	0.90	
−11 to −20	147	0.94	1.13
−20 to −30	153	1.10	
−31 to −40	143	1.14	
−41 and under (minimum, −59)	64	1.60	

Prognosis in diabetes may be related to the blood fat, providing the blood fat remains constantly at the level at which it was first determined. Fortunately treatment will modify the prognosis, as shown by the results in Case No. 983, who showed the greatest increase of total fatty acids in the plasma among my early cases and yet now, twelve years later, is a mild diabetic. With her, the

[1] All specimens, admissions and later, on both fatal and living patients.

decrease in fat took place during the course of weeks. How different the condition of today. A total blood fat of 6.3 per cent in Case No. 2842 decreased with 63 units of insulin in four and a half days to 2.95 per cent. Clearly the prognosis in diabetes cannot be related to a single blood-fat value, but is dependent upon the modification of that blood value by treatment.

(*h*) **Insulin and Blood Fat.**—The condition of the blood of diabetics in regard to lipid content seems to be very different in this era of insulin treatment. No longer do we find a marked increase in blood lipids in diabetes. If plasma cholesterol can still be considered as an index of the variations in total lipids, we have to admit that blood lipids in the diabetic vary only slightly from the normal. Using Dr. Gray's table as a basis of comparison, we have classified 116 insulin-treated diabetics whom we have studied during 1926 and 1927[1] upon their plasma-cholesterol levels and find that whereas in 1917 upon the same classification only 27 per cent of them were mild cases, today we find 73 per cent mild cases. Rabinowitch[2] found normal values for plasma cholesterol in 61.6 per cent of 18 insulin-treated diabetics whose fasting blood sugars were normal. However, of his group of patients with more severe types of diabetes there were approximately only 25 per cent with normal cholesterol values.

TABLE 108.—CLASSIFICATION OF SEVERITY OF DIABETES IN 1927 BASED ON GRAY'S TABLE FOR CHOLESTEROL COMPILED IN 1917.

	H. Gray, 1917.		H. Hunt, 1927.	
Degree of severity.	Total cases.	Per cent.	Total cases.	Per cent.
Mild (cholesterol 0.250) . .	32	27	85	73
Moderate (0.260–0.360) . .	37	29	19	16
Severe (0.370+)	55	44	12	11

Is this the work of insulin alone? Does it mean that our low-fat diets in 1927 with higher carbohydrate values are successful in keeping the lipids of the average diabetic around the normal level? Is it partly that our diabetics are consuming less cholesterol—eggs? Insulin has a direct influence on lipid metabolism according to Chauffard[3] and that its influence is independent of carbohydrate metabolism is strongly asserted by Labbé.[4] In their series insulin brought the total lipids of one patient from 9.2 per cent down to 1.3 per cent in five months while the blood sugar remained fairly constant, and in two other cases studied by Labbé and Lamelet

[1] To be published.
[2] Rabinowitch: Can. Med. Assn. Jour., 1927, **17**, 171.
[3] Chauffard: Bull. de Soc. Méd des Hôp. de Paris, 1924, **49**, 1573.
[4] Labbé: Ibid., 1924, **49**, 1573.

dietetic treatment of diabetes failed to influence the cholesterol level which remained at 0.250 per cent. When insulin was used, the cholesterol fell in three days to 0.22 per cent and in eleven days it had fallen to 0.15 per cent. In another case very irregular variations were observed. The cholesterol level during insulin treatment fluctuated from 0.25 to 0.15 per cent but failed to remain at either extreme. From their observations these authors felt that insulin acts directly on fat metabolism independent of carbohydrate metabolism. The data recorded in Table 103, p. 244 suggest that insulin exerts a direct rather than an indirect action upon the blood fat, but simultaneously with its action upon carbohydrate metabolism. Although some insulin had been given to the patient, Case No. 6159, before she entered the hospital in coma and 150 units more between the time the first and second blood samples were taken, the blood sugar was steadily rising whereas the blood cholesterol decreased from 0.368 per cent to 0.313 per cent. The blood sugar five hours and fifteen hours later was decreasing, but the cholesterol kept pace with it and fell to 0.225 per cent by the third day. That the influence is indirect rather than direct, however, is strongly maintained by Blix[1] who feels that the improvement in fat metabolism is brought about only by a better carbohydrate metabolism. The second case in Table 103 is difficult to explain.

Nitzescu[2] believes that a certain type of cholesterolemia exists after pancreatectomy, which is different from any cholesterolemia produced in normals. This cholesterolemia and probably that occurring in diabetes are readily decreased by insulin, but he asserts insulin does not influence normal cholesterol.

How spectacular the decrease in lipids may be is evidenced by Rabinowitch's[3] patient whose blood fat was reduced by 1 pound over night and by another pound the next day. (See p. 691.)

In a series of 116 cases of insulin-treated diabetics of all ages, all degrees of severity and durations of disease, studied at the New England Deaconess Hospital during 1926–1927, the average cholesterol per cent was found to be 0.257. Of this number 60 per cent had cholesterol values below the accepted normal of 0.23 per cent. The average value for this group is 0.186 per cent, the average age of this group is 37.5 years, and the average duration of disease is 6.4 years. Contrasted with this we find the average cholesterol of the 40 per cent showing high cholesterol values to be 0.36 per cent, the average age 43 years, and the average duration of disease 6.9 years.

[1] Blix: Inaug. Dissert., Lund, 1925.
[2] Nitzescu *et al.*: Compt. Rend. Soc. d. Biol., 1924, **90**, 538.
[3] Rabinowitch: Personal communication.

TABLE 109.—SUMMARY OF DATA ON CHOLESTEROL IN THE BLOOD PLASMA OF DIABETICS (1926–1927).

No. of cases.	Values above normal of 0.23 per cent.		Values below normal of 0.23 per cent.		Plasma cholesterol, average per cent.	Average duration of diabetes, years.	Average age, years.
	No.	Per cent.	No.	Per cent.			
116	47	40	69	60	0.257	6.6	39.2

Cholesterol, per cent.		Cholesterol, per cent.	
Range.	Average.	Range.	Average.
0.236 0.955	0.360	0.10 0.23	0.186

The cholesterol values are low. The average cholesterol figure for the 60 per cent showing normal or low values is 0.186 per cent, a figure just below the lowest normal value recorded by Professor Bloor (Table 101). Just what this can mean is difficult to say at present. That these low values are important we are very sure and we feel that they need just as much investigation as the high values.

The relations between the different lipids have not been investigated in the recent work done on insulin-treated diabetics as it was assumed that cholesterol, acting as an index of activity of all the fat constituents, would give us the information we sought. However, a new series of investigations has been started to determine whether or not all the lipids are approximately normal in insulin-treated diabetics as is cholesterol or whether the fatty acids are differently distributed and cholesterol is no longer an index of their variation and response to metabolic disturbances and adjustments.

That duration of diabetes has little or no effect upon the cholesterol in the blood of insulin-treated diabetics is demonstrated by Table 110.

That the cholesterol in the blood does not increase with the duration of the disease is an argument against the progressive character of diabetes. This agrees well with the work done by White[1] on 13 cases of diabetes treated with insulin. White found further that there was little relation between the fasting blood fat and the fat intake. The nutritional condition of the patient seemed to have a more direct relationship than any other factor. Higher blood

[1] White: Quart. Jour. Med., 1926, **19**, 159.

fats were found in patients with subnormal body weights than in patients with supernormal body weights. (See Table 107.)

TABLE 110.—INFLUENCE OF DURATION OF DIABETES ON CHOLESTEROL AND SUGAR IN THE BLOOD OF DIABETICS.

Diabetes duration, years.	No. of cases.	Cholesterol, per cent.		Average blood sugar, per cent.
		Range.	Average.	
0– 1	6	0.120–0.236	0.184	0.17
1– 2	10	0.147–0.884	0.354[1]	0.25
2– 3	10	0.109–0.625	0.285	0.21
3– 4	9	0.155–0.535	0.254	0.22
4– 5	11	0.189–0.392	0.287	0.26
5–10	41	0.094–0.750	0.247	0.23
10–20	19	0.100–0.325	0.234	0.19
20+	5	0.134–0.242	0.183	0.20

(*i*) **Influence of Age Upon Cholesterol.**—Our Table 111 shows a marked increase in cholesterol values when the onset is in the second and third decades of life. The average cholesterol percentage during these two decades approaches the average value for diabetics found by Bloor in 1916. White found that age had no influence upon the blood lipids.

TABLE 111.—INFLUENCE OF AGE UPON CHOLESTEROL AND SUGAR IN THE BLOOD OF DIABETICS.

Decade of onset, years.	Total cases.	Cholesterol, per cent.		Blood sugar, per cent, average.
		Range.	Average.	
0– 9	14	0.120–0.316	0.198	0.17
10–19	19	0.109–0.884	0.316	0.28
20–29	9	0.134–0.882	0.364	0.30
30–39	22	0.109–0.492	0.245	0.20
40–49	23	0.100–0.366	0.236	0.21
50–59	18	0.155–0.346	0.230	0.19
60–69	7	0.154–0.375	0.236	0.20

(*j*) **Arteriosclerosis and Blood Fat.**—Arteriosclerosis is one of the most troublesome complications of diabetes today. It has supplanted coma as a cause of death in diabetes. That arteriosclerosis is due to faulty fat metabolism has been considered and suggested many times. Labbé and Heitz[2] say that arterial obliteration in diabetes is due to localization of cholesterol in the tunica intima.

[1] If the 2 cases of coma with extremely high cholesterol are not counted, the range of cholesterol for this duration of disease will be 0.147–0.380 per cent with an average of 0.221 per cent, thus bringing the whole series down to a normal value.

[2] Labbé and Heitz: Ann. Méd., 1925, **18**, 108.

Aschoff[1] attributes arteriosclerosis to the deposit of fat in the form of cholesterol esters in the arteries. The more fat there is in the blood, the more readily it is deposited. The subsequent calcification of the deposited cholesterol leads to calcified arteries. High cholesterol values in cases of arteriosclerosis have been found by Mjassnikow[2] and by Labbé and Heitz.[3] Can it be that the prevalence of arteriosclerosis in diabetes is to be attributed to the high-fat diets we have prescribed and more especially to those diets having been rich in cholesterol? I suspect this may be the case. At any rate it is reasonable to maintain the cholesterol in the blood of our patients at a normal level, and that I shall strive to do. This may result in the limitation of eggs, each one of which contains 0.38 grams cholesterol and even of olive oil containing about 1 per cent and corn oil more nearly 2 per cent. This therapeutic procedure is adaptable to experimental investigation and should not require long for solution. A study in our laboratory of the cholesterol values in diabetics with and without arteriosclerosis resulted in Table 112. To exclude all the children and young adults only patients twenty-five years old or older were considered.

TABLE 112.—BLOOD CHOLESTEROL VALUES IN DIABETICS WITH AND WITHOUT ARTERIOSCLEROSIS (1926–1927).

Arteriosclerosis, degree.	Total cases.	Cholesterol, per cent.		Average age, years.	Average duration, years.
		Range.	Average		
Absent	14	0.190–0.925	0.292	40	6.3
Slight	20	0.147–0.410	0.220	52	9.8
Marked	22	0.100–0.338	0.209	60	9.2

Our investigation shows no marked increase in cases of arteriosclerosis. Whether or not the fairly high value for the group without arteriosclerosis is indicative of an active depositing process and the lower values indicate a satisfactory equilibrium between deposition and circulation is a question. Further study of the group which clinically show no arteriosclerosis is demanded. Bloor[4] says that "deposition of cholesterol and its esters does not necessarily require a high blood cholesterol, but depends on the ability of the blood to keep in solution a substance which is probably in a state of supersaturation."

Bowen and Koenig[5] have just reviewed the subject of arteriosclerosis in diabetes and published their Roentgenological studies of the vessels of the lower extremities. They found arteriosclerosis

[1] Aschoff: Lectures on Pathology, Hoeber, N. Y., 1924.
[2] Mjassnikow: Ztschr. f. klin. Med., 1925, **102**, 65.
[3] Labbé and Heitz: Ann. Méd., 1925, **18**, 108.
[4] Bloor: Personal communication.
[5] Bowen and Koenig: Buffalo Gen. Hosp. Bull., 1927, **5**, 31.

in 63 per cent of their patients above the age of forty years, but in only 28 per cent of non-diabetic subjects of similar age. Arteriosclerosis appeared to them to vary with the duration of the disease and the neglect of treatment because it was not observed in cases of long standing when the diabetes was controlled. They discuss the bearing of hypercholesterolemia upon arteriosclerosis and add an excellent summary of the literature.

(*k*) **Cholesterol in Special Cases.**—Our 1926–1927 series which showed an average cholesterol of 0.257 per cent is marked by two special groups which are showing abnormally high values. One group is the acidotic group previously discussed, and the others the so-called "*adolescent high group*" of girls. Of 10 girls with an average onset of diabetes of twelve years and an average age at time of test of 17.5 years there are 5 who have cholesterol values above 0.31 per cent. Their average cholesterol value is 0.398 per cent. To be compared with these are 5 other girls whose cholesterol values are normal or low and these are shown in Section B of Table 113.

TABLE 113.—THE ADOLESCENT GROUP.

A. Those Showing High Plasma-cholesterol.

Case No.	Onset age, years.	Age at test.	Duration, years.	Gain in wt., lbs.	Insulin units per day.	Cholesterol, per cent.	Blood sugar, per cent.
					(80 coma)		
4232	14	19	5	20	50	0.395	0.29
2962	12	16	4.0–4.3[1]	55	45	0.500	0.48
						0.478	0.32
						0.312	0.29
2617	14	19	5.0–5.2[1]	–19	30	0.390	0.07
						0.490	0.25
2528	8	16	8	9	40	0.316	0.29
3078	12	16	4	22	60	0.392	0.31
Average	**12**	**17**	**5**	**15**	**45**	**0.398**	**0.29**

B. Those Showing Normal and Low Plasma-cholesterol.

Case No.	Onset age, years.	Age at test.	Duration, years.	Gain in wt., lbs.	Insulin units, per day.	Cholesterol, per cent.	Blood sugar, per cent.
4978	15	19	2.5–3.0[1]	46	60	0.197	0.29
						0.166	0.31
5707	14	16	2	–20	28	0.208	0.19
2847	10	17	7	33	48	0.156	0.39
4998	16	18	2	–2	35	0.238	0.29
1997	11	19	8	32	45	0.158	0.24
Average	**13**	**18**	**4.4**	**17**	**43**	**0.187**	**0.29**

[1] Period covered by tests.

Just how should these tables be interpreted? It is especially puzzling because the only difference, based on average values only, is in the cholesterol. Should we consider this high cholesterol value in each case of Section A to be indicative of a bad prognosis? It will be of great interest to follow this special group. We shall report later data. For what special changes or differences should we look in the two groups? I should venture a guess that the "A" group were really on a lower carbohydrate diet, but diet data for both sections are largely unreliable. It is possible that some other interpretation can be found but this table may be chiefly valuable for future reference.

3. **Cholesterol in Diabetic Children.**—Twenty-six diabetic children were included in the study. They all contracted diabetes before the age of fifteen years. With the exclusion of the post-adolescent girls just discussed the average value of cholesterol in this group was found to be 0.147 per cent. What do such low values signify? These, too, must be interpreted in the light of further study.

TABLE 114.—BLOOD CHOLESTEROL VALUES IN 26 DIABETIC CHILDREN.

	Clinical data.						Cholesterol, per cent.					
	Age at onset. years.		Duration, years.		Age at time of test.		Normal or below.			Above normal.		
							No.	Cholesterol.		No.	Cholesterol.	
No. cases.	Range.	Av.	Range.	Av.	Range.	Av.		Range.	Av.		Range.	Av.
26	2–14.9	8.0	3 mos. to 8 yrs.	4.0	5–18	12.3	21	0.109 to 0.226	0.146	5	0.312 to 0.500	0.385

C. THE TOTAL METABOLISM IN DIABETES.[1]

Two equally emaciated and severe diabetic patients come for examination. When asked to disrobe, the one who is bright-eyed with flushed cheeks and red, dry lips removes his clothes to the skin, refuses a blanket, says he is thankful to cool off, and stands awaiting further orders; his pale, sallow companion slowly undresses, regretfully removes his underclothes, and without invitation picks up a blanket, shivers, and sits down. The pulse

[1] Prior to the discussion of the effect of food upon the metabolism on page 329, various considerations upon metabolism in general are set forth, and the computation of metabolism is described on p. 461 and p. 959. See also Du Bois: Basal Metabolism in Health and Disease, 2d ed., Philadelphia and New York, Lea & Febiger, 1927.

of the former is rapid and that of the latter is slow. If put to a physical test, the difference between the two individuals would prove to be far less than the contrast in appearance would indicate.

An observer trained in the interpretation of metabolism tests could not fail to discern that the metabolism of the one was as distinctly above normal as that of the other was distinctly below normal. The two represent the dangerous extremes reached by patients having the same disease. So frequently were instances of the former type encountered among the diabetic patients studied at the Nutrition Laboratory in Boston before June, 1914, and so commonly those of the latter type after that date, and so clearly did the transition in type of these cases correspond to the abandonment of overnutrition and the adoption of undernutrition at that time, that no more appropriate title could be found by the writer for a monograph, based upon studies of diabetics between the years 1908 and 1917, by F. G. Benedict and himself than "Diabetic Metabolism with High and Low Diets."[1]

In what follows an attempt will be made to bring out the salient features of the diabetic metabolism which have been encountered in studies made upon 113 of the writer's patients prior to 1917, and the more recent observations begun in 1922,[2] and to refer rather freely to certain aspects of normal metabolism. The early investigations were made possible by the constant help and participation of F. G. Benedict and his co-workers at the Nutrition Laboratory of the Carnegie Institute of Washington situated in Boston. Valuable papers upon diabetic metabolism have appeared from the Russell Sage Laboratory embodying the work of DuBois in collaboration with Allen and Geyelin, and more recently with Richardson, who has become associated with the laboratory, as well as the discerning critical comments by Lusk. Falta has contributed also to our present knowledge, both by experiment and discussion. One of the most detailed investigations by Wilder, Boothby, and Beeler came from the Mayo Clinic in 1922, and in August, 1923, appeared a contribution from McCann, Hannon, Perlzweig, and Tompkins[3] which united clinical, chemical and respiratory data with a review of recent literature. Reference has already been made to the monograph of Holten. (See p. 61.)

The total metabolism, or more specificially the gaseous or respiratory metabolism, of diabetes attracted the attention of Petten-

[1] Joslin: Pub. No. 323, Carnegie Inst. of Washington, D. C., 1923. See also Benedict and Joslin: Metabolism in Diabetes Mellitus, Pub. No. 136, ibid., 1910. Benedict and Joslin: A Study of Metabolism in Severe Diabetes, Pub. No. 187, 1912. The literature is given in these monographs.

[2] These latter are discussed on p. 619.

[3] McCann *et al.*: Arch. Int. Med., 1923, **32**, 226.

koffer and Voit in 1867. They came to the conclusion that diabetic patients gave off less carbon dioxide and consumed less oxygen than the normal individual. In 1905, Magnus-Levy, in an excellently conducted study of four diabetic patients, showed an increased consumption of oxygen by the patient per kilogram body weight. Varying results were obtained by other investigators, but these were so divergent in character that the question still remained an open one in 1908. The problem was then taken up afresh with the writer's private patients and, with the coöperation of Prof. Benedict, investigations were carried on in the course of routine hospital treatment. Recognizing that the lack of uniformity in the results of other observers might be due to the fact that different types of diabetics were studied, our attention was directed almost entirely to the metabolism of severe diabetics. The metabolism of the mild and moderately severe diabetic was early recognized to be essentially normal. As years passed on, it developed that the same diabetic patient might exhibit a metabolism at one time distinctly above normal and at another time below normal.

Between 1908 and 1912, the metabolism of 22 severe diabetics was observed. Upon comparing these individuals with 20 normal individuals of approximately the same size and weight, the conclusion was reached that the average metabolism of the diabetic group exceeded that of the normal group by from 15 to 20 per cent. At that period normal standards for estimating the metabolism were unknown and the publication of these data called forth criticism as to the propriety of comparing the metabolism of the diabetic with normal but emaciated controls. This criticism stimulated the search for normal standards of metabolism to which subject it is appropriate to refer.

1. **Normal Standards of Metabolism.**—Normal individuals are so unlike one another that it is impossible to conceive of a fixed type from which so comprehensive an expression of their vitality as is their metabolism will not swerve. *A priori*, therefore, in the endeavor to create a normal standard of human metabolism, it should be conceded that success will be attained if the standard reached should prove to be a zone with considerable latitude rather than a line. How wide this normal zone should be is a matter for speculation, but there are few investigators in metabolism who would venture to narrow the zone to less than 10 degrees—in other words, to 5 per cent below or above a given base line. The Harris and Benedict and DuBois standards for normals, the two standards commonly employed, come within this rather narrow zone; in fact, when the two standards are compared, it has been shown that a metabolism of about −5 per cent according to the DuBois standard

corresponds with the Harris and Benedict base line. When the metabolism diverges greatly from the normal zone, the difference between the two methods of estimating the metabolism grows less. See pages 461 and 959 for methods of computing metabolism.

The metabolism varies not only for sex and age, height and weight, but also varies for race. Early work upon the metabolism of Oriental women showed it to be low, but recent work has reopened the question.[1] In general the standards of basal metabolism of women are about 5 per cent too high.[2]

Unless otherwise stated, the Harris and Benedict standards are employed throughout this book and more particularly in this chapter as a basis for the comparison of the metabolism of diabetic subjects.

2. **Metabolism of Diabetic Patients Before and After June, 1914.**—Comparing the results obtained with my diabetics between 1908 and 1914, with the Harris and Benedict standard, instead of with the originally selected emaciated controls, the metabolism will be found to be 12 per cent *above* normal. This was the metabolism of diabetics in what for me was the Naunyn Era of treatment. Similar patients with treatment by undernutrition in the Allen Era showed a metabolism nearly as much—11 per cent—*below* standard. The comparatively constant deviation from the normal zone of individuals with hyper- or hypothyroidism can be contrasted with the marked variation in the metabolism observed in diabetes. One might say that the metabolism of the disease diabetes, even of severe diabetes, varies but little from normal, but that the metabolism of the diabetic patient, particularly the severe diabetic patient, varies greatly from normal, not from intrinsic causes as with the thyroid patient, but from extrinsic causes of which the diet is the chief cause. L. Hédon[3] has noted an increase of metabolism of severe diabetics who lose weight on a diet poor in carbohydrate, but liberal in protein and fat. In severe acidosis it may exceed 30 per cent. But if these patients are first fasted and then given a limited amount of food the basal metabolism may become −40 per cent. Likewise depancreatized dogs show an increase in metabolism.

According to Hédon[4] the depancreatized dog always has increased metabolism. It may reach 30 per cent and is probably permanent. The cause may lie in the intermediary metabolism with formation of sugar out of protein and fat as Geelmuyden suggested. Hédon suggests the estimation of the severity of diabetes by studying the increase in metabolism of the patient.

[1] Okada, Sakuri, and Kameda: Arch. Int. Med., 1926, **38**, 590.
[2] Macleod, Crofts, and Benedict: Am. Jour. Physiol., 1925, **73**, 449.
[3] L. Hédon: Paris Méd., 1927, **63**, 446.
[4] Hédon: Arch. internat. de Phys., 1927, **29**, 175.

The fundamental change in treatment of my diabetics began about June, 1914, and it promptly exerted an influence upon the metabolism. The cause for a marked alteration in the aspect of the diseased patient was surely adequate. Prior to 1914, diabetic patients were overfed, all cases being treated with a low carbohydrate and high protein-fat diet. Excess of calories was encouraged, and to guard against coma, instead of limitation of fat and undernutrition, sodium bicarbonate was employed in large doses and continued for periods of months. Fat was given *ad nauseam*, and even such fatty foods as cheese and eggs were served, mixed with about equal proportions of butter. The good results of fasting days were overlooked; Naunyn's observation, von Noorden's recommendation, and Weintraud's proof that diabetic patients could subsist upon remarkably few calories, were known but unappreciated and considered more of scientific interest than of therapeutic significance. Hodgson, however, had grasped the principle and with it attained unusual success in practical treatment. It was at this time that Guelpa's conceptions of fasting and of the waning severity of diabetes in the presence of an emaciating disease were recognized, utilized, and enlarged by Allen into a system of treatment based upon a reduced caloric intake.

Patients given the fasting treatment when this procedure was first used were almost invariably underfed to a marked degree, because the hospital period was spent in securing quick results and these were most readily obtained by extreme dietetic restrictions.

In 1915, the writer recognized that fat was largely responsible for acidosis, and its omission at the beginning of treatment was emphasized. Sodium bicarbonate was abandoned in September, 1915, and has never been resumed. The sodium chloride which I have used freely for subcutaneous infusions in coma has undoubtedly served as alkali, but fortunately in smaller and safer quantity. The reduction of weight for therapeutic purposes was followed with some hesitancy, and lapses of treatment were more tolerated than at present.

In the presentation of the data acquired upon the metabolism the policy has been followed of studying the data on the basis of individual days rather more frequently than by grouping the results for the individual cases. This has been rendered necessary because a single case has so many phases. Thus, during the period of observation of a patient there may be changes in age, weight, and even occasionally in height, and almost certainly in degree of severity and acidosis, and with each of these factors the metabolism varies so that a single case becomes in reality many cases. If the postabsorptive metabolism of all diabetics (exclusive of the girl patients) is compared with the normal standard, it will be

found that before the change in treatment in June, 1914, to fasting and a reduced diet, the metabolism was above the standard for one hundred and seven days and below it on twelve days with an average metabolism of 12 per cent above normal. (See Table 115.) In the series made after June, 1914, the metabolism was below standard on two hundred and twenty-five days and above on fifty days with an average metabolism of 11 per cent below normal. The two average variations for the observations before and after June, 1914, are so nearly equal in distance from the normal standard that the average metabolism for the Naunyn and the Allen periods before and after June, 1914, is 0.

TABLE 115.—VARIATION IN BASAL METABOLISM OF DIABETICS FROM THE NORMAL STANDARD BEFORE AND AFTER INAUGURATION OF TREATMENT BY UNDERNUTRITION IN JUNE, 1914.

Period of observation.	Number of observation days with metabolism.		Average variation from standard.	Average metabolism computed from cases.		Average variation from standard.
	Above standard.	Below standard		Above standard.	Below standard.	
Before June, 1914:						
29 cases . .	107	12	+12	27	2	+13
After June, 1914:						
76 cases . .	50	225	−11	19	57	−7

If the results for the different cases are compared, the general trend of the metabolism is seen to be like that observed in the other comparison. Before June, 1914, 27 cases showed a metabolism above, and only 2 cases below, the normal standard, while after that date the metabolism with 19 cases was above, and with 57 cases below, standard. The average variation by cases before June, 1914, is + 13 per cent, but the percentage below normal after that date is −7 per cent.

(*a*) **High and Low Metabolism in Diabetes** —The wide divergence which may be found in the metabolism of diabetics is strikingly shown in Table 116, which presents the 6 cases with the highest and the 7 cases with the lowest metabolism in the entire series, as indicated by the percentage variation from standard. With all of these cases the diabetes was severe.

For the cases with high metabolism the percentage variation ranged between +26 per cent and +33 per cent. Perhaps the best idea of the gravity of the conditions under which the subjects were living is obtained from the duration of life following the recorded observations. Case No. 1412, succumbed to the disease within three days. Cases Nos. 549, 210, and 246 lived

from one to six months, Case No. 220 lived nearly a year and a half, and Case No. 983 is still alive in 1927. Comment upon the latter exceptional case is made elsewhere. (See p. 279.) It is sufficient to state here that this patient was markedly obese, being 43 per cent above normal weight. Her high metabolism and accompanying acidosis would appear to be due to sudden restriction of carbohydrate and free use of protein and fat for the week preceding entrance to the hospital. This is an example of what occurs when such measures are adopted. The carbohydrate given for the four days before the test was 80, 55, 50 and 50 grams, and although for these same days the caloric intake amounted to but 545, 414, 321, and 240 calories, large quantities of body fat were drawn upon for active caloric needs. This case is also particularly instructive, because it showed in 1916 that a marked increase in metabolism and acidosis may be temporary and not necessarily of bad prognostic import.

In contrast to the cases with high metabolism are 7 patients with an exceptionally low metabolism, these averaging 32 per cent below standard. Despite this extraordinary decrease in metabolism, the life of these patients was evidently not in so great jeopardy as those with high metabolism. Of these patients with low metabolism one succumbed within a month, but the others lived between six months and two years and five months from the date of the observation here recorded. Evidently, therefore, a diabetic patient whose metabolism is far below normal is, on the whole, in a safer condition than the diabetic patient whose metabolism is exceptionally high, though either extreme in metabolism may be dangerous, but not necessarily of fatal significance.

The respiratory quotients are strikingly different. With the omission of Case No. 983, the 5 remaining patients with the highest metabolism had an average quotient of 0.7, while with the 7 patients with the low metabolism the average quotient was 0.84. The significance of this wide variation in the respiratory quotient is discussed on p. 306 *et seq.*

The average loss in weight from maximum of 5 of the 6 patients with the high metabolism was 21 per cent. The losses in weight of the 7 patients with low metabolism were decidedly greater. Thus, the average loss in weight below maximum was 37 per cent, and the average variation in weight from the normal standard was −34 per cent. Three patients were 46 to 49 per cent below normal weight. The low metabolism was evidently connected with an exceptional loss of body weight, but this was not the only factor.

With one exception the cases with the highest metabolism had an extreme degree of acidosis, but of the 7 cases with the lowest metabolism 3 showed no acidosis, while with the other 4 cases acidosis

TABLE 116.—HIGHEST AND LOWEST POSTABSORPTIVE METABOLISM OF DIABETICS AS EXPRESSED BY VARIATION FROM STANDARD (ALL CASES SEVERE).

Case No.	Date.	Variation of metabolism from normal standard, per cent.	Loss from maximum body weight, per cent.	Variation from normal standard of body weight,	Acidosis.	Sugar in blood, per cent.	Urinary nitrogen per kg. of body weight per 24 hours.			Sugar in urine on preceding day, gm.	Respiratory quotient.	Duration of life after this observation, years.
							For days preceding observation.		On observation day, gm.			
							Number of days.	Nitrogen.				
					HIGHEST METABOLISM.							
210	Aug. 2- 3, 1910	+26	24	−27	+++	..	7	0.325	0.315	268	0.71	0.3
220	Mar. 13–14, 1909	+32	24	−25	+++	..	..	..	..	..	0.69	1.4
246	June 8- 9, 1909	+28	15	+ 1	++	..	1	0.210	..	104	0.67	0.5
549	Nov. 5- 6, 1912	+30	18	−14	+++	..	2	0.370	..	185	0.69	0.1
983	Feb. 2- 3, 1916	+28	..	+43	+++	0.30	1	0.145	0.125	72	0.73	11.5[1]
1412	Oct. 18–19, 1917	+33	22	−23	+++	0.37	..	..	0.380	170	0.72	Living
	Oct. 19–20, 1917		22	−23	+++	..	..	..	..	167	0.76	3 days
					LOWEST METABOLISM.							
765	Feb. 9–10, 1916	−27	23	−31	++	0.23	7	0.180	0.110	14	0.76	0.8
821	Apr. 3- 4, 1916	−30	25	−17	+	..	7	0.260	0.225	0	0.81	0.5
	Apr. 10–11, 1916		26	−19	+	0.20	7	0.285	0.210	+	0.82	
1011	Nov. 23–24, 1917	−37	49	−49	0	0.29	7	0.285	0.260	42	0.94	0.8
1085	Oct. 11–12, 1916	−40	50	−43	0	..	..	..	..	0	0.81	0.1
	Oct. 31–Nov. 1, 1916		54	−46	++	0.35	7	0.275	0.165	15	0.81	
1196	Dec. 15–16, 1916	−27	29	−22	++	0.15	6	0.255	0.115	35	0.80	1.0
	Jan. 6- 7, 1917		34	−27	0	..	3	0.415	0.380	0	0.80	
1233	Feb. 19–20, 1917	−33	30	−23	0	0.13	1	0.280	0.210	0	0.86	1.3
1378	Nov. 13–14, 1917	−29	31	−46	0	0.24	..	..	..	..	0.88	2.4

[1] Alive July 1, 1927.

was either absent in some of the tests or not more than moderate in degree in others.

A considerable number of determinations were made of the urinary nitrogen, either for the day of the observation or within one week. The average urinary nitrogen per kilogram body weight of the cases with high metabolism (omitting Case No. 983) for the days preceding the observation and also for the day of the test was 0.32 gram, and the average urinary nitrogen for the patients with lowest metabolism was 0.255 gram per kilogram body weight. The nitrogen excretion per kilogram body weight for a normal adult is about 0.165 gram. It will be observed that the highest value for urinary nitrogen per kilogram body weight was encountered with Case No. 1196, whose metabolism was −27 per cent. The significance of a high urinary nitrogen is twofold. A high urinary nitrogen implies the disintegration of much protein, usually superabundant in the diet, and this leads to a high metabolism under ordinary conditions, as is universally recognized. On the other hand, a high urinary nitrogen due to disintegration of body protein and loss of body nitrogen is an entirely different situation, because it represents the last resort of the body to preserve existence and occurs when the metabolism is at its lowest ebb. (See p. 290.)

(*b*) **Variations in the Metabolism of Individual Diabetics.**—The course of the metabolism of 5 severe cases of diabetes was noted during intervals of from one to one and eighth-tenths years. The average metabolism was lowered 12 per cent as a result of this interval. In 3 of these cases the metabolism was above normal at the first observation and below normal at the second observation. Corresponding to this lowering of the metabolism, there was an average decrease of body weight of 17 per cent. Calculating the decrease in metabolism in terms of calories instead of in standards, the fall in metabolism was exactly the same as that of loss in body weight, namely, 17 per cent. The average pulse-rate fell during the period 11 beats. In sharp contrast to this alteration of the basal metabolism is the metabolism of 6 patients studied after food at intervals of one and one-tenth to one and seven-tenth years. No loss in the response of the metabolism to food was observed.

A classic example of the marked variations in the metabolism of a single diabetic is well exemplified by a case studied by Geyelin and DuBois.[1] A young man, aged nineteen years, weight 172 pounds, began to grow thin November 1, 1915, and on November 20, weighed about 150 pounds. Before he came to the authors, carbohydrate had been greatly restricted and protein (and pre-

[1] Geyelin and DuBois: Jour. Am. Med. Assn., 1916, **66**, 1532.

sumably fat) much increased with resulting severe acidosis. Between December 7 and 11 he was fasted, and 50 to 114 grams sodium bicarbonate were given daily. He was then fed (see Table 117), alkali continued, and the metabolism studied. From the table it can be seen that: (1) The metabolism varied from 73 calories per hour (31 calories per kilogram body weight per twenty-four hours) to 43 calories per hour (23 calories per kilogram body weight per twenty-four hours) in the course of a few weeks;[1] (2) that a dextrose-nitrogen ratio in excess of Lusk's 3.65:1 ration, was obtained on three successive days, to wit: 3.97:1, 4.01:1, 3.87:1; (3) that the nitrogen in the urine was extreme, being 29.8 grams on the second day of fasting and 38.27 grams even when 99 grams of protein were ingested; (4) that the acidosis was extreme, for the β-oxybutyric acid eliminated amounted on one day to 87 grams. The case is remarkable in all of the above particulars and will always remain a classic in diabetic metabolism,

TABLE 117.—CLINICAL AND EXPERIMENTAL DATA IN CASE OF CYRIL K. (GEYELIN AND DUBOIS).[1]

Date.	Carbohydrate, gm.	Protein, gm.	Fat, gm.	Output, glucose, gm.	Urine nitrogen, gm.	D:N ratio.	β-oxybutyric acid, gm.	Blood CO_2, mm. Hg.	Average R. Q.	Average calories per hour.
1915–1916.										
Dec. 8– 9	0	0	0	74	27.9	2.68	43	30		
9–10	0	0	0	78	29.8	2.61	34			
10–11	0	0	0	74	24.8	2.95	..	26		
11–12	41	17	17	108	30.6	2.17	60	21		
12–13	50	50	69	112	34.5	1.80	53	22		
13–14[2]	50	55	58	118	35.4	1.92	57	22		
14–15	53	58	51	118	37.7	1.73	55			
15–16	23	118	41	167	36.6	3.97	70	19	0.687	81
16–17	0	99	5	153	38.2	4.01	75	19	0.714	76
17–18	0	39	2	140	36.2	3.87	87	35		
18–19	0	0	0	55	20.0	2.76	58	35	0.707	73
19–20	0	0	0	44	16.7	2.65	56	49		
20–21	1	10	0	35	14.0	2.44	41	52	0.721	66
21–22	1	20	0	39	14.4	2.65	26			
22–23	5	21	0	25	18.2	1.12	10	52	0.734	62
Feb. 16[3]	..	..	..	0	..	0	0	..	0.915	42
Mar. 8[4]	..	..	..	0	..	0	0	..	0.860	50

[1] Geyelin and DuBois: Loc. cit., p. 209.

[2] Transferred to Bellevue Hospital.

[3] Transferred to Bellevue Hospital. Liberal diabetic diet the days before these calorimeter observations.

[4] After meals which might cause increase in metabolism of 5 to 10 per cent above basal.

[1] Gephart, Aub, DuBois and Lusk (Arch. Int. Med., 1917, **19**, 908) discuss this case more in detail.

but to me it is far more interesting from other points of view, and my interpretation of it is as follows: A fat young man develops diabetes rather acutely. Such cases we know now are quickly amenable to moderate undernutrition consisting of a non-fat diet but if placed upon a protein-fat diet with little carbohydrate, as was this case nearly twelve years ago, develop severe acidosis which is not easily overcome save with insulin. Fat patients, as well as fat depancreatized dogs, are especially prone to develop such an acidosis. (See Case No. 983 on p. 279.) On December 11–12 a diet with 42 grams carbohydrate, 18 grams protein, and 18 grams fat lowered the D:N ratio. It is true the acidosis increased, but this may be explained by large doses of sodium bicarbonate. At any rate, when protein and fat were increased on the following three days, the severity of the case increased and the phenomenon noted above occurred. Is it not probable that if fat has been decreased in the diet at the very beginning of treatment, acidosis would have been avoided? Did not the sodium bicarbonate act harmfully by setting free β-oxybutyric acid which previously was innocuously combined? Had not the case been intrinsically a comparatively mild case, as was later shown by a toleration of 169 grams carbohydrate, and a youthful individual, death from coma must have resulted. As it was, the case survived (*a*) an initial nearly non-carbohydrate diet; (*b*) the increase of fat in the diet when acidosis was well under way; (*c*) the setting free of enormous quantities of β-oxybutyric acid through the use of alkalis, and (*d*) a furuncle, which, though small, undoubtedly increased the severity of the case (see Case No. 610, p. 603) and recovered when (1) fat was eliminated from the diet and protein in moderate quantities given; (2) this was followed after two days by fasting. Was it not in this case, as in so many of my own in the past, though with less fortunate terminations, the hand of man that made the diabetes severe, just as later the hand of man made it mild?

Carrasco Formiguera[1] cites in contrast one of his own cases who eliminated 15 grams of nitrogen in twenty-four hours. When put upon a Petrén diet of carbohydrate 66 to 87 grams, protein 24 to 27 grams, and fat 202 grams, the nitrogen rapidly fell and he excreted daily 5.56, 5.07, 3.33, 3.05, 2.38, 2.50, 1.74 grams. Carrasco emphasizes this as a result of the protection to the nitrogenous metabolism which the fat afforded. His subsequent course was excellent.

(*c*) **Age.**—The influence of age upon the metabolism of the diabetic patient is distinct. All the results available indicate, that both prior and subsequent to June, 1914, in the two decades fifty-one to seventy years the metabolism varied only 1 per cent from

[1] Carrasco Formiguera: Joslin: Tratamiento de la Diabetes Sacarina, Montaner y Simon, Barcelona, 1925, p. 210.

normal. The normal diabetic metabolism for these decades corresponds to the generally accepted idea of the mildness of the disease at this epoch; in fact, of the 18 cases studied 10 were mild or moderate in severity. Greeley[1] from his experience at Hodgson's clinic several years ago emphasized the connection between the decreasing severity of the diabetes with the simultaneous decrease in normal metabolism which advance in age brings.

Both prior to and after June, 1914, the metabolism in the second decade (eleven to twenty years) varied respectively 4 per cent above and 4 per cent below normal. These are significant figures when considered in relation to each other, because they show for this decade the same tendency of rise and fall in metabolism for the two periods as the entire series. On the other hand, the data are so nearly within normal limits that they confirm the impression already furnished by Table 115, that the diabetic metabolism is essentially normal. The disease in youth is so apt to be severe and has universally been considered to be so severe that it is also important and encouraging that the metabolism should prove to be so nearly normal for these boys.

The three decades between twenty-one and fifty years present an average increase above normal of 17 per cent before June, 1914, and an average decrease below normal of 10 per cent after that date. It may be that these peculiarities in the metabolism can be explained by the fact that in the decades with an average metabolism either notably above or below the normal standard the patients were treated most strictly and showed the effect of overfeeding or low diet, whereas the patients in the decade eleven to twenty years were less amenable to treatment, and those in the decades subsequent to fifty years did not require rigorous treatment.

(*d*) **Sex.**—Sex affects normal metabolism in that females have a lower metabolism than males of the same age, height, and weight, and in diabetes the same relation holds .

3. **Pulse-rate and Metabolism.**—(*a*) **In Health.**—A study of normal individuals such as those which furnished the basis for the Harris and Benedict standards of metabolism furnished evidence that when the pulse-rate is low there is a tendency for the metabolism to be low and when the pulse-rate is high there is a distinct tendency for the metabolism to be high. The average pulse-rate for 121 of the 136 men in the Harris and Benedict group of normals was 61 and that for the men in the DuBois series was the same.

(*b*) **In Diabetes.**—In the course of the studies on the metabolism of diabetic subjects at the Nutrition Laboratory between 7000 and 8000 records were made of the pulse-rate. In our early obser-

[1] Greeley: Boston Med. and Surg. Jour., 1916, **175**, 73.

vations between 1908 and 1912 it was shown that whereas the average minimum and maximum pulse-rates of the 25 normal, but somewhat similarly emaciated, male and female subjects used for comparison were 54 and 74 beats, respectively, the corresponding figures for the 24 male and female diabetics were 65 and 81. Without taking account of the sex the average pulse-rate of the normals was 63 and of the diabetics 73.

If we compare the pulse-rate of the diabetics treated since June, 1914, with values for 219 subjects from the same normal series, an entirely different picture is presented. Thus, the average diabetic pulse value, which is based upon 69 cases, was but 1 beat higher than the normal value, or 65 as compared with 64. This shows, therefore, that the average pulse-rate of diabetic subjects decreased markedly in the period subsequent to June, 1914, as compared to the period before that date.

TABLE 118.—RELATION BETWEEN PULSE-RATE AND POSTABSORPTIVE METABOLISM IN DAILY OBSERVATIONS WITH DIABETICS.

Range in pulse-rate.	Before June, 1914.		After June, 1914.	
	Heat output per kilogram of body weight per 24 hours, cals.	Variation in metabolism from standard, per cent.	Heat output per kilogram of body weight per 24 hours, cals.	Variation in metabolism from standard, per cent.
45–49	..	....	22	−16
51–60	30	+ 2	23	−14
61–70	30	+13	24	−10
71–80	31	+13	26	− 5
81–90	32	+22	26	− 1
91–122	37	+25	33	+18[1]

Coming now to the relation between the pulse-rate and the metabolism in diabetes, it is clear from inspection of the figures in Table 118, that both before and after June, 1914, the pulse-rate registers with considerable accuracy the changes in metabolism, the latter steadily rising as the pulse-rate increases. When, however, the values for the metabolism in the two periods are compared, we find that with the same range in pulse-rate the metabolism varies materially. *Accordingly similar conditions of living are requisite for an interpretation of the pulse-rate as a measure of the metabolism.*

(*c*) **Effect of Loss in Weight on Pulse-rate of Normal Individuals.**—The losses in weight of the diabetic patients below their maximum weight were so material that the question arises how much bearing

[1] Range of pulse-rate in this group after June, 1914, was 98 to 101.

similar losses in weight might have upon the pulse-rate of normal individuals. Fortunately the pulse-rates accompanying considerable losses of body weight in a series of experiments carried out by the Nutrition Laboratory are available. The pulse-rates were determined for a group of 11 healthy young men in the International Young Men's Christian Association College at Springfield, Massachusetts, when they were upon a normal diet and also when they had lost on an average of 9 per cent of their weight as a result of a reduced diet.[1] In consequence there was an average decrease in pulse-rate of 14 beats, or 25 per cent. All of the men registered a fall in rate, but this was by no means uniform. These individuals lost on the average but 9 per cent of their initial weight, whereas 111 of the 113 diabetics under observation had an average loss in body weight from maximum of 25 per cent. From these data acquired with normal subjects it would appear that in view of the marked loss in weight of the diabetics, a decrease in the pulse-rate should be very considerable. Before considering the relationship between the loss of weight with diabetics and their pulse-rate, however, various factors should be mentioned which may have an influence upon this relationship.

(1) *Factors Influencing Relation Between Pulse-rate and Loss in Weight.*—At the present moment it is prudent to state that the changes in pulse-rate observed with the normal subjects studied at Springfield *accompanied* the 9 per cent loss in weight rather than were *dependent* upon it. This is necessary, because while these normal individuals were losing weight, they were also losing large amounts of body nitrogen, since 10 of the 11 men lost, on the average, 175 grams of body nitrogen between October 4, the initial day of the reduced diet, and January 27, inclusive. It is yet to be determined whether the changes in pulse-rate and also in metabolism which were observed were due: (1) To the loss in weight which had already taken place; (2) to the loss in body nitrogen; or (3) what appears to be the most probable cause, to the continued underfeeding.

The losses in weight described above with normal individuals took place during a few months, whereas the losses in weight with the diabetic patients usually occurred during a few years. It is possible that the greater loss in weight of the diabetic patients might be counterbalanced to some extent by the greater length of time during which it occurred. With the diabetics, however, there was a fourth factor, namely: the growing weakness due to the progress of the disease which accompanied their loss in weight. This, however, is not so simple a factor as would appear at first

[1] Benedict, Miles, Roth and Smith: Carnegie Inst. of Washington, D. C., Pub. 280, 383.

thought, because this weakness is manifestly of at least two types. The first type of weakness develops rather rapidly in the diabetic who has been living upon a stimulating protein-fat diet, is associated with and perhaps dependent upon acidosis, and is most evident as he is about to pass into coma preceding death. It is akin to the weakness of the patient with hyperthyroidism and high metabolism. Then there is the second type of weakness due to inanition. For the former type of weakness there are few comparable data upon the pulse-rate with normal individuals, though perhaps exhaustion after strenuous exertion might serve, and strangely enough the same may be said of the latter, since inanition seldom occurs in uncomplicated form. Complications are less frequent in cancer than in cardiac or renal disease, yet what data exist upon the pulse-rate in the successive months of cancer? Here is a field for research.

(2) *Effect of Loss in Weight on Pulse-rate of Diabetics and Comparison with Normals.*—That diabetics, whose body weight has suffered so great a loss from their maximum body weight, should have a pulse-rate as high or even higher than normal, must be of significance. In the Springfield series of experiments in which the pulse-rate averaged rather low, even with normal diet, the subjects were normal, healthy men who maintained their muscular vigor, as was proved by physical tests, despite the loss of weight. The loss in weight of the diabetics, on the other hand, can be considered to have been accomplished by a greater loss of muscle as well as of fat. This was a *fait accompli* and in the period before June, 1914, they were actually being overfed, though the food was not wholly utilized and showed an increased pulse-rate; in the period after June, 1914, they were underfed and the pulse-rate was far lower.

Both before and after June, 1914, the diabetic subjects were markedly underweight. Before that date the loss in weight of 30 diabetics from their maximum was, on an average, 21 per cent, yet in spite of this loss the average pulse-rate was 73 beats, or 31 beats (74 per cent) greater than the average pulse-rate of 42 beats found with the group of normal men on reduced diet after a loss in weight of approximately half as much, or 9 per cent. This brings out strikingly the increased pulse-rate of the diabetics before June, 1914. Subsequent to June, 1914, the loss in weight from maximum of 66 diabetics averaged 27 per cent. Notwithstanding that this loss in weight was three times that of the normals, the average pulse-rate of this group of diabetics was reduced only to 65 beats in contrast to the undernourished normals whose average pulse-rate was 42 beats. It is thus seen that both groups of diabetics, with a much greater loss in weight than the undernourished

normals, had higher pulse-rates than the latter and that the highest pulse-rates were obtained with the diabetics before June, 1914, when they were overfed. Despite the fact that the loss in weight of the group of diabetics after June, 1914, was greater than that of the normal subjects and despite the fact that their intake of food was low, the diabetic still maintained a higher pulse-rate than the normals. The evidence is not sufficient to show that the difference in the pulse-rate of 42 of the normals with 9 per cent loss of weight and of 65 of the diabetics with 27 per cent loss of weight can be entirely explained on the ground that the normals were still losing, but the diabetics had lost their weight. At present, therefore, we are forced to conclude that an increased pulse-rate is characteristic of diabetes.

(*d*) **Relation of Severity of Diabetes to Pulse-rate.**—If the pulse-rate in diabetes is characteristic of the disease, one would anticipate a variation with the degree of severity. Tabulation of the data discloses that with increasing severity before June, 1914, the pulse-rate rose, but after June, 1914, it fell. The force of severity cannot act in opposite directions. Obviously these changes in pulse-rate are either not due to severity *per se*, or the effect of severity is overcome by stronger influences, *e. g.*, acidosis and difference in the quantity of food administered.

(*e*) **Relation of Acidosis to Pulse-rate.**—The average pulse-rate for 45 cases without acidosis was 63 beats and for 24 cases with severe acidosis 73 beats. Two cases on the verge of coma had pulse-rates of 98 and 101. Excellent examples of increases in pulse-rate associated with rising acidosis are also to be found in the publications of Allen and DuBois[1] and Gephart, Aub, DuBois, Lusk.[2]

4. **Edema.**—Perhaps no one gross observation made during the course of diabetes mellitus is of greater significance and causes greater alarm, both to the patient and to the physician, than the persistent loss in body weight. On the other hand, slight changes in body weight which may accompany dietetic alterations or the ingestion of sodium chloride and sodium bicarbonate are looked upon as material gains and are thus liable to be misunderstood by the patient. To interpret intelligently these changes, it is necessary both for the physician and for the patient to realize the factors affecting the body weight of normal as well as pathological cases. Few realize that the normal individual is continually undergoing changes in body weight throughout the twenty-four hours. Even during sleep it has been shown that a man of 85 kilos loses 30 grams per hour, and a woman of 65 kilos 29 grams per hour. With exercise

[1] Allen and DuBois: Arch. Int. Med., 1916, **19**, 855.
[2] Gephart, Aub, DuBois and Lusk: Arch. Int. Med., 1917, **19**, 908.

this is, of course, greatly increased and may amount to 6.4 kilos for a foot-ball player during one hour and fifteen minutes of active exercise. Skelton[1] points out that approximately one-half of the water in the body is in muscles, one-fifth in the skin, and only one-fourteenth in the blood.

Edema is a common source of error and it is important to recognize it as a cause of gain in weight in diabetes. Patients may seem to be gaining when in reality they are losing weight because of insufficient diet. Edema occurred most frequently in former years following oatmeal days and the administration of alkalis, while later it was common with fasting diabetics of severe type and was apparently related to the large quantity of salt which they ingested with broths and vegetables. In these days of insulin it is quite likely the result of carbohydrate storage which simultaneously implies water storage. See p. 271 for a further discussion of this aspect of the subject. See also von Noorden and Isaac[2] and Rabinowitch.[3]

The edema may become extreme and one of my patients (Case No. 922), whom I had not seen for months, called in a laryngologist and barely escaped tracheotomy for edema of the larynx. This quickly disappeared with the omission of salt and a diet of water and a few oranges. The patient later entered the hospital, became sugar-free and developed a tolerance for 49 grams carbohydrate, 69 grams protein and 143 grams fat. Case No. 3739 during coma developed edema following the removal of an intubation tube inserted on account of laryngeal obstruction and reinsertion of the tube was necessary. (See p. 659.)

Diabetic patients should be weighed, preferably naked, before breakfast, and after the urine has been voided, for a patient frequently voids a pound at a time.

(*a*) **Water Content of the Body.**—A factor which should be taken into consideration in interpreting changes in body weight is the fluctuation in the water content of the body. It should be realized that the average man at rest without food oxidizes per day about 75 grams of protein, 25 grams of glycogen and 200 grams of fat—a total of 300 grams of water-free, organized body tissue. It can readily be seen, therefore, that with the subjects at rest, large and rapid changes in weight must be due not to the oxidation of organic material, which amounts to only 300 grams per day, but to large excretions of water. Under certain conditions it is possible for the body to retain considerable quantities of water, and conversely, to be deprived of considerable amounts of water that would normally be retained. Campbell[4] found that an increase in weight of 6

[1] Skelton: Arch. Int. Med., 1927, **40**, 140.
[2] Von Noorden and Isaac: Loc. cit., p. 175.
[3] Rabinowitch: Canadian Med. Assn. Jour., 1927, **17**, 685.
[4] Campbell and Macleod: Medicine, 1924, **3**, 195.

pounds would take place after the diuresis due to drinking 10 liters of water had ceased, and furthermore that this increase in weight persists for several weeks without evidence of edema. Since about 60 per cent of the body is water, any change of water content may result in material gains or losses in body weight. A man, weighing, for example, 65 kilograms, may have an absolute water content of 39 kilograms, so that a relatively small change in the percentage of water in the body may produce a change in body weight of 1 kilogram.

(*b*) **Influence of Fat and Carbohydrate Diets Upon Weight.**—Remarkable changes in the weight of normal individuals will also occur, if the proportion of fat to carbohydrate is altered, although the caloric value of the diet remains constant. A diet rich in carbohydrate brings about an increase in weight, whereas a diet of exactly the same number of calories, though chiefly made up of fat, lowers the weight. These changes undoubtedly are due simply to the retention of water by the tissues upon a carbohydrate diet and loss of water upon a fat diet. Such changes appear reasonable because the storage of 1 gram carbohydrate in the body demands the retention of 3 grams of water,[1] 1 gram of protein would appear to require the same amount, and 1 gram of fat requires only 0.1 gram of water. These changes are well illustrated by the following table:

TABLE 119.—CHANGES IN WEIGHT WITH FAT AND CARBOHYDRATE DIETS. CARBOHYDRATE DIET.[2]

Date, 1904.	Food and drink. Solid matter, gms.	Water, gms.	Total gms.	Body weight, kg.	Gain (+) or loss (−), gms.
Apr. 16	...	..	..	75.086	
16–17	970	3577	4547	75.443	+357
17–18	966	3553	4519	75.414	− 29
18–19	966	3491	4457	75.269	−145
		FAT DIET.			
Apr. 19–20	750	3108	3859	74.319	−950
20–21	745	4150	4896	73.480	−839
21–22	747	4152	4899	72.528	−952

Average gain per day, carbohydrate diet, +61 gms.
Average loss per day, fat diet, −914 gms.
Water stored per day, carbohydrate period, +165 gms.
Water lost per day, fat period, −906 gms.

It is important to bear in mind the effect upon weight which must occur when a carbohydrate-free diet is prescribed, for otherwise the loss of the few pounds which is bound to ensue might cause undue apprehension or be interpreted as loss of tissue.[2]

An increase in weight following a marked increase of carbohydrate in the diet is strikingly illustrated in severe diabetic patients under the oatmeal treatment. Under these conditions the weight may

[1] Zuntz: Biochem. Ztschr., 1912, **44**, 290. [2] Carnegie Pub. No. 176, p. 93.
[2] See p. 658 for gain in weight in coma, partly to be explained by glycogen storage following large doses of insulin.

rise 4.5 kilograms during one or two days; edema develops. Insulin acts similarly by promoting the storage of glycogen in liver and muscles, and likewise edema may occur with its use. That this storage or delay of excretion of water is accentuated in the presence of diseased kidneys is common knowledge.

(*c*) **Influence of Sodium Chloride Upon Weight.**—The quantity of salt in the diet also affects the weight. For example, in the study of an individual upon a salt-free diet consisting of the whites of 18 eggs (216 calories), 120 grams olive oil (1080 calories) and 200 grams crystallized sugar (800 calories), total 2096 calories, or 30 calories per kilogram body weight, the weight fell from 70.2 kilograms on the first day to 64.9 kilograms on the thirteenth day, as will be seen from the following table:

TABLE 120.—LOSS OF WEIGHT COINCIDENT WITH A SALT-FREE DIET.[1]

Day	Intake of H_2O. c.c.	Urine. c.c.	Urinary analysis. Sp. gr.	P_2O_5. gms.	Cl., gms.	Weight, kg.
1	1470	1720	1012	1.29	4.60	70.2
2	1550	1810	1010	1.29	2.52	
3	1560	1430	1012	1.28	1.88	
4	1290	930	1017	1.20	0.87	67.4
5	1290	1100	1013	1.43	0.69	
6	1545	1170	1012	1.04	0.48	66.6
7	1200	850	1015	1.15	0.46	
8	1125	1000	1013	0.78	0.40	66.1
9	1290	1160	1011	0.95	0.26	
10	1200	860	1015	0.89	0.22	
11	1260	650	1018	0.76	0.22	
12	1215	510	1023	0.79	0.17	65.1
13	1170	560	1023	0.86	0.17	64.9
15	Diet unrestricted.	940	1029	..	3.50	
16	..	..	..	..	..	69.0
17	..	4090	1017	..	25.76	

The subject was then put upon a free diet and three days later the weight had risen to 69 kilograms.

(*d*) **Influence of Sodium Bicarbonate Upon Weight.**—The administration of sodium bicarbonate is frequently followed by a gain in weight. Thus, in Case No. 220 the changes in weight during the administration of sodium bicarbonate were as follows:

TABLE 121.—GAIN IN WEIGHT COINCIDENT WITH ADMINISTRATION OF SODIUM BICARBONATE.

Date.	Sodium bicarbonate gms.	Body weight, kilos.	Date.	Sodium bicarbonate gms.	Body weight, kg.
Nov. 2	0	48.1	Nov. 7	20	50.7
3	0	48.6	8	20	51.5
4	0	49.0	9	20	52.4
5	0	48.6	10	20	53.3
6	20	49.3	11	20	53.3

[1] Goodall and Joslin: Experiments with Ash-free Diet, Arch. Int. Med., 1908, 1, 615.

In order to show that this gain in weight was not directly due to the alkali but rather to retention of salt, the weights of another diabetic patient, Case No. 135, were taken while upon a salt-free diet.

TABLE 122.—ABSENCE OF GAIN IN WEIGHT COINCIDENT WITH ADMINISTRATION OF SODIUM BICARBONATE WHEN THE DIET IS SALT-FREE (CASE NO. 135).

	Diet. Salt-free.						Urine.								
Date, 1908.	$NaHCO_3$, gms.	Carbohydrate, gms.	Protein, gms.	Fat, gms.	Alcohol, gms.	Liquids, c.c.	Vol., c.c.	N, gms.	NH_3, gms.	Acetone and diacetic acid, gms.	β-oxybutyric acid, gms.	P_2O_5 gms.	Cl., gms.	Sugar, gms.	Weight, lbs.
Jan. 26	0	135	110	185	..	3500	3720	21.8	4.2	7.9	20	4.4	8.2	160	88¼
27	0	135	110	185	..	3500	3940	19.6	4.3	7.8	29	4.5	6.3	165	89¼
28	0	135	110	185	..	3500	3210	20.5	4.4	7.3	24	4.6	5.9	160	86¾
29	0	135	90	155	..	3500	3210	19.2	4.1	7.3	26	4.2	4.8	163	85¾
30	25	135	70	185	..	3500	3190	16.3	3.5	8.7	33	4.1	1.6	146	85
31	25	120	60	95	23	5370	4600	19.1	4.3	12.6	51	5.1	2.3	146	83¼
Feb. 1	37	130	100	130	45	5250	4050	18.7	3.3	10.7	39	4.3	2.0	137	82¼
2	52	70	60	95	45	5370	3510	16.0	3.5	10.2	37	3.9	2.1	121	81¾
3	..	15	15	30	45	800	360	15.0	..	..	..	..	..	86	

It will be seen that while upon the salt-free diet the weight steadily fell and, despite the administration of sodium bicarbonate later, no increase in weight occurred. This observation has been confirmed by Levison.[1] The explanation of the usual gain in weight of diabetic patients following the use of sodium bicarbonate was pointed out by Goodall and Joslin[2] some years ago. Apparently the administration of sodium bicarbonate, by favoring the excretion of large quantities of retained acid bodies, leads to irritation of the kidneys, resulting in their inability to excrete salt in the normal manner. If the salt in the diet is restricted, there is less to be retained and consequently no gain in weight results.

The explanation of the edema which is found in severe diabetics is by no means simple. Falta[3] has recently shown that if sodium bicarbonate is replaced by potassium bicarbonate the edema will disappear although the salt in the body and in the diet is low. Labbé[4] explains the edema by the retention of the sodium and not of the chlorine. Atchley, Loeb and Benedict[5] have removed the edema of a diabetic with the use of 20 to 35 grams of calcium chloride a day.

[1] Levison: Jour. Am. Med. Assn., 1916, **64**, 326.
[2] Goodall and Joslin: Jour. Am. Med. Assn., 1908, **51**, 727.
[3] Falta: Wiener Arch. f. inn. Med., 1922–23, **5**, 581.
[4] Labbé and Cumston: Diabetes Mellitus, New York, 1922, p. 115.
[5] Atchley, Loeb and Benedict: Jour. Am. Med. Assoc., 1923, **80**, 1643.

I might here make the clinical observation that a salt-free diet in diabetes is inadvisable. It is noteworthy that patients during the period of coma markedly lose weight. Edema, which may be present just prior to coma, disappears during coma; in fact, I remember to have seen but one patient in coma who showed edema.

The severe diabetic during coma utilizes apparently all possible liquid in the tissues to aid in the excretion of toxic bodies. The importance of maintaining sufficient fluid in the body deserves emphasis. Hodgson[1] has thoroughly appreciated it for years and endeavored to make his patients retain large quantities of fluid.

(*e*) **Weights and Losses of Weight in Diabetic Patients.**—During a series of observations upon a single diabetic individual the variations in weight were sometimes considerable. Not infrequently these were due in large measure to the increase or decrease of water in the body, which was often demonstrated by the presence of edema. As a result conclusions based upon the metabolism of diabetics are especially liable to error. This is evident in the case of Freda, a little girl of sixteen years, Case No. 1012. She weighed 26.3 kilograms on September 22, 1917, 33.2 kilograms on October 2, on which date the salt was excluded from the diet, and on October 25 the weight had again fallen to 26.3 kilograms. The transitory gain in weight in early October was obviously due to edema and represented a gain in weight of 26 per cent. (!) If the actual body weights are employed for the period from October 9 to December 1, the variation in the metabolism from standard would range from +7 to +31 per cent, but if the weight of September 22 is accepted as the correct weight for the entire period, the metabolism oddly enough would vary in just the reverse manner: that is, from +31 to +7 per cent.

The percentage of loss in body weight of some 200 of my cases in the Naunyn Epoch was computed for me by the Nutrition Laboratory. The average loss previous to the first visit was 16 per cent, and between this time and the last observation a further loss of 3 per cent occurred. This is good evidence that these cases came almost uniformly late for treatment. The loss would have been far greater in the Allen period, but not in the Banting Era when a gain in the weight would be registered.

(*f*) **The Loss of Weight Prior To and During Coma.**—The loss in weight of patients immediately prior to and during coma has always appeared to me to be great, but from the nature of the case it has been difficult to determine this point. A hint of this was afforded by noting the marked loss in weight which occurred in Case No. 135, from whose diet salt was excluded, but a still better example was

[1] Hodgson: Jour. Am. Med. Assn., 1911, **57**, 1187.

that of Case No. 513, referred to on page 782, who lost 35 pounds in the eleven days preceding the third day before death in coma. Further observations of this character should be made.

(*g*) **The Caloric Value of a Kilogram of Body Weight and Hypothetical Estimations Connected Therewith.**—L., the Nutrition Laboratory normal subject, in the course of his thirty-one day fast, lost 13.2 kilograms, or an average of 0.7 per cent of his original body weight each day. Each kilogram lost represents a metabolism of 3258 calories if the estimated total metabolism of each day of L's. fast is used for the computation. If the first four days of the fast are excluded, when the loss was somewhat rapid, and the remaining twenty-seven days, when the loss was more gradual, are employed for the calculation, *each kilogram of body material lost would represent 3766 calories and the average loss of body weight each day would be 0.62 per cent.*

In computing the metabolism of a patient the factor of the error introduced by edema should be borne in mind.[1]

For a given percentage loss of weight the metabolism of a group of normal Y. M. C. A. students fell more rapidly than that of diabetics, presumably because the latter lost weight more gradually.

TABLE 123.—DECREASE IN BODY WEIGHT AND METABOLISM COMPARED.

Group.	Number of individuals.	Decrease in weight, per cent.	Decrease in metabolism, total, per cent.	Decrease in metabolism per kilogram, per cent.	Time.
Y. M. C. A. series . .	11	10	19	1.90	3 mos.
Diabetic	20	35	22	0.63	5 yrs.
Normals, comparable to diabetics at their maximum and minimum weights	20[2]	35	18	0.51	

(*h*) **Diabetic Variations from Standard in Metabolism and Weight Compared.**—Prior to June, 1914, no relation is apparent between the variation of the metabolism from standard and the percentage variation of the body weight from standard, when the metabolism was more than 10 per cent above standard. But, when the metabolism was 10 to 5 per cent above standard, the average variation of the weights of the patients from normal was −2 per cent and when the metabolism was 35 to 40 per cent below standard, the average variation from standard weight was the most subnormal in the series, namely, −48 per cent. Between these extremes mentioned, almost uniform gradations are registered.

[1] In the Carnegie Monograph Pub., No. 323, p. 65, the subject is discussed in more detail and more facts presented.

[2] Minimum weights computed at 35 per cent reduction from maximum and metabolism predicted for these weights.

5. **Relation of Severity of Diabetes to Metabolism.**—The relation of the degree of severity of the diabetes to the postabsorptive metabolism is shown in Table 124. As heretofore the experiments are classified according to whether they took place prior to or subsequent to June, 1914. Before June, 1914, the mild cases showed a normal metabolism in the daily observations, the few moderate cases a metabolism of 14 per cent above normal, and the severe cases a slightly less variation, +12 per cent. After June, 1914, the metabolism in most of the daily observations with mild cases and with moderate cases as well was lower than standard, but the average in each group was still within the normal zone. The daily observations with severe cases averaged 13 per cent below standard. In general, prior to June, 1914, the severer types of diabetes gave a higher metabolism than the mild, while subsequent to that date, on the contrary, the severest type of the disease exhibited a lower metabolism than the mild and moderate forms.

TABLE 124.—RELATION OF SEVERITY OF DIABETES TO BASAL METABOLISM BEFORE AND AFTER 1914.

Percentage variations from standard metabolism.	Daily observations before June, 1914.			Daily observations after June, 1914.		
	Mild diabetes.	Moderate diabetes.	Severe diabetes.	Mild diabetes.	Moderate diabetes.	Severe diabetes.
Above standard:						
35–30 . . .	..	1	1	..	..	2
30–25 . . .	..	..	8	..	..	2
25–20 . . .	..	1	12			
20–15 . . .	..	7	15	..	1	1
15–10 . . .	..	5	18	..	3	6
10– 5 . . .	3	3	15	1	6	1
5– 0 . . .	1	3	14	5	13	12
Below standard:						
0– 5 . . .	1	..	7	7	13	25
5–10 . . .	1	..	2	5	9	19
10–15 . . .	..	..	1	3	20	22
15–20 . . .	..	..	..	1	6	33
20–25 . . .	..	..	..	..	1	34
25–30 . . .	..	..	..	..	..	18
30–35 . . .	..	..	..	..	..	6
35–40 . . .	..	..	..	..	..	4
Aver. percentage variation, all experiments .	+4 (6 days)	+14 (20 days)	+12 (93 days)	−4 (22 days)	−5 (72 days)	−12 (185 days)

The force of severity cannot act in opposite directions. It is, therefore, reasonable to conclude that one or more extraneous influences must have been present before and after June, 1914, to bring this about.

Of four extraneous factors which might influence metabolism—drugs, exercise, diet and acidosis—little need be said regarding the first two. Drugs were never given to either group of patients with the exception of sodium bicarbonate, and this was discontinued after September, 1915. There is no evidence that sodium bicarbonate exerts the slightest influence upon the metabolism in health, and a critical study of the protocols of these diabetic patients bears out the same conclusion, as does the work of others.[1]

Exercise played no role, because the experiments were basal, and exercise was not a part of the routine when these were made.

The change in the character of the diet is of far more importance in determining the cause of the change in the metabolism of these patients after June, 1914. The severe cases underwent strenuous overfeeding before June, 1914, and strenuous underfeeding after June, 1914, and the quantitative changes in the diet appear nearly adequate to account for this phenomenon of changing metabolism.

6. **Relation of Acidosis to Metabolism of Diabetes.**—Does a state of acidosis increase the metabolism? I am inclined to think it does and in what follows have assembled all the data my experiments show to prove it. Wilder, Boothby, and Beeler[2] believe it does not. DuBois[3] expresses doubt as to whether we shall ever know. From the clinical point of view the essential fact is that a high diet predisposes to acidosis and with it the metabolism is increased and that a low diet is seldom accompanied by acidosis and the metabolism is decreased. Moral: Avoid a high diet in diabetes, either of exogenous food or of endogenous food as in hyperthyroidism or fever.

(*a*) **Acidosis.**—It may occur in all types of the disease and can easily be made extreme in a mild case, just as it can with a healthy individual. During the years that these experiments were in progress, acidosis was undoubtedly responsible for two-thirds of all the deaths from diabetes in the community and possibly for three-fourths of these deaths. Of the fatal cases studied at the Nutrition Laboratory before June, 1914, 86 per cent of those who later died succumbed to coma, and of those studied from that date to the end of the research, December 5, 1917, 72 per cent of the deaths were due to coma.

The relation of the acidosis to the total metabolism is exhibited in Tables 125 and 126 in which the results of 398 observations upon 106 cases of diabetes are recorded. These indicate that with the development and increase of acidosis there is a steady rise in the metabolism.

[1] Haldane, Wigglesworth and Woodrow: Proc. Roy. Soc., London, 1924, B **96**, 15.
[2] Wilder, Boothby, and Beeler: Jour. Biol. Chem., 1922, **51**, 312.
[3] Du Bois: Loc. cit., p. 248.

TABLE 125.—ACIDOSIS AND METABOLISM WITH 106 DIABETICS ON FOUR HUNDRED DAYS.

Degree of acidosis.	Number of observation days.	Average variations of metabolism from standard, per cent.
+++	61	+10
++	144	− 5
+	82	− 5
0	111	− 9

TABLE 126.—ACIDOSIS AND BASAL METABOLISM OF DIABETICS BEFORE AND AFTER JUNE, 1914.

Percentage variations from standard metabolism.	Before June, 1914, variation with acidosis.				After June, 1914, variation with acidosis.			
	+++ per cent.	++ per cent.	+ per cent.	0 per cent.	+++ per cent.	++ per cent.	+ per cent.	0 per cent
Above standard:								
35–30	+32	+31	..	..	+33			
30–25	+29	+27	..	..	+28			
25–20	+22	+22	+22	+23				
20–15	+18	+18	+16	+17	..	+19	+16	
15–10	+14	+13	+13	+13	..	+12	+12	+12
10– 5	+ 8	+ 9	+10	+ 9	..	+ 8	+ 8	+10
5– 0	+ 4	+ 3	+ 5	+ 5	+ 1	+ 3	+ 2	+ 3
Below standard:								
0– 5	− 2	− 2	− 1	− 3	− 5	− 2	− 3	− 3
5–10	..	− 7	..	− 9	− 6	− 8	− 8	− 8
10–15	..	−12	..	..	−13	−14	−12	−13
15–20	..	..	..	..	−18	−18	−18	−18
20–25	..	..	..	..	−23	−23	−23	−23
25–30	..	..	..	..	..	−28	−29	−28
30–35	..	..	..	..	..	−32	..	−33
35–40	..	..	..	..	..	−38	..	−39
Av. variation for all daily observations	+13	+13	+12	+10	+1	−12	−8	−13

Prior to June, 1914, acidosis was of frequent occurrence. Of the one hundred and nineteen experimental days included in Table 126 for this period there were but eighteen on which no acidosis was found, but after June, 1914, of the two hundred and seventy-nine experimental days on only thirteen experimental days was the acidosis severe.

In the earlier period there was a tendency for the metabolism of the diabetic with acidosis to be higher than that of the diabetic without severe acidosis, and the same relation holds after June, 1914. Since June, 1914, acidosis has had less opportunity to exert an influence upon the metabolism.

Observations are available upon 12 patients before June, 1914, and upon 24 patients after June, 1914, whose metabolism was observed, in each instance, during at least two stages of acidosis. Prior to June, 1914, the average metabolism of those individuals without acidosis was 8 per cent above standard, with slight and moderate acidosis, 14 per cent above standard, and with severe acidosis, 15 per cent above standard. After June, 1914, during the period of undernutrition, the group with no acidosis showed the lowest metabolism, 17 per cent below standard, and the group with the most severe acidosis the highest metabolism, 5 per cent below standard.

Confining our attention to severe cases of diabetes, the effect of acidosis upon the metabolism is still more clearly evident. With 22 cases in various stages of acidosis observations were made on ninety-three days prior to June, 1914. On only nine of these days was the metabolism below normal. On two days with cases without acidosis the average metabolism was 9 per cent above standard. On five days with slight acidosis the metabolism was 12 per cent above standard, on thirty-eight days with moderate acidosis likewise 12 per cent, and on forty-eight days with severe acidosis 13 per cent above standard.

After June, 1914, experiments were made on one hundred and eighty-five days with 41 cases of severe diabetes. The lowest average metabolism found on forty-nine days with diabetics having no acidosis was 19 per cent below standard. On thirty-seven days with mild acidosis present, the metabolism was 14 per cent below. The experiments on eighty-seven days with moderate acidosis indicated a metabolism 12 per cent below standard. On the twelve days with severe acidosis the metabolism was 2 per cent above standard. In conclusion, therefore, it can be said that an examination of the influence of acidosis upon the metabolism of diabetics of different degrees of severity supports the view that acidosis raises the metabolism of severe cases. (See L. Hédon, p. 257.)

(*b*) **Acidosis and Metabolism of Individual Diabetics.**—Certain cases are worthy of special discussion because of the opportunity they present for a comparison of acidosis and metabolism. The experimental data of Case No. 983, show clearly such association in a fat diabetic. This patient stated that she had eaten little for a week preceding January 29. How true this is one cannot say, but the presence of acidosis, despite 6.3 per cent of sugar in the urine, leads one to infer that presumably the relations for the carbohydrate, protein, and fat in the diet at least may have been altered. The effect of the caloric content of the daily diet upon the acidosis and metabolism is brought out by the data in Table 127. From these records it is seen that the postabsorptive metab-

olism of this woman in the course of six days decreased from 28 per cent to 12 per cent above normal, the urinary nitrogen per twenty-four hours for the experimental days fell from 13 grams to 5.3 grams, and the sugar in the urine disappeared. The decrease in the excretion of nitrogen, sugar, and ammonia, and the fall in the metabolism were coincident with the marked reduction in the total diet, namely, a change from a diet so abundant as to allow 6.3 per cent of sugar on January 29, 1918, to a diet so low that it averaged but 76 calories a day for the six days preceding the last metabolism test. The decrease in the metabolism of protein, which amounted to but 46 grams ($13 - 5.3 = 7.7 \times 6$) for a woman weighing 90 kilograms, appears insufficient to explain the change in metabolism.

Despite the fact that the patient was fat, that she was upon a very low diet, and was ultimately given a total fast, the acidosis decreased. This behavior is absolutely different from that of the fat women reported by Folin and Denis[1] when fasted for two four-day, and one five-day periods, whose acidosis continually advanced in each period from day to day, though the total acidosis decreased in successive periods. In the diabetic the acidosis decreased upon fasting, whereas with the normal individual it developed. The explanation is found by computing the actual values of carbohydrate, protein, and fat burned at the beginning and end of the period. This has been done in the usual way with the use of the non-protein quotient and by having added 20 per cent to the heat output per twenty-four hours as computed from the basal metabolism. On February 2–3 the carbohydrate in the diet was 50 grams, but the carbohydrate actually burned by the patient was 7 grams, whereas on February 8–9, the carbohydrate ingested was 5 grams, but the carbohydrate burned by the patient was 38 grams. Using Shaffer's formula (see p. 523) the theoretical quantity of carbohydrate sufficient to prevent acidosis upon the first day would have been 25 grams. As the patient only actually burned 7 grams, the deficiency of carbohydrate was 72 per cent corresponding to the severe acidosis which she showed on that day. On the last day the theoretical quantity of carbohydrate sufficient to prevent acidosis would be 31 grams. On this day 38 grams were actually burned which would be as much as required. Corresponding to this improvement in the oxidation of carbohydrate, the acidosis decreased but was still present, and is explainable, as Shaffer has stated, on the ground that each ketogenic molecule does not meet its antiketogenic molecule in the body. This led him to advise giving twice the theoretically sufficient carbohydrate.

[1] Folin and Denis: Jour. Biol. Chem., 1915, **21**, 183.

TABLE 127.—THE METABOLISM OF A DIABETIC (CASE NO 983, FEMALE) WITH HIGH ACIDOSIS.

(Age, fifty-five years; average weight, 90.4 kg.; height, 160 cm.; diabetes, severe. All experiments postabsorptive.)

Date.	Blood sugar, per cent.	Acidosis.			Urinary nitrogen per 24 hours.		Urinary sugar per 24 hrs., gm.	Diet.			Respiratory quotient.	Heat output per 24 hours. (Basal).		Body materials, katabolized.			Carbohydrate. (Shaffer).	
		CO_2 in alveolar air, mm. Hg.	Diacetic acid.	NH_3, gm.	Total, gm.	Per kg., gm.		Carbohydrate, gm.	Protein, gm.	Fat, gm.		Total calories.	Variations from H. and B. standard, per cent.	Carbohydrate, gm.	Protein, gm.	Fat, gm.	Required to prevent acidosis, gm.	Deficiency in metabolism of Case 983, per cent.
1916.																		
Jan. 30–31	0.39	..	++	..	..	..	130[1]	80	35	10								
Jan. 31–Feb. 1	..	..	++	4.3	..	..	86	55	25	10								
Feb. 1–2	..	24	++	4.4	13.0	0.145	72	50	20	5								
Feb. 2–3	0.30	23	++	4.3	11.2	0.125	56	50	10	0	0.73	1989	+28	7	67	216	25	72
Feb. 3–4	..	26	+++	4.6	11.7	0.130	42	40	10	0								
Feb. 4–5	..	..	+++	3.3	7.7	0.085	10	0	0	0								
Feb. 5–6	0.25	28	+++	3.1	5.8	0.065	0	0	0	0	0.72	1858	+19	8	35	214	33	76
Feb. 6–7	..	..	+++	..	..	..	..	0	0	0								
Feb. 7–8	0.20	29	+++	2.2	5.3	0.060	0	0	0	0								
Feb. 8–9	0.18	29	++	2.0	5.4	0.060	0	5	25	15	0.73	1757	+12	38	32	189	31	0

[1] Six and three-tenths per cent of sugar was determined in specimens of urine on January 29, preceding the night urine of January 29–30, 1916. Sugar in urine for twelve hours on night of January 29–30, 1916, was 126 grams.

Case No. 1026, a fat man with a mild type of diabetes, was also treated upon a low diet quite similar to that given to the fat woman, Case No. 983. In contrast he at no time showed more than a slight to moderate acidosis. His metabolism changed from −8 to −15 per cent in seven days. This is again in contrast to Case No. 983, who, with marked acidosis, presented a metabolism of +28 per cent and six days later, with far less acidosis, a metabolism of +12 per cent. *With the decrease in acidosis the metabolism fell twice as rapidly with Case No. 983 as with Case No. 1026, who had no acidosis.* The difference in the metabolism of these two cases is not to be explained by the diet, for Case No. 983, during the first six days of treatment received 3.2 (0.3 net) calories per kilogram body weight per twenty-four hours.

With Case No. 1181, there was a gradual and consistent decrease in the metabolism as compared with the standard from −1 per cent to −24 per cent, as determined in postabsorptive experiments on nine days in the course of a period of sixteen days. The body weight and urinary nitrogen remained essentially constant during these sixteen days. The energy in the diet on successive days ranged from 40 to 575 calories with six fasting days in all. In this instance it is plain that the decrease in metabolism occurred during a period of continual undernutrition. The acidosis gradually decreased and eventually disappeared.

With Case No. 765, the metabolism decreased between January 22, and February 12 from −1 per cent to −25 per cent and coincidentally the acidosis which was originally high disappeared. The urinary nitrogen for the first three days varied between 0.175 and 0.150 gram per kilogram body weight and for the last two days between 0.130 and 0.135 gram per kilogram body weight. The fall in metabolism and the disappearance of acidosis are independent of marked changes in the urinary nitrogen.

Table 128 is a recomputation of an exhaustive study of the metabolism of a case of diabetes by Wilder, Boothby, and Beeler.[1] It shows that the metabolism is definitely related to the degree of acidosis, for when the metabolism is highest, the acidosis is highest, and when the metabolism is lowest, the acidosis is least. In the following table three other factors are introduced which, singly or together, may be of importance in this supposed relation. These are the nitrogen excreted and the fat and total calories ingested. From Table 129 it will be seen that with each of these factors the metabolism varied as with the acidosis. Shall one ascribe the entire cause of the variation to the nitrogen or in part to the acidosis which the fat and excessive diet caused? From evidence already

[1] Wilder, Boothby, and Beeler: Jour. Biol. Chem., 1922, **51**, 312.

submitted, and to be submitted, the latter alternative appears as the more reasonable explanation. It is not for a moment denied that protein increased the metabolism of this individual, but that 40 grams of protein raised the metabolism of this patient to so great an extent as here shown appears improbable. In their own study of Bessie B., Wilder, Boothby, and Beeler believe they can demonstrate that the change in metabolism preceded the change in acidosis.

TABLE 128.—VARIATIONS IN BASAL METABOLISM AND ACIDOSIS (COMPUTED FROM WILDER, BOOTHBY AND BEELER.)

Variation from DuBois standard, per cent.	Metabolism.		Acidosis.		
	Blood.		Urine (preceding day).		
	Carbon dioxide, vol., per cent.	Acetone bodies (as acetone), gm.	NH_3, gm.	$\frac{NH_3 - N}{\text{Total N, per cent.}}$	Acetone bodies (as acetone), gm.
− 1 to −10 . .	38	0.057	1.58	10	8.1
−11 to −20 . .	49	0.028	1.19	13	4.2
−21 to −30 . .	52	0.020	0.50	7	2.0

TABLE 129.—COMPARISON OF BASAL METABOLISM WITH FAT AND CALORIES IN THE DIET AND NITROGEN EXCRETED (COMPUTED FROM WILDER, BOOTHBY AND BEELER).

Variation of metabolism from DuBois standard, per cent.	Urinary nitrogen of preceding day, gm.	Fat in diet of preceding day, gm.	Total calories in diet of preceding day.
− 1 to −10	13.7	127	1587
−11 to −20	9.4	104	1225
−21 to −30	7.0	95	1074

7. **Relation Between Metabolism and the Blood.**—(*a*) **Relation Between Blood Sugar and Metabolism.**—The percentages obtained for the blood sugar secured before breakfast from diabetics of all types of severity when compared with the metabolism indicate no general relationship between the two. If the comparison is limited to severe cases, a different picture is presented inasmuch as the metabolism rose as the blood sugar increased. The data are sufficiently numerous to warrant some significance being attached to this mutual change, though the extreme values are both based upon only two experiments. The lowest percentages of blood sugar (0.05−0.11) are associated with an unusually low metabolism of −21 per cent, of (0.12—0.20) per cent with −15 per cent, (0.21−0.30) per cent with −14 per cent (0.31−0.40) per cent with −11 per cent, and the highest (0.41−0.43) with an average metabolism of +5 per cent.

This definite relation for the severe cases of diabetes between the increasing percentage of blood sugar and increasing metabolism has further interest in view of the reverse relationship found between the blood sugar and the respiratory quotient, which will be subsequently discussed. (See p. 325.) The low blood sugar in diabetes, like the low metabolism, may be an expression of inanition.

(*b*) **The Relation Between Blood Fat and Metabolism.**—The relation between the fat in the blood and the metabolism was noted in a few patients and indicated that the metabolism decreased as the percentage of blood fat increased. The patients with the lowest percentage of blood fat had an average metabolism of −5 per cent, but when the blood fat was highest, that is, over 2 per cent, the average metabolism was −25 per cent. It is possible that this association of low metabolism with high blood fat simply results from inanition in which lipemia in non-diabetics is known to exist. In passing it may be stated that the patients whose blood-fat values average nearest the normal had a body weight 8 per cent below standard, and as the blood fat increased in quantity there was a steady loss in body tissue. These three factors, therefore, are in some relation: high blood fat, low metabolism, and loss in body weight.

(*c*) **Relation Between Non-protein Nitrogen in the Blood and Metabolism.**—The 17 instances in which the non-protein nitrogen was determined at the time the metabolism was estimated are so few as to merit but brief notice and are recorded simply to indicate the desirability of further study. In this limited series the metabolism varied inversely with the non-protein nitrogen, the average variation of the metabolism from standard for the group with low non-protein nitrogen being −6 per cent, for the group with normal non-protein nitrogen values −17 per cent, and for the group with the highest non-protein nitrogen values the average variation was −22 per cent. In this series the non-protein nitrogen rose as the body weights successively fell below the normal standard.

The respiratory quotient directly followed the course of the non-protein nitrogen. With the lowest values it averaged 0.77, with the normal values it averaged 0.81, and with the group with the highest non-protein nitrogen values it was 0.83. While not wishing to attach undue importance to this limited series of cases, the facts herewith brought out regarding the non-protein nitrogen and its various relations suggest that the high values obtained were due to an unusual activity in protein metabolism with retention not attributable to diseased kidneys. The evidence is consistent with one explanation of the high respiratory quotients observed with some of the patients and described later. (See p. 317.) According to this theory, such quotients might be due to the

katabolism of the protein molecule, the oxidation of the carbohydrate portion, and the retention of the non-carbohydrate portion, the latter condition presumably being connected with the need of the body for new protein synthesis.

Finally, it must be mentioned that in cases of diabetes with acidosis shortly before death high non-protein nitrogen values are often encountered. Such values are in all probability simply an evidence of retention of non-protein nitrogen. Thus, Case No. 3079, Case No. 1924, and Case No. 2595 had non-protein nitrogens of 60 to 75 mgm. shortly before death.

(*d*) **Relation Between Urinary Sugar and Metabolism.**—Freedom of the urine from sugar was associated with lowering of the metabolism, both before and after June, 1914. Between the extremes of sugar-free urine and a content of over 100 grams of sugar the transitions from low to high metabolism are not uniform, but it can be stated that the metabolism of a patient voiding over 100 grams of sugar is usually increased.

8. **Nitrogen Excretion.**—How dependent the nitrogen excretion of diabetic patients is upon the diet is evident when one notes the quantity present in the urine of an untreated severe diabetic. Occasionally values of 25 to 30 grams nitrogen are obtained in contrast to half this quantity for the normal individual. Under modern treatment the nitrogen excretion of a diabetic patient falls to the neighborhood of 8 to 12 grams per day.

I used to think an abnormal nitrogenous excretion in diabetes lacking, but one of my own cases, Case No. 513, p. 782, while ingesting 11 grams protein daily, excreted an average of 33.8 grams nitrogen daily for five days ending the second day prior to coma. This patient had multiple abscesses originating in a carbuncle. Another similar case is that of Geyelin and DuBois, already cited on p. 262, who excreted an average of 33.2 grams nitrogen daily between December 8–9 and December 17–18, inclusive, while the average of the protein intake during this period was 44 grams daily. He also had an infection. Now we realize an infection makes a diabetic worse, possibly, as Lawrence[1] suggests, by its stimulating action on the thyroid, thus rendering insulin less potent. At any rate, increased protein destruction might be explained by the small quantity of food given the patient, forcing him to resort to an endogenous supply. In the light of modern theories I can hardly agree with Carrasco[2] that when there exists an increase in protein katabolism it is always due to some cause which is not a direct result of the diabetic disturbance of protein metabolism.

[1] Lawrence and Buckley: Brit. Jour. Exp. Path., 1927, **8**, 58.

[2] Carrasco Formiguera: Joslin: Tratamiento de la Diabetes Sacarina, Montaner y Simon, Barcelona, 1925, p. 234.

Münzer and Strasser report the nitrogen in the urine of a man fasting, during the first day of coma to be 32 grams; the patient died the next day.

Case No. 1196 is remarkable because he differs from all the above in that he showed no acidosis, although he excreted a daily average of 25.5 grams nitrogen for eight days, losing much in weight and becoming so weak as to be barely able to raise his hand. The case later began to improve and is described in full under the discussion upon inanition. He had no infection. At the time it did not seem possible that broths could account for the high nitrogen.

Prior to June, 1914, the nitrogen excretion based upon 37 cases is known for four hundred and fifty-eight days, and subsequent to June, 1914, for 75 cases for one thousand and fifty days. The data, therefore, are so extensive that they give a clear picture of the diabetic nitrogenous metabolism, both before and after June, 1914, in the Naunyn and Allen Eras, respectively. Approximately one-fourth of the nitrogen values obtained were for days upon which observations of the metabolism were made. The balance of the values were largely for the day immediately preceding the metabolism test. In a way these values serve as a better indication of the nitrogenous metabolism at the time of the metabolism test, because they represent the dietary conditions in the twenty-four hours immediately preceding the observations of the metabolism. The diabetic patients vary so much in weight that the nitrogenous excretion will be discussed as grams per kilogram body weight per twenty-four hours.

Prior to June, 1914, the diabetic patient excreted on the average 0.265 gram of urinary nitrogen per kilogram body weight. After June, 1914, the excretion averaged about one-third less or 0.185 gram per kilogram body weight. This latter quantity computed as protein would amount to a little over 1 gram of protein per kilogram body weight. This is generally considered as an ample allowance of protein for a normal individual, though it is possible to exist with even one-third less,[1] and even as Millard Smith has recently shown on as little as 4.4 grams average total intake for twenty-four days.[2] Perhaps the fact that the nitrogen excretion was not further reduced after June, 1914, is due not so much to the character and the amount of the food ingested as to the undernourishment of the patients during this period which obliged them to draw upon body protein for energy. If more calories are supplied, either in carbohydrate or fat, the quantity of nitrogen metabolized and, in consequence, excreted may be decreased. The work of

[1] Sherman: Jour. Biol. Chem., 1920, **41**, 97.
[2] Smith: Jour. Biol. Chem., 1926, **68**, 15.

Marsh, Newburgh, and Holly[1] proved it to be unnecessary that a considerable proportion (10 per cent) of the total calories be supplied in the form of carbohydrates in order to decrease protein metabolism. These writers based their conclusion on observations upon their patients, which appeared to show that nitrogen balance can be maintained when the carbohydrate is but 3.8 per cent of the total caloric intake, the remainder of the diet being made up of 0.68 gram of protein per kilogram body weight and of fat sufficient to bring

Calories of Carbohydrate, Protein and Fat in Diet and Metabolism Compared. (DuBois and Richardson.)

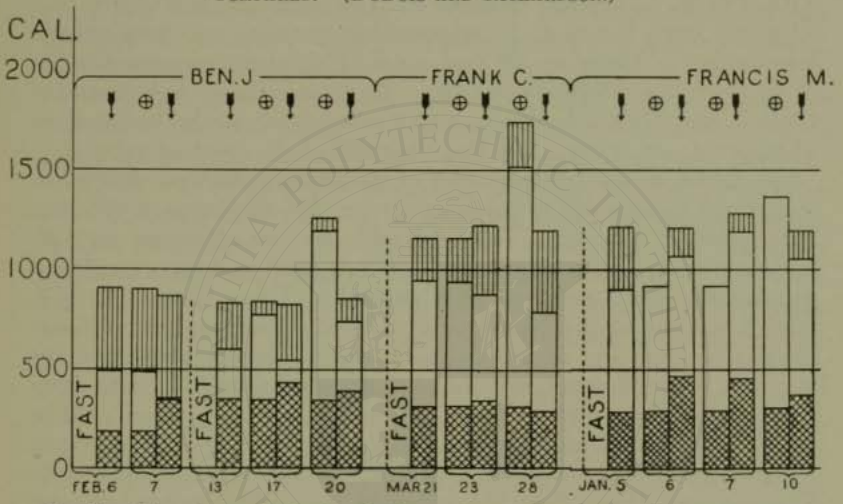


Fig. 20.—The columns indicate calories per twenty-four hours, the lowest portion indicates protein, the middle, fat, the upper, carbohydrate. The circles ⊕ indicate calories in diet, the arrows, ↓ calories metabolized. The diet was given, divided into two-hour intervals, and the calorimeter observations were made after the last meal.

In the chart comparison may be made between calories metabolized on different days under different conditions of diet, or between the calories of the diet and those metabolized on any given date. Ben. J. was a boy with severe emaciation and a high respiratory quotient.

the total energy of the diet up to 33 calories per kilogram body weight. Recent work of DuBois and Richardson, however, makes it clear that it is inaccurate to compute the carbohydrate burned from that ingested and it is probable the Newburgh and Marsh patients oxidized more carbohydrate than was supposed. It is surely very important for diabetic patients to be kept in nitrogen equilibrium save for temporary periods, particularly if by analogy protein loss is regained with as great difficulty as loss in weight.

[1] Marsh, Newburgh, and Holly: Arch. Int. Med., 1922, **29**, 97.

The influence of the character of the food given and the food metabolized is shown by a chart placed at my disposal by Dr. DuBois and Dr. Richardson.[1] When the same quantity of food was given on February 7, to Ben. J., as he had metabolized fasting February 6, (1) his metabolism decreased, (2) the protein burned doubled and (3) the quantity of carbohydrate rose, while (4) the metabolism of fat was almost eliminated. On February 20, when the fat in the diet was greatly increased, the metabolic record shows that not even one-half of it was burned and the total metabolism remained unaffected. These results were duplicated with Frank C. With Francis M., although carbohydrate was withheld from the diet, an appreciable quantity of carbohydrate was burned. *Therefore, the food given is by no means an indication of the food burned on the same day.* I consider these experiments of DuBois and Richardson not only fundamental in the explanation of diabetic metabolism, but also clinically of the greatest value.

(*a*) **Errors in the Interpretation of the Urinary Nitrogen Excretion.**—Strange figures are often encountered for the urinary nitrogen with diabetic patients. It is desirable to call attention to such instances because the nitrogen excretion is more and more employed in planning the treatment of a patient.[2] Thus, Case No. 1673, once a patient at the New England Deaconess Hospital and later cared for elsewhere, according to Dr. A. A. Hornor, presented the anomaly of a minus nitrogen balance amounting to 8.7 grams daily for a period of six days. When, however, the nitrogen was quantitated in the broths and bouillon cubes which the boy surreptitiously received, the explanation was found, because this amounted to 8 grams and thus offset the nitrogen loss. This same boy also voided between 19 and 24 grams of sodium chloride daily, and the source of this large excretion was likewise found in the broths and bouillon cubes.

(*b*) **Individual Variations in Excretion of Urinary Nitrogen.**—Individual variations in the nitrogen excretion were considerable, both before and after June, 1914. Prior to June, 1914, the lowest excretion of urinary nitrogen per kilogram body weight per twenty-four hours was 0.08 gram (Case No. 707) and the highest excretion was 0.835 gram (Case No. 550), representing a total excretion for the twenty-four hours of 4.1 grams and 48.1 grams, respectively, when calculated according to the patients' weights, or 4.8 grams and 50.1 grams when calculated for an individual with a body weight of 60 kilograms.

The nitrogen excretion for Case No. 550 was not only the highest value obtained before June, 1914, but was the highest value noted

[1] Richardson: Boston Med. and Surg. Jour., 1923, **189**, 813.
[2] Shaffer: Jour. Biol. Chem., 1922, **50**, 26.

for the entire series of patients. This patient was an Italian, the only one of the 113 cases not finally traced,[1] who just before commencement of treatment voided in twenty-four hours 7000 cc. of urine containing 48.3 grams of nitrogen. This illustrates the large quantity of protein food which an untreated diabetic consumes.

After June, 1914, the lowest excretion of nitrogen per kilogram body weight was that of Case No. 1207, amounting to 0.05 gram, and the highest was 0.515 gram for Case No. 1011. It is of particular interest that the latter case showed upon another occasion a nitrogen excretion of 0.055 gram per kilogram body weight.

(*c*) **Low Nitrogen Excretion.**—The very low excretion of urinary nitrogen of the boy, Case No. 707, mentioned above; namely, 0.08 gram per kilogram body weight, took place in May, 1914. At that time he was receiving a diet containing a large number of calories which were chiefly in the form of fat. Various tests were being made with vegetable days and oatmeal days, and on May 16–17, he was given a diet consisting of 3 eggs and 180 cc. of olive oil. The case is mentioned to illustrate that with a large caloric intake, even though the amount of carbohydrate is extremely small or temporarily absent from the diet, the nitrogen excretion can be depressed to a very low degree, in this instance to 4.1 grams in the twenty-four hours or 0.08 gram per kilogram body weight. This value, however, is by no means as low as those obtained by Newburgh and Marsh[2] and Petrén[3] with diabetics or Millard Smith[4] with a normal individual. Lauter and Jenke[5] record a nitrogen minimum of 1.2 to 3.4 grams with a moderately severe diabetic and and Hannon and McClellan[6] maintained a diabetic in nitrogen equilibrium on 32 grams of protein per day. Frequently in their cases with high-fat diets for long periods, the daily quantity of urinary nitrogen excreted was under 3 grams.

The low values for urinary nitrogen after June, 1914, were due to other causes. (1) They were associated with obese patients who had been placed upon a very low diet or even fasted, and (2) they were obtained with diabetic patients in a stage of extreme inanition, often combined with a diet actually low in calories or whose net caloric value was low for the patient in question because unassimilated. Thus Case No. 1026, whose weight was 98 kilo-

[1] On July 1, 1927, there remained but 18 cases alive of the original 113 studied. They were Cases Nos. 177, 184, 428, 436, 511, 558, 632, 757, 965, 970, 983, 1007, 1026, 1182, 1207, 1232, 1364 and 1427. I record these case numbers, because they are so frequently mentioned in publications from the Nutrition Laboratory.

[2] Newburgh and Marsh: Arch. Int. Med. 1920, **26**, 647.

[3] Petrén: See foot note therein. A review of a paper by Petrén is given by Allen: Jour. Metabolic Research 1922, **1**, 421.

[4] Smith: Jour. Biol. Chem., 1926, **68**, 15.

[5] Lauter and Jenke: Deut. Arch. f. klin. Med., 1925, **146**, 323.

[6] Hannon and McClellan: Proc. Soc. Exper. Biol. and Med., 1926, **23**, 817.

grams or 59 per cent above normal, voided 0.055 gram nitrogen per kilogram body weight upon April 24–25, 1916, having taken but 6 calories per kilogram body weight per twenty-four hours for the preceding sixteen days. Case No. 983, was another obese woman, weighing 91 kilograms or 44 per cent above normal. Following an average caloric intake per day of 1 calorie per kilogram body weight for five days, she excreted upon a fasting day 0.06 gram nitrogen per kilogram body weight. Case No. 1207, a woman with a body weight of 88 kilograms, or 43 per cent above normal, excreted upon a fasting day 0.05 gram nitrogen per kilogram body weight. These three individuals, excreting a low quantity of nitrogen, may be placed in comparison with Case No. 707, just cited, who also had a low nitrogen excretion. The three fat women protected their body protein by their endogenous fat, while the latter (the thin boy) protected his body protein by the excessive quantity of fat which he ingested.

Examples of a low urinary excretion of nitrogen due to inanition may also be cited. Case No. 1011, on March 26–27, 1916, excreted 0.055 grams of nitrogen per kilogram body weight. At that time her weight was 30 per cent below normal. *In the preceding ten days she had received a total of 750 calories, or approximately 2 calories daily per kilogram body weight.* This in itself would appear to be a sufficient example of the extremes to which treatment by undernutrition was carried in the early days of its use, were not other still more striking evidences at hand based upon analyses of the urinary nitrogen of this patient and of that of Case No. 1085, already described and mentioned later. (See p. 216 and p. 290.)

(*d*) **High Nitrogen Excretion.**—A high excretion of urinary nitrogen may simply reflect the diet as has already been noted in the instance of Case No. 550, or may reflect exactly the opposite condition, namely, the extreme state of inanition reached just before death in which a so-called prelethal rise of nitrogen takes place. This prelethal rise was found with Case No. 1011, the patient just described as having shown an extremely low value for urinary nitrogen in the spring of 1916. She returned for treatment in the fall of 1917. Her diet was low at this time also and her weight had fallen to 26.4 kilograms or 52 per cent below normal in contrast to 38.8 kilograms or 30 per cent below normal in March, 1916. The diet varied from day to day, but for the days immediately in the neighborhood of the date on which the high nitrogen excretion of 0.515 gram per kilogram body weight was observed, it consisted of carbohydrate 10 grams, protein 40 grams, fat 27 grams, and alcohol 23 grams. The high nitrogen excretion on this day was not exceptional for this patient. Thus, upon eleven days in the two weeks before the day cited the average nitrogen excretion

was 0.305 gram per kilogram body weight. Her basal metabolism varied between 878 and 686 calories and the calories in her diet varied between 1213 and 210.

DuBois[1] calculates that 46 per cent of the total heat of this patient "must have been derived from protein, a percentage reached by normal men only after an exceedingly large protein meal * * *. We see that Joslin's patient, No. 1011, November 27 to 28, 1917, on a diet containing carbohydrate, 10 grams; protein, 40 grams; fat, 27 grams; and alcohol, 23 grams, was existing on as high a plane of protein metabolism as Bessie B. or the Sage dwarfs while they were digesting a meal of 660 grams of chopped beef, a meal so large that it required an hour of steady eating." The desirability of comparing the carbohydrate, protein, and fat given with that metabolized as shown by experiments in the calorimeter led me to secure the privilege of inserting Fig. 20 in the present edition of this book. I doubt, however, if such calculations should be considered as entirely reliable. The intermediary metabolism is by no means simple and there may be many types of interchanges between the three food elements.

Criticism may rightly be raised that Case No. 1011 did not exhibit a true prelethal nitrogen, as she did not die until October of the following year, 1918. This is readily explained. The patients who died of inanition, and they were fortunately few in number, by no means proceeded to death in a mathematical fashion, but irregularly. High feeding was interspersed with low feeding. This patient was undoubtedly near her end when this high value was obtained, but she left the hospital, broke her diet, ate liberally, and it would appear thereby prolonged her life for upward of one year, though eventually she succumbed to diabetic coma as a result of excessive food. For the severe diabetic in 1918, it was Scylla or Charybdis, but it is not so today.

Case No. 1085, represents still more clearly a prelethal high nitrogen. This patient on October 18–19, 1916, excreted 0.51 gram of nitrogen per kilogram body weight. A few days later, on November 10, the blood sugar had fallen to less than 0.1 per cent. This was the first case of inanition with low blood sugar which had come to the writer's attention, and the need of carbohydrate feeding was not recognized. The patient, realizing her desperate condition, desired to go home, and left the hospital. Five days later she succumbed to inanition. Attention is directed to the sudden fall in weight of this patient from 34.2 kilograms to 30.4 kilograms in the course of eight days during the period when the high nitrogen value was obtained. This loss in weight was

[1] DuBois: Loc. cit., p. 260.

apparently only in part due to the removal of edema and was accompanied by an extreme loss of strength. The relationship between high excretion of urinary nitrogen, reduction in weight, extremely low metabolism, and high respiratory quotient will be considered in detail later. (See p. 293 and p. 317.)

The relative excess of nitrogen in the urine prior to June, 1914, goes a long way toward explaining the increased metabolism found for the patients in that period and is probably the best confirmatory evidence at hand that these patients were overfed. It is not meant to imply that the increased metabolism was due alone to the excessive amount of protein consumed, but rather that the excessive nitrogen was an index of an excessive protein and, by inference, excessive caloric intake. Following June, 1914, undernutrition was the practice, and these nitrogen values are very likely high in comparison with the intake, because the body tissues of the subjects were more frequently called upon to supply calories, and these were often obtained at the expense of body protein as well as of body fat. The fact that metabolism is lowered on an undernutrition diet served to keep these patients as well as they were. It preserved 69 children to the Banting Era, and of these 52 were alive in July, 1927.

If one examines the values from the point of view of the severity of the disease, it will be found that the mild cases invariably showed a lower nitrogen excretion than the severe cases. The conclusion may be drawn from the values for both periods that the excretion of nitrogen increased with the severity of the disease. It is not yet proved, however, that the severity of the diabetes was due to the high nitrogen excretion in that it represented a high protein intake, but the evidence is strong that the severe cases, both before and after June, 1914, were undergoing an unusually active protein katabolism. Before June, 1914, a high protein intake must be admitted, but after June, 1914, the protein given was not above the normal quantity taken in health and usually it was far less, and yet the cases of greatest severity in this period showed the very high nitrogen excretion to be explained only by the katabolism of body protein. One must admit, as Carrasco Formiguera[1] points out, that under similar dietary circumstances a normal individual might do the same. Manifestly it would be of the greatest importance if it could be proved that patients would be safer if they were fed either 10, 20, or even 30 per cent less than the customary 1 or 1.5 grams of protein per kilogram daily or 10, 20, or 30 per cent more than this amount. This is not readily demonstrated, because such special diets should be continued for years, in fact, essentially during the remainder of the life of the patient.

[1] Carrasco Formiguera: Joslin: Tratamienta de la Diabetes Sacarina Montaner y Simon, Barcelona, 1925, p. 240.

A relation between the nitrogen excretion and acidosis was not found. After June, 1914, the highest nitrogen excretion was found usually when the acidosis was absent and the loss of weight was greatest. Does it not mean that at this low stage of nutrition the diabetic was utilizing the carbohydrate of the protein, and indeed fat as well, which he received or appropriated from his own body? These patients were usually maintained either with little or no glycosuria.

(*e*) **Relation of Excretion of Urinary Nitrogen to Basal Metabolism.** —The relation of the urinary nitrogen to the basal metabolism of the diabetics under observation, both before and after June, 1914, is shown in Table 130. The average nitrogen excretion of 21 diabetics prior to June, 1914, was 0.24 gram per kilogram body weight per twenty-four hours and for 69 diabetics after June, 1914, 0.15 gram per kilogram body weight per twenty-four hours. Oddly enough this latter figure corresponds rather closely with the average excretion of the subject L., during his thirty-one days of fast at the Nutrition Laboratory, which was 0.17 gram per kilogram body weight per twenty-four hours, and with that of a healthy young woman, later described, undergoing the routine treatment of a severe case of diabetes during twenty days, which was 0.14 gram per kilogram body weight per twenty-four hours.

Prior to June, 1914, the nitrogen excretion followed the course of the metabolism, both above and below standard. Thus, when the metabolism was 35 to 30 per cent above the basal standard, the nitrogen excretion was 0.38 gram per kilogram body weight, and when the metabolism was 5 to 10 per cent below standard the nitrogen excretion was 0.095 gram per kilogram body weight. After June, 1914, a radical change is noted in the relation of the basal metabolism and the urinary nitrogen. When the metabolism was within 10 per cent of the normal standard, the nitrogen excretion was constant, but when the metabolism was decreased to 10 to 15 per cent below standard the nitrogen excretion was 0.13 gram per kilogram body weight and thereafter progressively rose as the metabolism decreased until the highest value for the nitrogen excretion, 0.215 gram, was reached with a subnormal metabolism of 35 to 40 per cent.

A rising nitrogen excretion associated at one time with increasing metabolism and at another with decreasing metabolism certainly suggests that the nitrogen metabolism in and of itself does not control the metabolism of the diabetic.

Prior to June, 1914, the high nitrogen excretion would seem to indicate the large quantity of protein food which the patients consumed, this being an index also of the total quantity of food in the diet. After June, 1914, the occurrence of the highest excretion of nitrogen was associated with rare exception with those patients

having the lowest metabolism and must be explained in an entirely different manner. All these patients were free from acidosis, yet their diabetes was of the severest type. The more severe the diabetes, the less the food administered. Accordingly, the tissues of these diabetics must have been taxed severely to provide not only calories but protein. Furthermore, as has been pointed out already, the body fat of these patients was largely exhausted, and so to supply calories it was all the more necessary for body protein to be drawn upon.

TABLE 130.—RELATION OF URINARY NITROGEN TO BASAL METABOLISM OF DIABETICS BEFORE AND AFTER JUNE, 1914.

Percentage variation in metabolism from standard,	Before June, 1914.				After June, 1914.			
	No. of observation days.	Nitrogen excretion per kg. of body weight per 24 hours, gm.	Variation in the body weight from normal standard, per cent.	Average respiratory quotient.	No. of observation days.	Nitrogen excretion per kg. of body weight per 24 hours, gm.	Variation in the body weight from normal standard, per cent.	Average respiratory quotient.
Above standard:								
35–30 . . .	1	0.380	− 5	0.73	1	0.380	−23	0.72
30–25 . . .	3	0.290	−27	0.71	1	0.125	+43	0.73
25–20 . . .	10	0.255	−26	0.73				
20–15 . . .	12	0.250	−18	0.72	2	0.105	+18	0.75
15–10 . . .	11	0.245	−20	0.73	8	0.150	− 9	0.74
10– 5 . . .	13	0.240	−16	0.74	4	0.165	− 2	0.76
5– 0 . . .	12	0.245	−20	0.74	23	0.145	−11	0.77
Below standard:								
0– 5 . . .	4	0.135	−19	0.76	38	0.145	−14	0.75
5–10 . . .	2	0.095	−16	..	27	0.140	−17	0.77
10–15 . . .	..	..	..	..	38	0.130	−14	0.78
15–20 . . .	..	..	..	..	31	0.145	−23	0.77
20–25 . . .	..	..	..	..	29	0.145	−23	0.79
25–30 . . .	..	..	..	..	18	0.185	−31	0.80
30–35 . . .	..	..	..	..	6	0.205	−39	0.82
35–40 . . .	..	..	..	..	2	0.215	−48	0.88
Average . . .	68[1]	**0.240**	**−20**	**0.73**	228[2]	**0.150**	**−18**	**0.77**

Evidence of the extreme degree of inanition which these patients with subnormal metabolism had reached is also supplied by Table 130, for the data show that in the period of undernutrition after

[1] The metabolism was above standard on sixty-two days, below standard on six days.

[2] The metabolism was above standard on thirty-nine days, below standard on one hundred and eighty-nine days.

June, 1914, the body weight was likewise subnormal and followed the course of the decreasing metabolism. Thus, when the average metabolism of 31 patients was 15 to 20 per cent below standard, the average weight was 23 per cent below normal, and when the lowest metabolism was reached, namely, 35 to 40 per cent below standard, the weight was −48 per cent. The high nitrogen excretion of these extremely emaciated diabetics with the lowest metabolism clearly indicates a prelethal rise of urinary nitrogen.

TABLE 131.—UNUSUALLY LOW EXCRETION OF URINARY NITROGEN UPON A HIGH-FAT, LOW-PROTEIN AND LOW-CARBOHYDRATE DIET.

(Case No. 707, male, aged seventeen years; height, 176 cm.).

Date.	Body weight naked, kg.	Urine per 24 hours.						Diet.				Variation of basal metabolism from norma standard, per cent.
		Volume, cc.	Diacetic acid.	NH_3, gm.	Nitrogen.		Sugar, gm.	Carbohydrate, gm.	Protein, gm.	Fat, gm.	Calories.	
					Total.	Per kg. of body weight, gm.						
1914												
May 15–16	51.8	900	++	..	5.9	0.115	18	50	30	185	1985	
16–17	51.7	570	+++	..	4.1	0.080	5	0	20	200	1880	− 8
17–18	51.7	570	+++	2.7	4.8	0.095	Trace	15	20	115	1175	− 4
18–19	51.7	900	+++	3.1	7.5	0.145	7	35	45	145	1625	0
19–20	52.2	900	+++	3.8	7.8	0.150	7	0	0	0	0	+ 1
20–21	51.6	720	++	2.2	6.7	0.130	29	115	40	105	1565	− 3
21–22	52.5	540	..	3.1	5.5	0.105	..	35	20	100	1120	− 6
22–23	52.8	..	..	..	..	..	..	..	..	..	..	−12

The independence of the nitrogen excretion and the metabolism is well shown by 2 cases of extreme inanition, Cases Nos. 1011 and 1085. With Case No. 1011 the nitrogen excretion was almost the lowest in the series, *i. e.*, 0.08 gram per kilogram body weight, with the metabolism 19 per cent below standard, while at another time it was 0.445 gram per kilogram body weight, or nearly at the highest mark, with the metabolism 18 per cent below standard. With Case No. 1085, the nitrogen excretion was 0.51 grams per kilogram body weight, with the metabolism 35 per cent below standard, and later it was 0.19 grams per kilogram body weight, with the metabolism 40 per cent below standard. Furthermore, when the nitrogen excretion was extremely low as a result of the oxidation of large quantities of fat, either exogenous (see Case No. 707 in Table 131) or endogenous, (see Cases Nos. 983, 1026, and 1207) the metabolism with different individuals varied to a great degree and to a considerable degree with the same individual.

Case No. 591, see p. 357, furnishes evidence upon the relative importance of protein and acidosis in raising the metabolism.

The relation of urinary nitrogen, as an index of protein katabolism to the metabolism, has been extensively discussed by Bernstein and Falta.[1] They, as well as Wilder, Boothby, and Beeler,[2] believe the protein katabolism an all controlling factor in regulating the metabolism of the diabetic. The data of the latter admit of various interpretations, and to the writer the evidence does not seem to warrant this assumption.

(*f*) **Dextrose-nitrogen Ratio.**—The relation between the excretion of dextrose and that of nitrogen—the dextrose-nitrogen ratio—was considered of great importance by Lusk.[3] [4] [5] He reached the conclusion, based upon many observations with dogs following injections of phlorizin, upon one case of diabetes coming under his personal observation, and upon others selected from the literature, that in the severest diabetic the dextrose-nitrogen ratio was 3.65 to 1. By this he meant that when the patient was on an exclusively fat-protein diet 3.65 grams of dextrose appear in the urine for 1 gram of nitrogen or the 6.25 grams of protein which it represents. In other words, 60 per cent, actually 3.65 divided by 6.25 equals 58.4, of the protein burned by the body appeared in the urine in the form of sugar. Lusk considered that this was the greatest possible amount of sugar which could appear in the urine on a carbohydrate-free diet, and he assumed that it came wholly from protein. He collected in a table notable illustrations of such ratios. A dextrose-nitrogen ratio in the neighborhood of 3.65 to 1 Lusk showed to be of very serious prognostic import, although not necessarily fatal.

TABLE 132.—D : N RATIOS. (AFTER LUSK.)

Phlorhizin.			Diabetes mellitus in man.			
In dog.	In man.					
Lusk.	Benedict, S. R.	Mandel and Lusk.	Grünwald.	Foster.	Mosenthal.	Joslin
3.65	3.58	3.60	3.75	3.58	3.75	3.69
3.66	3.82	3.65	3.56	3.38	3.85	3.67
3.62	3.66	3.66	3.70	..	3.44	3.67
3.64	3.68	3.64	3.64	3.48	3.66	3.68

Light upon the D : N ratio was also furnished by Janney,[6] who worked out an exact method for the determination of the formation of glucose in the animal body. He showed that various food proteins

[1] Bernstein and Falta: Deutsch. Arch. f. klin. Med., 1916, **121**, 95.
[2] Wilder, Boothby, and Beeler: Loc. cit., p. 230.
[3] Mandel and Lusk: Deutsch. Arch. f. klin. Med., 1904, **81**, 479.
[4] Lusk: Arch. Int. Med., 1909, **3**, 1; also Harvey Lectures, J. B. Lippincott Company, Philadelphia, 1908–1909, Metabolism and Diabetes.
[5] For a full discussion of the subject see Lusk, The Science of Nutrition, Philadelphia, 1917, 3d Edition.
[6] Janney: Am. Jour. Med. Sci., 1917, **153**, 44.

yielded 40 to 80 per cent glucose. One hundred grams of one such proprietary protein really was equivalent to 61 grams glucose. By feeding various forms of animal protein to fasting phlorizinized dogs he demonstrated that 58 per cent of these proteins went over into glucose, the same amount yielded by the body proteins of man. By these direct experiments and other proofs which cannot be entered into here, he concluded that the actual D : N ratio is 3.4 to 1.

Unfortunately one cannot be sure that in the disintegration of the protein molecule the nitrogen and carbohydrate leave the body hand in hand. As a rule, the nitrogen loiters behind, greatly to our annoyance in estimating the source of the sugar in the urine. Mendel and Lewis[1] were able to show that this delay was increased if either indigestible substances or cotton-seed oil formed a prominent part of the diet—just the sort of foods which our diabetic patients eat. Even the amount of water taken can markedly influence the rate of digestion. Consequently in attempting to determine the quantity of carbohydrate derived from protein, this irregularity in the excretion of nitrogen must be considered. Tileston and Comfort[2] were among the first to point out that nitrogen retention occurred in coma and now values above 100 mgs. per 100 cc. are not uncommonly reported. See p. 657. There is good ground, therefore, for the supposition that retention of nitrogen might easily complicate a dextrose-nitrogen ratio. And this is not the whole of the story. The dextrose-nitrogen ratio presupposed that little carbohydrate came from fat. Today the evidence is much stronger that a considerable amount of sugar is thus derived. Meyerhof[3] and Lusk[4] have discussed the opposing sides of this question in detail. I[5] have already referred to it. The dextrose-nitrogen ratio, therefore, appears destined to play less of a role in diabetes in the future. However, it has been of the utmost value in that it showed the possibilities of the formation of sugar from protein. When one adds to these difficulties that of determining what share the quantity of residual carbohydrate in the body bears to the total sugar excreted the complexity of the problem increases. Case No. 1213, with apparently no tolerance for carbohydrate, excreted only 10 per cent of the 60 grams levulose given, and her weight was but 31 kilograms.

In Table 133 are collected a series of dextrose-nitrogen ratios in excess of that of 3.65 to 1. Hitherto a patient who showed dextrose-nitrogen ratio above 3.65 to 1 has frequently stood convicted of larceny if not of perjury. The reputation of these workers will allow no such interpretation. Higher ratios are illustrations of

[1] Mendel and Lewis: Jour. Biol. Chem., 1913–1914, **6**, 19, 37.
[2] Tileston and Comfort: Arch. Int. Med., 1914, **14**, 620.
[3] Meyerhof: Biochem. Ztsch., 1925, **158**, 218.
[4] Lusk: Ibid., 1925, **156**, 334.
[5] Joslin: Loc. cit., p. 104.

irregularities in excretion of the two substances or proof of formation of sugar from fat. That 4 cases should have recovered with such ratios is confirmatory of this conclusion. DuBois emphasizes the fact that although a few of the ratios are over 3.65 to 1 it is surprising that there is not more of a scattering of the figures and they suggest one is approaching a definite end point.

TABLE 133.—DEXTROSE-NITROGEN RATIOS IN EXCESS OF 3.65 TO 1

Author.	D : N ratios upon successive days.							Immediate outcome.
Murlin and Craver[1] .	4.20	4.00	4.00	3.50	3.10	..	..	Recovery.
Geyelin and DuBois[2] .	1.73	3.97	4.01	3.87	2.76	..	..	Recovery.
Christie[3]	3.18	2.40	3.93	2.51	3.27	.	..	Recovery.
Allen and DuBois[4] .	2.28	3.93	3.14	3.10	3.44	..	3.82	Recovery.

If one would determine the dextrose-nitrogen ratio accurately in patients, the following requisites should be fulfilled: (1) An exclusive fat-protein diet or fasting; (2) surroundings which make errors in diet impossible; (3) a period of observation of at least seven days to exclude the washing out of stored carbohydrate; (4) a constant (not falling) D : N ration of 3.65 to 1 for the last three of the seven days.

9. **Heat-production per Kilogram of Body Weight as Index of Caloric Needs of Diabetics.**—The highest basal metabolism per kilogram body weight recorded in this series was 41 calories per kilogram body weight and corresponded to 22 per cent above standard by the Harris and Benedict method, Case No. 295. The lowest value on this basis was obtained with Case No. 1207, and it amounted to 15 calories per kilogram body weight, or for this patient 15 per cent below standard. The highest basal metabolism on the percentage basis of the Harris and Benedict standard was with Case No. 1412, who showed 33 per cent above normal on two days, and the lowest was with Case No. 1085, who showed 40 per cent below standard on two days. The basal metabolism ranged between 15 and 20 calories per twenty-four hours with 18 patients, and the average heat production was 19 calories. The largest group of subjects, 61, gave a range of basal metabolism of 21 to 25 calories and averaged 23 calories per kilogram body weight. A third group nearly as large comprised 45 patients whose basal metabolism ranged between 26 and 30 calories with an average of 28 calories.

[1] Murlin and Craver: Jour. Biol. Chem., 1916, **28**, 301.
[2] Geyelin and DuBois: Jour. Am. Med. Assn., 1916, **66**, 1532.
[3] Christie: Jour. Am. Med. Assn., 1917, **68**, 170.
[4] Allen and DuBois: Arch. Int. Med., 1916, Part II, **17**, 1010.

Another group of 25 patients showed a range in basal metabolism of 31 to 35 calories and averaged 32 calories per kilogram body weight. The metabolism of 5 cases ranged from 36 to 40 calories with an average of 38 calories per kilogram body weight.

Clinically these data are of importance because they show that only one-sixth of a large group of diabetics examined in periods of treatment of both over- and undernutrition required more than 30 calories per kilogram body weight to maintain the basal metabolism. It is equally of clinical importance to observe that in only 1 out of every 12 observations was there a basal metabolism of 20 calories or less per kilogram body weight. Undernutrition is temporarily justifiable if a gain in tolerance for carbohydrate or for a larger amount of food is achieved, but it is almost as bad practice for a physician to keep his patient sugar-free by requiring him to live permanently upon a diet below the caloric needs as it is, through carelessness, to allow the presence of glycosuria and thus bring the net caloric intake below the necessary minimum. The treatment of the diabetic should be planned for a period of years rather than of months.

10. **Fasting and Undernutrition in Health.**—Undernutrition plays such an important part in the treatment of diabetes that its significance, both with a healthy individual and with a diabetic patient, should be kept clearly and constantly in view. As a basis for a true understanding of the effects of undernutrition upon diabetic patients, it is, therefore, desirable to study first the results of observations with individuals during prolonged fasting or undernutrition when living under conditions similar to those of the diabetic patients.

(*a*) **Metabolism of a Healthy Individual During a Prolonged Fast.**—No data are better fitted for studying the metabolism during a long fast than those obtained with the normal subject L., with whom observations were made at the Nutrition Laboratory during a fast of thirty-one days in the year, 1912. These are recorded in Table 158, p. 362.

It is a curious coincidence that the range in metabolism of this individual from 5 per cent above to 14 per cent below standard as determined before the beginning of his fast and again at the end of the fasting period closely approximates that of the diabetic patients, +13 per cent before June, 1914, in the Naunyn period, when they were in a state of overnutrition, and −7 per cent after June, 1914, when in the Allen period they were in a state of undernutrition.

The metabolism of L. at the end of his fasting period had decreased during the thirty-one days of fasting from 1526 to 1118 calories per twenty-four hours, or 27 per cent. The loss in weight of L. during

his period of fast was 13.2 kilograms, or 22 per cent. Comparing this loss in body weight of 22 per cent with the decrease in metabolism of 27 per cent, it is evident that L's. decrease in metabolism proceeded more rapidly than his loss in weight. If one should select two individuals and compute their metabolism for the weights of L. at the beginning and end of the fast, the metabolism of the lighter would be 12 per cent less. Thus, to the fast must be attributed the 15 per cent greater decrease in L's. metabolism. *This illustrates the importance of not only considering the metabolism of a given individual on a given day, but also of considering what the diet has been in the preceding period.* This principle also holds in estimations upon the percentage of sugar in the blood.

If one accepts the current view that 3 per cent of the body weight is due to nitrogen, the body of L., with an initial weight of 60.6 kilograms, would contain 1818 grams of nitrogen. As he lost 277 grams of nitrogen during the fasting period, this loss amounted to 15 per cent of the original amount of nitrogen in the body. This decrease in body nitrogen of 15 per cent was distinctly less than the decrease in the body weight, which was 22 per cent, and considerably less than the decrease in the basal metabolism of 27 per cent. The tissue lost by this subject amounted to 13.2 kilograms, and each kilogram of body tissue thus lost contained 2.1 per cent of nitrogen which is one-third less than the 3 per cent of nitrogen per kilogram body weight which body tissue has been assumed to contain. The body, therefore, conserved its nitrogen. The percentage of nitrogen being katabolized per kilogram body weight at the beginning of the fast was more than that being katabolized at the end of the fast. The point was evidently not reached by this individual when there was insufficient body fat to supply the metabolic needs. In contrast to this normal individual who fasted thirty-one days and maintained a proper proportionate excretion of nitrogen at the end of the period are certain of the diabetic patients whose proportionate nitrogen excretion after prolonged undernutrition was much greater.

1. *Calorie Equivalent of each Kilogram Body Weight Lost.*— The number of calories represented by each kilogram body weight lost by the normal subject L. may be determined since his activities were somewhat definitely estimated, thus giving the material for computing with a fair degree of accuracy his total metabolism for each twenty-four hours. The total metabolism for the thirty-one days, when computed in this way, amounted to 43,010 calories,[1] or 1387 calories per day. This would be equivalent to 3258 calories for each kilogram body weight lost. Knowing the loss in body nitrogen for the period, the total metabolism for the twenty-four

[1] Benedict: Carnegie Inst., Washington, Pub. No 203, 1915, p. 403.

hours can be apportioned to the carbohydrate, protein, and fat oxidized daily by using the proper factors involved in the method.[1]

The computations of the body material lost show that, on the basis of per kilogram body weight lost, the average amount of carbohydrate oxidized during the thirty-one days was 15 grams per kilogram,[2] of protein 125 grams, and of fat 277 grams. The remaining 582 grams of each kilogram body weight lost must therefore, be attributed to a loss of water and, to a slight extent, of salts. *These 3258 calories per kilogram or 1500 per pound* lost by L. during his decrease in body weight probably represent with a fair degree of accuracy the calories which a diabetic subject would also lose with the reduction of each kilogram body weight.

All clinicians are in practical agreement today that overnutrition must be avoided in diabetics. It is seldom that more than 5 or 10 per cent of extra food can be taken by a diabetic patient without injury to his carbohydrate tolerance. This being true, it is evident that the loss of a kilogram body weight, or the equivalent of 3200 calories, by an individual whose ordinary metabolism is 1500 calories, would require twenty-two days for replacement, providing he could take an excess of 10 per cent of calories per day, and forty-four days if he could bear but 5 per cent excess. Is it therefore strange that a loss of a kilogram body weight by a diabetic patient was seldom regained before the introduction of insulin?

Metabolism During Growth.—The metabolism during the process of growth has been studied by Wierzuchowski and Ling[3] in Lusk's laboratory. It was proved that the body had a capacity for using one-half of the carbohydrate for storage as fat and the remainder for basal metabolism. Respiratory quotients rose to 1.40 and on one occasion to 1.58. The production of fat from carbohydrate reached as much as 125 grams per day. The observations were made upon hogs.

(*b*) **Metabolism of a Healthy Young Woman Undergoing the Routine Undernutrition Treatment of a Diabetic.**—Whereas thousands of diabetic patients are placed on a diet, which radically departs from the normal, it is almost unique for a healthy individual to undergo the same regime. On this account it was decided in 1916 to observe the effect upon a normal individual of methods then commonly employed in the treatment of diabetes: namely, fasting, followed by a progressively increasing diet.

[1] In these computations no allowance is made for the loss of nitrogen in feces, as the bowels did not move during the fasting period. It is, of course, incorrect to assume that no feces were formed during these thirty-one days and that no nitrogen was thus lost to the body, for the feces, though subsequently proved to be small in amount, simply accumulated in the intestinal tract, but for these somewhat gross compilations the nitrogen lost in this way may be disregarded.

[2] The oxidation of carbohydrate, however, occurred wholly in the first thirteen days of the fast.

[3] Wierzuchowski and Ling: Jour. Biol. Chem., 1925, **64**, 697.

TABLE 134.—THE METABOLISM OF A HEALTHY YOUNG WOMAN SUBJECTED TO THE TREATMENT OF A DIABETIC PATIENT.

(Age, twenty-five years; height, 170 cm. All experiments were postabsorptive.)

Day.	Weight, kg.	Blood sugar, per cent.	Acidosis.					Urinary nitrogen.		Diet.				Pulse-rate.
			CO_2 in blood, vols., per cent.	CO_2 in alveolar air, mm. Hg.	Diacetic acid.	NH_3. Total gm.	NH_3. Total nitrogen, per cent.	Total gm.	Gm. per kg.	Carbohydrate,[1] gm.	Protein, gm.	Fat, gm.	Calories.	
1	57.2	0.12	60.9	41	0	..	..	4.9	0.085	0	0	0	0	
2	56.8	0.11	..	..	0	..	..	7.7	0.135	0	0	0	0	
3	55.8	0.10	..	41	++	1.2	11	8.8	0.155	0	0	0	0	
4	55.0	0.10	..	36	+++	1.9	17	9.4	0.170	0	0	0	0	62
5	54.0	0.09	36.2	29	+++	2.7	25	8.9	0.165	10	5	0	60	78
6	53.1	0.11	..	31	++	2.8	30	7.7	0.145	20	10	0	120	76
7	..	..	..	32	++	2.5	31	6.5	0.120	30	15	0	180	
8	53.1	0.08	..	34	++	2.5	31	6.9	0.130	40	20	0	240	68
9	53.5	..	..	36	++	2.1	29	6.0	0.110	40	35	20	480	65
10	53.2	0.09	52.2	39	++	2.0 +	25	6.6+	0.120+	50	50	30	670	60
11	53.1	..	..	40	+++	1.7	20	7.2	0.135	55	60	45	865	
12	53.2	0.09	..	43	+++	1.4	18	6.5	0.120	55	75	70	1150	
13	53.8	..	..	41	+	1.4	15	8.0	0.150	55	60	60	1000	63
14	..	..	..	41	+	1.4	12	9.7	0.180	55	75	85	1285	
15	54.0	0.09	59.4	41	Sl. +	1.1	11	7.7	0.145	55	70	105	1445	
16	54.2	..	..	40	0	0.9	9	7.9	0.145	55	75	115	1555	
17	53.6	0.09	..	39	0	..	..	9.2	0.170	55	85	120	1640	57
18	53.5	..	63.8	43	0	..	..	11.2	0.210	60	75	130	1710	
19	53.2	0.11	..	39	0	..	..	7.5	0.140	155	90	145	2285	59
20	53.1	..	..	43	0	..	..	6.2	0.115	200	75	140	2360	61
22	53.6	0.13	..	44	0	..	..	5.3	0.100					

Day.	Metabolism.[2]							Materials katabolized per 24 hours.				
				Heat output per 24 hours.					Carbohydrate and fat.			
									Method I.[3]		Method II.[3]	
	CO_2 per min., cc.	O_2 per min., cc.	Respiratory quotient.	Total calories.	Calories, per kg.	H. and B., per cent.	Non-protein respiratory quotient.	Protein (N × 6.0), gm.	Carbohydrate, gm.	Fat, gm.	Carbohydrate, gm.	Fat, gm.
1	149	180	0.83	1254	22	−10	0.83	29.4	137	83	137	83
2	159	202	0.79	1393	25	0	0.79	46.2	99	110	99	110
3	152	193	0.79	1331	24	− 4	0.78	52.8	81	107	81	107
4	138	179	0.77	1228	22	−11	0.76	56.4	53	105	53	105
5	138	184	0.75	1256	23	− 8	0.74	53.4	35	118	10	129
6	141	180	0.78	1238	23	− 9	0.78	46.2	76	101	20	126
7	..	..	..	..	..	..	..	39.0				
8	141	189	0.75	1290	24	− 5	0.73	41.4	27	131	40	126
9	152	177	0.86	1243	23	− 9	0.87	36.0	176	62	40	123
10	144	185	0.78	1272	24	− 7	0.77	39.6	70	111	50	120
11	132	173	0.76	1184	22	−13	0.75	43.2	44	110	55	105
12	148	179	0.80	1237	23	− 9	0.84	39.0	141	75	55	114
13	142	187	0.76	1280	24	− 6	0.75	48.0	47	118	55	115
14	..	..	..	..	..	..	..	58.2				
15	130	158	0.82	1098	20	−20	0.83	46.2	111	68	55	93
16	142	186	0.76	1273	24	− 7	0.76	47.4	57	113	55	115
17	138	175	0.79	1207	23	−12	0.79	55.2	81	90	55	103
18	140	178	0.79	1228	23	−10	0.78	67.2	70	92	60	98
19	151	199	0.76	1362	26	0	0.75	45.0	51	128	155	84
20	147	175	0.81	1213	23	−11	0.85	37.2	150	69	200	50

[1] The experiments were made for the most part between the hours 9 A.M. and 12 NOON.

[2] An increase of 20 per cent over metabolism for the twenty-four hours is assumed as the effect of food and exercise

[3] In Method II the non-protein respiratory quotient is used as obtained from the morning experiment on the first four days. For the remaining days it is assumed that the carbohydrate burned is represented by the carbohydrates in the food for the day and that the remainder of the estimated heat production was from protein and fat.

[4] Does not represent the complete volume of urine for this day.

Miss L., a healthy nurse, long familiar with diabetic patients, volunteered to undergo such a test. Her age was twenty-five years, body weight without clothing 57.2 kilograms, and height 170 centimeters. The observations were begun June 5, 1916, (first day), and were concluded June 24, 1916 (twentieth day), covering a period of twenty days.

For the first four days of the period of study, Miss L. fasted, save for small quantities of weak bouillon, Thereafter the carbohydrate in the diet was steadily increased from 10 grams on the fifth day to 155 and 200 grams on the nineteenth and twentieth days. The protein, which was 5 grams on the fifth day, amounted to 90 grams on the nineteenth day, and 75 grams on the twentieth day. The fat, which was begun on the ninth day with 20 grams, reached 145 and 140 grams on the nineteenth and twentieth days. The ultimate diet reached represented an intake of 2360 calories, or 44 calories per kilogram body weight.

The body weight of this normal subject while taking the diabetic diet decreased 4.1 kilograms. The body weight was the same on the sixth and twentieth days of the experiment, although on the days between there were fluctuations upward of 0.1 to 1.1 kilograms. For the entire period of twenty days the net deficit in calories computed from the basal metabolism plus 20 per cent for hospital activity after deducting the caloric value of the food taken was 13,000 calories or 3170 calories for each kilogram body weight lost, which corresponds quite closely to the 3258 calories per kilogram of reduction in body weight of the subject L. in his fast of thirty-one days.

The heat output per kilogram body weight was 22 calories at the beginning of the observation and 23 calories on the last day.

The urinary nitrogen for the first day of fasting was 0.085 gram per kilogram body weight, but thereafter steadily rose until at the end of the fourth day of fasting it was 0.17 gram per kilogram. Thereafter it dropped to between 6 and 7 grams daily, an average of 0.125 gram per kilogram body weight, and increased but slightly when additional food was given, an obvious nitrogen retention taking place. Each kilogram body weight lost contained less nitrogen and more water than body tissues.

Upon the nineteenth and twentieth days of the experiment Miss L. was given 2285 and 2360 calories, representing 43 and 44 calories per kilogram body weight. Upon this diet she failed to gain weight, but there was marked retention of nitrogen, the excretion for the two days being but 7.5 and 6.2 grams, respectively. The average metabolism upon these two days was actually less than the average metabolism for the first four days when the patient was fasting. In other words, *fasting does not immediately lower the basal metab-*

olism nor does an excess of food following a period of restricted diet immediately raise it. The organism does not at first decrease metabolism with sufficient rapidity to save body tissue. Conversely, feeding does not immediately raise the metabolism, for the surplus food is utilized to replace body tissue lost.

The postabsorptive blood sugar decreased from 0.12 per cent at the beginning of the experiment to 0.08 per cent on the eighth day. During the preceding seven days the subject had taken a total amount of food containing carbohydrate 60 grams, protein 30 grams, and fat none. Thereafter the blood sugar gradually rose, until upon the second morning after the conclusion of the experiment, when the patient was on full diet, it had reached 0.13 per cent, essentially the same as at the beginning of the experiment. *This is an excellent illustration of hyperglycemia in a normal individual developing upon transfer from a low to a normal carbohydrate diet.*[1]

Evidence of acidosis appeared after two days of fasting. This sufficed to produce a positive reaction for diacetic acid and an ammonia excretion of 1.2 grams, but the carbon dioxide in the alveolar air remained unchanged. All tests appeared or were more marked following the third day of fasting, and if the subject had been a diabetic, she would have been said to exhibit mild acidosis. This became great enough during the fifth to eighth days to be classified as moderately severe. This did not begin to subside until the subject had taken 30 grams of carbohydrate, representing 15 per cent of the calories of the total basal metabolism plus 20 per cent additional for effect of food and exercise. *The acidosis did not entirely disappear until the carbohydrate, with gradually increasing protein and fat, had risen to 55 grams and had been continued for an additional five days.*

The basal metabolism varied between 1393 calories (for the second day) and 1098 calories (for the fifteenth day), or from 26 to 20 calories per kilogram body weight. The striking feature of the metabolism is that upon all but two of the eighteen days on which it was determined, it was subnormal. If the average is taken for the entire period, it was 8 per cent below the normal standard. These observations, therefore, show that a normal individual who lived for twenty days upon a diet similar to the routine diet advised for diabetics had a metabolism which was 8 per cent subnormal. As the diabetics frequently have a smaller diet and for a portion of the period while under treatment in addition lose calories in the form of sugar, it is readily understood why their metabolism should be somewhat more subnormal than that of Miss L.

The respiratory quotient fell steadily from 0.83 to 0.75 during the four days of fasting. It was the same upon the morning of the

[1] Odin Acta Med. Scand., 1927, Supp. 18, p. 388.

eighth day as might be expected, since the carbohydrate in the diet of the preceding day was 30 grams and the protein 15 grams. From this point onward, however, the respiratory quotient was higher. The average respiratory quotient for the ten days during which the subject was taking but 40 to 55 grams of carbohydrate daily was 0.79, which differs but slightly from the average respiratory quotient of 0.81 for 68 female subjects whose postabsorptive metabolism was observed when they were on a full diet.[1]

The materials katabolized were computed from the non-protein respiratory quotient. Obviously it is inaccurate thus to estimate the materials katabolized for the entire day, because the experiments in this case were in the morning and they approximated only two hours in duration. A suggestive picture of the kind of katabolism which was taking place may be gained, however, and although the defects are realized, it is presented.

The loss of carbohydrate for the first four days of fasting was marked, amounting to 370 grams, an amount similar though larger than that usually observed by others in fasting experiments. Even though the actual figures might be somewhat less, if based on longer calorimetric periods, it presents vividly the enormous drain upon the glycogen reserves of the body which fasting entails. The fasting subject, L., at the Nutrition Laboratory lost 154 grams glycogen in the same space of time and other subjects studied in this laboratory have katabolized amounts between 119 and 259 grams. Even in the following two days the katabolism of carbohydrate averaged over 50 grams per day. This quantity of carbohydrate would appear to have come almost exclusively from carbohydrate as such, because the nitrogen excretion remained low. (Looking back upon this experiment after an interval of ten years, one wonders if a certain amount of carbohydrate did not also come from the metabolism of fat. Does not the acidosis suggest this?)

The protein katabolized gradually increased from 29.4 grams on the first day to 56.4 grams on the fourth. This may be compared with L's. values, which were 42.6 and 71.2 grams on the first and fourth days, respectively. His weight on these days averaged but 2 kilograms more than that of our subject.

The quantity of fat metabolized varied between 83.3 grams on the first day and 104.8 grams on the fourth, rising to 109.9 grams on one of the intervening days. These values are but slightly below L's., which were 135, 142, 130 and 136 grams.

11. **The Respiratory Quotient in Health and Diabetes.**—The relation which the volume of carbon dioxide produced by an individual bears to the volume of oxygen required during the same

[1] Benedict and Emmes: Jour. Biol. Chem., 1915, **20**, 253.

interval of time constitutes his respiratory quotient. This has been found to be dependent upon the character of the material in the body which is oxidized or burned at this time. An examination of the composition of the carbohydrate molecule will show that it contains sufficient hydrogen to unite with all the oxygen present during its oxidation. Consequently, for each volume of oxygen used in the oxidation of carbohydrate a volume of carbon dioxide will be produced and the respiratory quotient of such a carbohydrate as glucose ($C_6H_{12}O_6$) will therefore be 1. It matters not whether the oxidation takes place rapidly outside of the body in a flame, or less obtrusively in the body during twenty-four hours. Protein, on the other hand, does not contain sufficient oxygen for the oxidation of the hydrogen atoms contained in its molecule. As a result, in the burning of protein, oxygen must be used not only for the carbon in the molecule, but for the hydrogen as well. The denominator of the fraction is thus increased, and the final quotient of protein must be less than 1 and is 0.81. The protein molecule is made up of many component parts and while the respiratory quotients of these parts vary greatly, yet for protein as a whole the above quotient (0.81) holds. With fat a similar condition exists to that in protein, only there is still more hydrogen present to require oxygen, so that the amount of oxygen necessary for the combustion of fat is still greater, and as a result the respiratory quotient falls to 0.71. The respiratory quotient of alcohol is still lower, and is 0.67. β-oxybutyric acid, which can be taken as the chief one of the group of acid bodies formed in diabetes, has a respiratory quotient of 0.89, diacetic acid of 1 and acetone of 0.75, so that one will not go far astray to take 0.89 as a common respiratory quotient for these three acid bodies.

TABLE 135.—THE RESPIRATORY QUOTIENT (R. Q.) OF A FOOD IS OBTAINED BY DIVIDING THE VOLUME OF CARBON DIOXIDE PRODUCED DURING ITS OXIDATION BY THE VOLUME OF OXYGEN ABSORBED.

Carbohydrate: $C_6H_{12}O_6 + 6O_2 = 6CO_2 + 6H_2O$	R. Q.
Oxygen is required for oxidation of the carbon alone	
Volume $6CO_2$ produced / Volume $6O_2$ absorbed =	1.00
Fat: Oxygen required for carbon and a large quantity of hydrogen	0.71
Protein occupies an intermediate position	0.81
Alcohol (C_2H_6O)	0.67
B-oxybutyric acid ($C_4H_8O_3$)	0.89
Diacetic acid ($C_4H_6O_3$)	1.00
Acetone (C_3H_6O)	0.75

The respiratory quotient of an individual can be determined by measurement of the quantity of carbon dioxide exhaled and the oxygen absorbed. When this is done information is obtained

concerning the character and total amount of the combustion taking place in the body. Since the urinary nitrogen gives us a definite idea of the quantity of protein metabolized, if we calculate what this represents in terms of carbon dioxide and oxygen, and subtract it from the total carbon dioxide exhaled and the total oxygen absorbed we have left the combustion derived simply from fat and carbohydrate. Knowing the respiratory quotient produced when fat and carbohydrate are oxidized as well as that of the individual, it is possible, by computation, to determine the share which these two variables have taken in the total metabolism.

There is always a temptation to calculate the body materials burned when the values for the O_2 intake, CO_2 output, and nitrogen excretion are known. Such calculations are not warranted unless the measurements of the metabolism occur throughout many of the hours of the twenty-four. Even under such circumstances an allowance for the increased metabolism due to muscular exercise is problematical. Krogh[1] has advanced the hypothesis that fat is formed from carbohydrate when the available supply of carbohydrate is in excess of that of fat. This formation is distinct when the respiratory quotient rises above 0.90. When the total quotient has risen above unity, the katabolic quotient has only reached 0.95. This transformation takes place with a loss in energy, and, in consequence, there is a slight rise in metabolism. When fat is in excess of the available carbohydrate, then carbohydrate is formed, and though the total quotient may reach 0.71, the katabolic quotient would be 0.74. This process likewise takes place with a loss of energy and consequent rise in metabolism. Therefore, not alone is carbohydrate needed for the oxidation of fat, but, what has not been previously contended, fat is needed for the oxidation of carbohydrate. Extremes in respiratory quotient are thus theoretically disadvantageous. Already extremes in metabolism have been shown to be disadvantageous clinically, and the next few pages will show also by clinical evidence that this is true of extremes in the respiratory quotient.

The respiratory quotient of normal individuals twelve hours after a meal has been determined by Benedict, Emmes, Roth and Smith, and is summarized in Table 136.[2]

TABLE 136.—RESPIRATORY QUOTIENT AND TOTAL METABOLISM OF NORMAL INDIVIDUALS AT REST AT A PERIOD TWELVE HOURS OR MORE AFTER THE LAST MEAL.

Individuals.	Average respiratory quotient.	Calories per kilo per twenty-four hrs.
89 men	0.83	25.5
68 women	0.81	24.9

[1] Krogh and Lindhard: Biochem. Jour., 1920, **14**, 290.
[2] Benedict, Emmes, Roth and Smith: Jour. Biol. Chem., 1914, **18**, 139.

If the fast is prolonged the respiratory quotient will fall because the individual is forced to draw upon fat and protein for nutritive material, and it will be remembered that these have a respiratory quotient of 0.71 and 0.81 respectively, in comparison with carbohydrate, which is 1. The respiratory quotients of the individual studied at the Nutrition Laboratory[1] who fasted for thirty-one days, are shown in the following Tables 137 and 138.

TABLE 137.—THE RESPIRATORY QUOTIENTS OF A MAN DURING A PROLONGED FAST.

Period.	Time.	Respiratory quotient.	Calories per kg. body weight per 24 hours.
Preliminary period	Days 1–4 before fast	0.85 (av.)	30
Period of fast	Days 1–5 of fast	0.77 (av.)	29
	Days 6–31 of fast	0.72 (av.)	26
After period	Second day after breaking fast	0.78	
	Third day after breaking fast[2]	0.94	

TABLE 138.—QUANTITIES OF PROTEIN, CARBOHYDRATE AND FAT OXIDIZED BY FASTING MAN AT NUTRITION LABORATORY.[3]

Period of fast.	Respiratory quotient.		Quantities oxidized.			Calories per kilo per twenty-four hours.
	Actual.	Non-protein.	Protein, gms.	Carbohydrate, gms.	Fat, gms.	
1st day	0.78	0.76	43	69	135	30
2d day	0.75	0.74	50	42	142	30
3d day	0.74	0.74	68	39	130	29
4th day	0.75	0.71	71	4	136	28
5th day	0.76	0.72	63	15	133	28
6th to 31st day av.	0.72	0.70	53	0[4]	114	26

It will be seen that the respiratory quotient became approximately that of fat within six days and remained there for the balance of the period; that it rose sharply within two days after breaking the fast, and upon the third day reached 0.94, showing that the individual must have taken an extraordinarily large quantity of carbohydrate food.

The respiratory quotient in mild cases of diabetes differs little from that of normal individuals, when the urine is free from sugar and the carbohydrate in the diet large. The respiratory quotient of these same mild cases of diabetes will be lowered by fasting or by the withdrawal of carbohydrate, as shown above in the case of the normal fasting man. Evidence is thus afforded that the limited quantity of carbohydrate in the diet in cases of severe dia-

[1] Benedict: A Study of Prolonged Fasting, Carnegie Inst. of Washington, No. 203.

[2] Twelve hours after food.

[3] Determined from the daily metabolism, the urinary nitrogen and the calculated non-protein respiratory quotient.

[4] Actually a total of 32 gms. carbohydrate were burned during the sixth to thirteenth day inclusive, and later none.

betes is responsible to a large degree for the low respiratory quotient which such patients exhibit. It is not that the patient is unable to burn carbohydrate, but rather that he has little carbohydrate to burn. Magnus-Levy called attention to this, and so have other observers.

The problem of drawing inferences from the respiratory quotient in diabetes is further complicated by the fact that much of the little carbohydrate which is given to a diabetic patient is lost in the urine. The patient really approaches the condition of the fasting man in that he is living largely on fat and protein, although in this case not necessarily that of his own body. If all the carbohydrate ingested is lost in the urine, his respiratory quotient has been computed to be 0.72 upon the assumption that 15 per cent of the metabolism is due to protein and 85 per cent to fat. But there are other complications. Occasionally cases of diabetes are seen where the sugar in the urine exceeds that of the diet, and speculation at once arises as to the source of this excess of sugar. Magnus-Levy has pointed out that if the sugar in the urine amounted to 60 grams and the protein in the diet to 100 grams, the additional quantity of oxygen which would be demanded to form this amount of sugar out of protein would lower the respiratory quotient to 0.7. The situation is still further complicated by the presence of unoxidized acid bodies in the urine, amounting frequently to 20 to 40 grams and occasionally to 60 grams calculated as β-oxybutyric acid. The amount of oxygen consumed in the formation of these bodies, for β-oxybutyric is far richer in oxygen than are protein and fat, would again lower the quotient, and it has been calculated again by Magnus-Levy[1] that the respiratory quotient of a case of diabetes presenting 60 grams of sugar in the urine for 100 grams of protein in the diet, and excreting 20 grams of β-oxybutyric acid, would fall as low as 0.69.

TABLE 139.—THEORETICAL RESPIRATORY QUOTIENTS (FROM MAGNUS-LEVY).

Diet.	Calories.	Respiratory quotient.
Protein, 100 gm. $100 \times 4.1 = 410$ Carb., 567 gm. $567 \times 4.1 = 2325$	2735	0.97
Protein, 100 gm. $100 \times 4.1 = 410$ Fat, 250 gm. $250 \times 9.3 = 2325$	2735	0.72
Loss in urine		
Sugar, 60 gm. $(60 \times 4.1 = 246)$	2489	0.70
Sugar, 60 gm. $60 \times 4.1 = 246$ B-oxy. acid, 20 gm. $20 \times 4.7 = 94$	2395	0.69

[1] Magnus-Levy: Ztschr. f. klin. Med., 1905, **56**, 83.

(*a*) **Low and High Respiratory Quotients.**[1]—The respiratory quotient represents the proportions of fat and carbohydrate burned at any given moment. It cannot be expected to change unless there is a change in this proportion. In general, if carbohydrate is being burned, the quotient will remain high, but if carbohydrate is not being burned, the respiratory quotient will fall.

There are two sources of carbohydrate which the individual can burn, the exogenous and the endogenous, and from each source carbohydrate may be obtained in three forms: (1) From carbohydrate, 100 per cent; (2) from protein, 58 per cent; and (3) to a slight extent from fat, 10 per cent. So far as the quotient is concerned, save in exceptional instances, one deals only with carbohydrate obtained from carbohydrate, as starch and sugar in the diet, or glycogen and sugar stored in the body. If the diet contains no starch and sugar and if there is no storage of glycogen or sugar in the body, then the only methods by which the quotient can continue high or rise are: (1) By the liberation and oxidation of carbohydrate derived from the excessive katabolism of protein and the non-oxidation of the protein residue, or (2) by that which has hitherto been undemonstrated with the severe diabetic, though an everyday occurrence in normals, the transformation of carbohydrate into fat. By the former method it is theoretically immaterial whether the protein so metabolized is supplied from without the body or from the body itself, but so far as is known the oxidation of protein from without the body has never raised the respiratory quotient above the characteristic protein quotient of 0.81. On the other hand, some observations upon our diabetic patients appear to indicate that when an excessive amount of body protein is oxidized, as is evidently the case when the body has reached a stage of extreme inanition with almost complete exhaustion of its stored fat, the quotient will then rise above the respiratory quotient of protein.

Then, too, the possibility exists of the conversion of carbohydrate into fat, for which hypothesis evidence will be submitted in the discussion of high respiratory quotients in diabetes following the administration of levulose.

The factors which influence the respiratory quotient in diabetes are therefore many. Not only are we dealing with the standard quotients for carbohydrate, protein, and fat, of 1, 0.81 and 0.71, respectively, and already mentioned, but with many other quotients. If the glucose derived from protein is not burned, the quotient for

[1] This question is discussed very fully by Du Bois, loc. cit., p. 250, and he gives an additional group of extremely low and high quotients of more recent origin. He points out still more causes for perplexity in the solution of their cause. In my own discussion I have adhered to the classical formulæ of Lusk and Woodyatt, but the reader might compare pp. 103 and 317 for recent views.

protein reverts to 0.632,[1] but if the amino-acid molecules in protein, which are producers of fat, are not burned, a different quotient results. During periods of acidosis ammonia is formed and excreted. The nitrogen thus removed from the body does not require oxygen, and in consequence the quotient tends to rise to 0.88 if all the nitrogen of protein metabolism is eliminated as ammonia.[2] Nor does the metabolism of fat run smoothly with the diabetic. Imperfect oxidation may take place and β-oxybutyric acid, diacetic acid, and acetone be formed which have very different quotients from that of the mother molecule. The formation of these bodies from fat tends to lower the respiratory quotient, their oxidation to raise it. Magnus-Levy[3] calculated that from 100 grams of fat it is possible to form 36.2 grams of β-oxybutyric acid. If this should take place, the respiratory quotient for fat would be 0.669, instead of 0.707. In the light of all these variations taking place in the diabetic organism, one may expect strange quotients, and their explanation at present is fraught with difficulties.

(*b*) **Relationship Between the Respiratory Quotient and the Metabolism of Diabetics.**—The metabolism, not only of diabetics but of normal individuals as well, has been considered quite unrelated to the respiratory quotient, the belief being general that the latter merely registered the quality and not the quantity of material burned. Inasmuch as great variations have been seen to take place in the metabolism of these 113 diabetics, it is especially worth while to investigate this supposed non-relationship between their metabolism and respiratory quotients. The data for such a comparison have therefore been gathered together in Table 140.

TABLE 140.—RELATION BETWEEN RESPIRATORY QUOTIENT AND BASAL METABOLISM IN SEVERE DIABETES.

Before June, 1914.			After June, 1914.		
Respiratory quotient.	Number of observations.	Average variation of metabolism from standard, per cent.	Respiratory quotient.	Number of observations.	Average variation of metabolism from standard, per cent.
0.68	16	+17	0.68	7	− 1
0.72	63	+13	0.73	75	− 7
0.76	11	+12	0.77	51	−14
0.80	1	+10	0.81	47	−19
0.86	3	+12	0.85	18	−23
....	..	....	0.94	1	−37
0.73	**94**	**+14**	**0.77**	**199**	**−13**

It will be seen from Table 140, based upon severe diabetics, that before June, 1914, the average respiratory quotient for 94 observations was 0.73, and after June, 1914, the average respiratory quotient was 0.77 for 199 experiments. The average metabolism in

[1] Lusk: Arch. Int. Med., 1915, **15**, 939.
[2] Grafe: Ztschr. f. physiol. Chem., 1910, **65**, 48
[3] Magnus-Levy: Ergeb. d. inn. Med., 1908, **1**, 384.

these same observations was 14 per cent above standard prior to June, 1914, and 13 per cent below standard after June, 1914. The respiratory quotient in diabetes, therefore, appears to bear a definite relation to the metabolism in that it is low when the metabolism is high and high when the metabolism is low. This is in striking contrast to the universally accepted idea that the respiratory quotient is independent of the metabolism. As Carrasco[1] points out, it would be of much interest to know the respiratory metabolism of patients treated by the Petrén method, but insulin prevents the acquirement of comparable data.

Prior to June, 1914, the lowest average quotient of the series, 0.68, was accompanied by the highest average metabolism of the series, namely, 17 per cent. With the higher respiratory quotients the metabolism fell to as low as 10 per cent, but with the highest average quotient, it increased again to 12 per cent. After June, 1914, the metabolism steadily fell from a variation of 1 per cent to 37 per cent as the average respiratory quotient rose from 0.68 to 0.94.

The inferences to be drawn from this table as to the relationship between the respiratory quotient and the metabolism are of the utmost clinical importance. With the low carbohydrate diet of the diabetic a low respiratory quotient is to be expected, and was found, as evidenced by the average quotient of 0.73 for the cases before June, 1914. The low quotient is in contrast to the average quotient of 0.83 found with 236 of the 239 normal individuals in the Harris and Benedict series.[2] After June, 1914, the average quotient for the diabetics was higher than previous to that date, namely, 0.77, which is still somewhat below the normal. In looking for a cause for the difference in the quotients in these two periods, we have not the usual recourse to variations in the amount of carbohydrates in the diet because in both epochs this was low, certainly averaging less than a fourth of the normal quota, with a difference between the two periods of probably less than 25 grams. Moreover, after a postabsorptive period of fourteen hours, the small amount of carbohydrate taken would have but little influence upon the quotient. Some other cause, therefore, than the usual oxidation of carbohydrate must be found for these varying quotients, and it is not easy to explain them by the normal metabolism of protein and fat.

Associated with this change in respiratory quotient between the two periods is a change in the metabolism of 27 per cent (from +14 to −13 per cent) with the severe cases. A high metabolism with diabetic patients is found to be associated with a low respira-

[1] Carrasco Formiguera: Joslin: Tratamiento de la Diabetes Sacarina, Montaner y Simon, 1925, p. 264.

[2] Harris and Benedict: Carnegie Inst. Washington, Pub. No. 279, 1919, pp. 40 and 44, Tables C and D. The respiratory quotients are not printed in these tables, but have been calculated.

tory quotient. As the respiratory quotient approaches that of normal individuals, the metabolism tends toward the normal level. When the metabolism attains a very low level, the respiratory quotient rises to a level abnormally high for a severe diabetic.

With the cases of severe diabetes we find that both excessively low and excessively high respiratory quotients are usually associated with an abnormal metabolism, so that, although a high respiratory quotient is welcomed in such a disease as diabetes because it suggests the ability of the patient to burn carbohydrate, one must not lose sight of the fact that it is obtained only through a metabolism of threateningly low degree. The causes of the low respiratory quotients and the accompanying high metabolism and the high respiratory quotients and low metabolism must be eradicated for successful treatment of a case. The data here set forth show that an added significance can be attached to the respiratory quotient in diabetes. Our observations are quite in line with the opinions expressed by Krogh.

In the arrangement of the diet for the diabetic, therefore, one must bear in mind that a diet which produces a low quotient in its utilization is a diet which calls for a higher metabolism than a diet which produces a high quotient.

(*c*) **Low Respiratory Quotients in Diabetes.**—The studies of Means,[1] upon fat individuals also show unusually low quotients. His Case No. 1 gave respiratory quotients of 0.69, 0.69, 0.68 and 0.74, respectively, during four days of fasting. Corresponding to this low quotient the metabolism itself was below standard rather than above, amounting to 2 per cent. In a second period of fasting, about ten days later, the respiratory quotients were 0.75, 0.75, 0.72, 0.71 and 0.73, with which rise of quotient the metabolism was −8 per cent, thus corresponding to the general relation between respiratory quotients and metabolism observed with diabetics. Also, during the third period, when the respiratory quotients were practically the same as in the second period, the metabolism was correspondingly low, namely, −10 per cent. His other observations upon the same case are significant in that they confirm the accuracy of the data given, because they show that, as the respiratory quotient rose with this normal obese individual, not only the metabolism fell, but also, incidentally, the acidosis lessened.

Extremely low respiratory quotients have been noted in the past in the literature, but usually have been looked upon with suspicion and often considered the result of poor technic. Such quotients, however, have been obtained far too frequently in health and disease and by too many authors to be disregarded. A study of the

[1] Means: Jour. Med. Research, 1915, **27**, 121.

literature indicates that the diabetic patients who gave these low quotients were living upon a fairly strict non-carbohydrate diet or upon a diet with high protein and fat.

Magnus-Levy[1] reports quotients in a series of studies upon diabetics of 0.654, 0.657 and 0.651. His patient excreted about 100 grams of sugar in the urine daily and the diet contained carbohydrate about 40 grams, protein 100 to 150 grams, and fat 200 to 300 grams.

In Leimdorfer's[2] series following the periods of non-carbohydrate diet the patients were placed upon a diet of vegetables with fat in the form of butter, or bacon and eggs, or egg yolks and some alcohol. Still later he gave three oatmeal days during which the oatmeal amounted to 250 grams, but 250 grams of butter were also given, as well as alcohol. As a result the above patients showed quotients respectively of 0.655, 0.655 and 0.691.

The Russell Sage Laboratory, in all of their publications, report but one low respiratory quotient with a diabetic.[3] With Cyril K., a quotient of 0.687 was obtained, the quotient in one of the periods being 0.656.

In contrast to this one quotient below 0.69 from the Russell Sage Laboratory are 17 such quotients ranging as low as 0.65 which were reported by Wilder, Boothby, and Beeler[4] in the course of 44 experiments with a single case of diabetes. The case was not exceptionally severe. This is shown by the absence of glycosuria for four successive days (May 15–18) with a diet containing approximately 1 gram of protein and 30 calories per kilogram body weight with carbohydrate amounting to 14.7 grams, and again later for seven days (June 4–10) upon a diet of $\frac{2}{3}$ gram of protein and 33 calories per kilogram body weight. None of the low quotients was obtained when the patient had received upon the preceding day over 20 grams of carbohydrate, save with one exception. The protein and fat in the diet shortly preceding the tests were comparatively high. Thus, the fat with these quotients varied between 83 and 151 grams, save on May 30, which was but three days after an eight-day period of the ingestion of 151 grams of fat daily. At no time were quotients below 0.69 obtained when the energy in the diet was less than 30 calories per kilogram body weight upon the preceding day, save in three instances when one or two days of lower diets or fasting intervened between periods of the administration of 51 to 57 calories per kilogram for four to seven successive days.

1. *Extremely Low Respiratory Quotients at the Nutrition Laboratory.*—Among the 113 patients studied at the Nutrition Laboratory

[1] Magnus-Levy: Ztschr. f. klin. Med., 1905, **56**, 83.
[2] Leimdorfer: Biochem. Ztschr., 1912, **40**, 326.
[3] Gephart, Aub, DuBois and Lusk: Arch. Int. Med., 1917, **19**, 908.
[4] Wilder, Boothby and Beeler: Jour. Biol. Chem., 1922, **51**, 311.

between 1908 and 1917, respiratory quotients of 0.69 or below were observed on 21 occasions with 9 patients in the postabsorptive state. The data for these observations are given in Table 141. Fifteen of these occurred in the Naunyn period before June, 1914, and six before May, 1915, in the early days of the Allen period, thus showing their relation to the period of overfeeding. Save for the 6 exceptions above noted, such low quotients were absent with the 80 patients studied since June, 1914, when they were in the postabsorptive condition. The hall-marks of overnutrition in the early period are apparent with these patients, and the overfeeding was chiefly in the form of fat.

It was not uncommon for patients to receive 200 or more grams of fat upon the day preceding the metabolism test. Case No. 786 was given alcohol freely upon admission to the hospital, but otherwise was upon a low diet for the intervening time. This was the patient with whom Bloor found 13.1 per cent total lipids in the blood plasma some months later, on June 15, 1916.

TABLE 141.—LOW RESPIRATORY QUOTIENTS (0.69 AND BELOW) IN POSTABSORPTIVE EXPERIMENTS WITH DIABETICS.

Case No.	Date.	Respiratory quotient	Variation from standard metabolism per cent.	Variation of body weight from standard, per cent.	Severity.	Acidosis	Urinary nitrogen per kilogram of body weight, gm	Urinary sugar on preceding day, gm.
220	Mar. 13–14, 1909	0.69	+32	−25	S	+++		
246	June 8– 9, 1909	0.67	+28	+ 1	S	++	0.211	104
	" 15–16, 1909	0.67	+22	+ 1	..	++	0.348	122
	" 25–26, 1909	0.69	+14	+ 1	..	++	0.357	123
	Oct. 25–26, 1909	0.69	+17	−10	..	+++	0.391	89
	" 28–29, 1909	0.66	+15	− 8	..	+++	0.349	134
	" 29–30, 1909	0.68	+ 8	− 8	..	+++	0.345	107
	" 31–Nov. 1, 1909	0.69	+ 7	− 8	..	+++	0.291	93
441	Oct. 9–10, 1911	0.68	+ 6	−31	S	+++	0.277	54
549	Nov. 5– 6, 1912	0.69	+30	−14	S	+++	0.312	185
	" 12–13, 1912	0.69	+16	−17	..	+++	0.155	92
591	Apr. 14–15, 1913	0.65	+15	−21	S	+++	0.144	77
	" 15–16, 1913	0.69	+10	−20	..	+++	0.140	48
740	Apr. 15–16, 1915	0.69	+ 1	−13	S	+++	0.276	
773	Oct. 10–11, 1914	0.69	+64[1]	−22	S	+++	0.216	52
786	Nov. 9–10, 1914	0.66	− 1	−25	Mo.	+	−	0
	" 12–13, 1914	0.68	−10	−25	..	+	0.144	0
806	Dec. 22–23, 1914	0.68	− 1	−14	S	++	0.135	0

Respiratory quotients of 0.69, or below, were obtained also in 24 instances after the ingestion of food. These occurred almost exclusively before January, 1915. The acidosis at the time was severe or moderate with one exception. All cases were severe in type. Like the low quotients secured by other observers, ours were

[1] Case No. 773 was a girl diabetic. Variation in metabolism on this day was +64 per cent by the Girl Scout Standard.

almost without exception found with patients who had ingested many calories, much fat, and occasionally alcohol.

With 1 patient, Case No. 707,[1] so many low quotients were obtained that they were originally rejected, but upon reëxamination of the protocols it appeared that the cause for rejection was inadequate and that the quotients of 0.65 which were obtained were well substantiated. These occurred after large meals of oatmeal and fat in an exceptionally severe diabetic. Moreover, with this patient there is no evidence that he was asleep, a factor which must be considered in the interpretation of low quotients, because Carpenter[2] has shown that there is a lowering of the quotient in sleep amounting to from 0.05 to 0.07.

Low quotients, and to a certain extent it can be said of dextrose-nitrogen ratios of 3.65:1, are *forced quotients* and *forced ratios*. They are not inherent in the ordinary metabolism of diabetes. The undisturbed diabetic has no such quotients. They are analogous to the condition produced by an overdose of digitalis in an individual with a moderately decompensated heart. When administered in moderate doses, digitalis, like fat and protein, does good, but in excessive doses auricular fibrillation results on the one hand, low quotients and dextrose-nitrogen ratios of 3.65:1 on the other, and the patients are brought to the verge of death. Low respiratory quotients and dextrose-nitrogen ratios of 3.65:1 are evidence of poor medical treatment. In the past these were frequently obtained through ignorance, but their occurrence today demands explanation.

(*d*) **High Respiratory Quotients in Diabetes.**—High respiratory quotients, when obtained with mild or moderately severe cases of diabetes, are readily explained by the combustion of carbohydrate in the diet or by the combustion of carbohydrate previously stored in the body. On the other hand, the explanation of high respiratory quotients found in observations with cases of severe diabetes is by no means simple, since carbohydrate as such is not available for combustion, either from the diet or from the body. Some evidence exists to show that the high respiratory quotients appear when the body is compelled to draw upon protein owing to a lack of available fat. There is also some evidence, which will be presented in the discussion of the experiments following the ingestion of levulose, that there is a transformation of carbohydrate into fat which would also sufficiently explain this unlooked for phenomenon. (See Tables 142 and 153.) Examination of the case histories of the severe type of patients whose experiments gave these high quotients shows that they were most often obtained when the individuals were *in extremis* and without acidosis. This precludes the explanation of

[1] Case No. 707 is described in detail in the Carnegie Pub. No. 323, p. 176.

[2] Carpenter: Am. Jour. Physiol., 1922, **59**, 440; Proc. Am. Physiol. Soc., 440.

TABLE 142.—HIGH RESPIRATORY QUOTIENTS OBSERVED IN POSTABSORPTIVE EXPERIMENTS WITH SEVERE DIABETICS.

Case No.	Date.	Respiratory quotient.	Variation of metabolism from standard, per cent.	Acidosis	Body weight naked, kg.	Variation in body weight from normal standard, per cent.	Urinary nitrogen per kg. of body weight per 24 hours.	Calories per kg. of body weight per 24 hrs. in diet for 7 to 10 days preceding observation day.	Carbohydrate balance of preceding day, gm.	Date of death
226	Dec. 6- 7, 1913	0.86	+ 8	++	64.4	−13	0.175	0	− 5	Nov. 26, 1915.
289	Sept. 30–Oct. 1, 1909	0.88	+12	++	52.3	−15	..	..	−40	Sept. 17, 1912.
	Oct. 4- 5, 1909	0.85	+16	+	52.3	−15	..	40	−40	
610	Mar. 22–23, 1917	0.84	− 7	0	51.2	−24[1]	0.195	11	+ 5	April, 1918.
	Apr. 18–19, 1917	0.85	− 2	0	52.6	−22				
786	Jan. 19–20, 1916	0.84	−23	0	48.6	−33	0.350	19	+ 5	Mar. 31, 1917.
	June 28–29, 1916	0.84	−24	++	51.0	−30	0.160	3	+60	
1011	Oct. 8- 9, 1917	0.85	−26	++	28.6	−48	0.245	27	+20	Oct. 1, 1918.
	16–17, 1917	0.84	−31	++	28 0	−49	0.265	28	+10	
	24–25, 1917	0.84	−30	++	27.3	−50	0.230	36	+30	
	Nov. 23–24, 1917	0.94	−37	0	27.6	−49	0.285	31	+40	
1069	Nov. 25–26, 1914	0.85	−11	+	33.7	−39	0.190	..	+15	Jan., 1916.
1070	Mar. 17–18, 1917	0.84	−23	+	50.9	−11	..	14	+30	Oct. 11, 1917.
1233	Feb. 19–20, 1917	0.86	−33	0	48.3	−22	0.280	17	0	June, 1918.
	26–27, 1917	0.87	−28	0	48.3	−22	0.220	22	+10	
	Mar. 5- 6, 1917	0.85	−29	0	51.3	−18	0.185	27	+30	
	12–13, 1917	0.84	−24	0	50.1	−20	0.245	27	0	
	19–20, 1917	0.86	−24	0	50.1	−20	0.225	26	+45	
	26–27, 1917	0.87	−27	0	47 2	−24	0.160	29	+35	
1259	Mar. 31–Apr. 1, 1917	0.86	−22	0	49.4	−33	0.185	20	+30	Nov. 19, 1917.
1378	Nov.. 9–10, 1917	0.90	−21	0	30.6	−45	..	22	+ 5	April, 1920.
	13–14, 1917	0.88	−29	0	30.6	−45				
1012[2]	Oct. 23–24, 1917	0.85	..	++	27.0	−36	0.165	19	0	Jan. 22, 1919.
	Dec. 1- 2, 1917	0.84	..	0	25.7	−39	..	26	+ 5	
1213[3]	Feb. 7- 8, 1917	0.85	..	0	31.2	−45	0.250	22	0	Feb., 1920.
	Mar. 1- 2, 1917	0.91	..	0	32.2	−44	0.240	29	+55	
	14–15, 1917	0.84	..	0	32.7	−43	0.230	29	+10	
	Apr. 4- 5, 1917	0.91	..	0	32.5	−43	..	28	+20	

[1] Two observations averaged 57 per cent below maximum weight, yet only 24 per cent below standard weight.

[2] Metabolism of Case No. 1012, when compared with metabolism of a series of Girl Scouts studied at the Nutrition Laboratory shows an almost steady fall from +22 per cent on October 23–24 to +15 per cent on December 1–2.

[3] Metabolism of Case No. 1213 varied on the same basis from 0 on February 7–8 to −8 per cent on March 1–2, rising to +12 per cent on March 14–15, with remaining values between these extremes.

the high respiratory quotients on the theory of oxidation of acid bodies which have high quotients, because, though this explanation would hold for a few days after the patient was apparently free from acidosis, it would hardly explain the phenomenon for long periods when no evidence of acidosis exists.

Respiratory quotients of 0.84 or over may be considered as unusual with severe cases of diabetes in the postabsorptive state. The average respiratory quotient for the 94 observations before June, 1914, was 0.73, and the average respiratory quotient for the 199 observations after June, 1914, was 0.77. (See Table 140). These same averages were found likewise for cases of all degrees of severity in 122 observations before, and in 292 observations after, June, 1914. Among these observations there were 35 tests with severe cases in which the respiratory quotient was 0.84 or over.

There was but 1 patient among the severe cases (Case No. 1011) with a respiratory quotient as high as 0.94. The metabolism at the time of this observation was −37 per cent, and a study of the protocols proves that this value was well supported by other data obtained with this young girl. She was, at that period, in a state of extreme inanition, with a body weight 49 per cent below normal, and was, moreover, free from acidosis. A feature possibly contributing to the explanation of this high quotient and low metabolism was her high nitrogen excretion at this time, which on the day preceding the observation amounted to 0.285 gram of urinary nitrogen per kilogram body weight. Three and four days after the experiment the excretion per kilogram body weight was 0.41 and 0.515 gram, respectively, with the protein in the diet during the six days between November 22 and 27, varying from 0 to 51 grams per day, or on the average 1.1 grams per kilogram of body weight.

The average respiratory quotient for all of these specially selected severe cases, including the girl diabetics, was 0.86. How unusual these quotients are is shown by noting the dates of the observations, there being but 3 of these quotients which were obtained before June, 1914. In fact they represented but a little over 10 per cent of the respiratory quotients obtained with the 67 severe cases for whom postabsorptive quotients were secured.

The high quotients in the 3 tests before June, 1914, were accompanied by a metabolism above standard, but those obtained after June, 1914, were accompanied in most instances by an extremely low metabolism, the average being −24 per cent.

A marked loss of weight also characterized the cases represented in this group of high quotients. Whereas the average greatest loss of weight from maximum during the experimental period for all of the diabetics was 25 per cent, the average loss of weight from

maximum of the severe cases in Table 142 was 33 per cent for the adult group and 28 per cent for the girl diabetics. That this loss of weight actually represented emaciation is better evidenced by their subnormal weights The adults with high quotients in Table 142 were 29 per cent below standard and the girl diabetics 41 per cent below standards.

In this connection one might also refer to Table 130 in which it is shown that after June, 1914, progressive lowering of the body weight was accompanied by a progressive lowering of metabolism and a progressive rise of the respiratory quotient and excretion of urinary nitrogen. This was especially notable in the severe cases of this series (Table 142) of experiments with high quotients, as the nitrogen in the urine was notably in excess, especially for the severe cases.

Acidosis was usually absent. In 8 of the observations with the severe cases it was present in moderate degree, and in 4 to a slight degree.

The energy in the diet preceding the observations was low in contrast to the high diets which preceded the very low quotients. With only 3 of the 18 observations with adult severe cases, for which the data regarding the preceding diet are available, did the energy exceed 30 calories per kilogram body weight during a period of several days before the experimental day. The loss of weight and the condition of these cases, however, is not so much to be attributed to the diet at this particular period as to the prolonged low diets or unselected diets during earlier stages of the disease.

The carbohydrate balances for the preceding day were positive, as a rule, but with the adult severe cases and the girl diabetics no instance occurred in which the positive balance exceeded 60 grams, and it was usually but half this amount. These meager balances rule out the possibility of explaining the high quotients by the carbohydrate intake.

Regrettably few observations were made of the non-protein nitrogen in the blood, and they are omitted from Table 142, but the few values obtained indicate an excess. As there was no reason for nitrogen retention, evidence favors the theory that excessive protein katabolism was going on and that the nitrogenous portion of the molecule was being retained instead of excreted. It is, however, inconceivable that these high quotients should continue for long if due to protein katabolism, because this would result in an excessive retention of non-protein nitrogen and would terminate in early death from toxemia. If death did not occur, it would mean that the respiratory quotient had fallen and the patient was taking a diet with fat which in such severe diabetes would eventually end in death from coma. Clinically, the above

reasoning is borne out by the subsequent histories of these patients. Therefore, it should not be considered that a low quotient alone is of grave significance in diabetes, for an extremely high quotient may be equally hazardous for the patient. When these experiments were performed, I could hardly bring myself to conceive that the extremely emaciated severe diabetic might have acquired the power to make a considerable quantity of carbohydrate as well as ketone bodies out of fat and then oxidize both.

The values obtained for the blood fat, although meagre in number, show that an excessive quantity was present in the circulating blood. The meaning of this is not clear. It is true that unusual quantities of fat have been reported in the blood of fasting individuals, and perhaps these large amounts signify no more than this. On the other hand, the body fat is constantly being drawn upon for body needs. Bloor[1] writes:

"In fasting it (the lipoid level) may or may not be disturbed, depending apparently on the nutritional condition of the subject, or rather perhaps on the availability of the stored fat, since it is apparently the case that fat may be more or less loosely stored, with the result that the stimulus of hunger may produce an excessive or merely adequate outflow, depending on the nature of the storage. It is significant that the increase in blood lipoids in fasting takes place only in the first days, and after that the lipoid content remains constant or slowly diminishes till the death of the animal."

Under such circumstances the passage of fat from the tissues into the blood is constantly taking place and not intermittently as after a meal, yet such high values for blood fat as those here recorded are seldom found. This explanation is, therefore, hardly satisfactory. Neither is the evidence satisfactory that the sugar in the blood of these patients is being transformed into fat. The data, however, so far as they go, supply some support to this latter idea, for while the blood fat is high, the blood sugar for this type of case is comparatively low. There is just enough hint of these two possibilities, the oxidation of the carbohydrate portion of the protein molecule with the retention of the nitrogenous portion and the conversion of carbohydrate into fat, to warrant seriously pursuing the study of other cases along these lines.

A mild case of diabetes may have a high respiratory quotient without any loss of body weight. A severe case of diabetes can have a high respiratory quotient only when the loss of weight is marked, but an extremely severe case of diabetes presents a high respiratory quotient only when the loss of weight is extraordinary.

A high postabsorptive respiratory quotient in an extremely

[1] Bloor: Physiol. Reviews, 1922, **2**, 92.

severe case of diabetes is only attained when the caloric intake is extremely low.

(*e*) **The Respiratory Quotient in Relation to the Different Types of Severity.**—In the earlier period the diabetics of mild and moderate severity had an average respiratory quotient of 0.76, while those of the severe type had the lower average quotient of 0.73. On the other hand, with the diabetics after June, 1914, in the three groups of mild, moderate, and severe, the average quotient was the same for all degrees of severity; *i. e.*, 0.78. These figures are significant, because they show the profound difference in the condition of the patients before and after June, 1914. While all three types of severity were observed in both epochs, yet after June, 1914, something took place which prevented the patients of a severe type from having a lower quotient than those of the milder types.

An explanation of the difference in the average respiratory quotient of 0.73 for all cases before, and 0.78 for all cases after June, 1914, may be the character of the diet, or perhaps we may better say the character of the diet and its utilization. Prior to June, 1914, it is possible that less carbohydrate was given, but at any rate less carbohydrate was utilized than after June, 1914. Conversely, prior to June, 1914, a much greater quantity of fat was given which, like the carbohydrate, was not well utilized, a considerable proportion being excreted as β-oxybutyric acid. With Case No. 344, 25 to 50 grams or more of β-oxybutyric acid were excreted almost daily for weeks.[1] The formation of this acid, therefore, would tend to lower the quotient more than even the fat alone. After June, 1914, the smaller quantity of fat consumed, the lesser quantity of β-oxybutyric acid formed, and the greater quantity of carbohydrate oxidized, would all tend to raise the quotient. The data collected, therefore, may be interpreted as showing that it was not so much the severity of the case which influenced the quotient as the relative quantities of carbohydrate and fat ingested and also oxidized by the patients irrespective of severity. See Table 80 Carnegie Monograph 323, p. 188.

(*f*) **The Respiratory Quotient in Relation to the Degree of Acidosis.**—It has been shown in the previous discussion that the principle appears to hold in diabetes that the lower the respiratory quotient falls the higher the metabolism will rise and *vice versa*. Support of this principle should be afforded by a study of the relation of acidosis to the respiratory quotient, because acidosis indicates primarily an abnormal fat metabolism, and this is of such a nature that it tends to lower the quotient.

[1] Benedict and Joslin: Carnegie Inst. Washington, Pub. No. 176, 1912, Table 65, p. 57 *et seq.*

The relationship between the respiratory quotient and acidosis is very plainly shown. With patients free from acidosis (0), there were no records of respiratory quotients below 0.70, and patients with severe acidosis (+++) supply none of the respiratory quotients above 0.83 and but one above 0.79.

Increasing acidosis was always accompanied by a falling respiratory quotient. It is also significant that 49 observations upon patients with severe acidosis before June, 1914, gave a respiratory quotient of 0.72, and that this is exactly the average quotient of the 17 observations upon patients after June, 1914, with similar acidosis. The definite relation between acidosis and respiratory quotient is thus very clearly demonstrated and incidentally the dependence of acidosis upon the fat metabolism.

TABLE 143.—RELATIONSHIPS BETWEEN RESPIRATORY QUOTIENT, METABOLISM AND ACIDOSIS IN POSTABSORPTIVE EXPERIMENTS WITH DIABETICS BEFORE AND AFTER JUNE, 1914.

Range in respiratory quotient.	Before June, 1914. No. of experiments with acidosis.				After June, 1914. No. of experiments with acidosis.			
	0	+	++	+++	0	+	++	+++
All cases:								
0.64–0.69	..	..	6	10	..	2	5	5
0.70–0.75	8	9	31	34	10	25	57	11
0.76–0.79	9	2	6	5	25	21	36	2
0.80–0.83	2	..	2	..	36	20	14	1
0.84–0.90	..	1	2	..	27	6	6	
0.91–0.94	..	..	..	..	7			
Average respiratory quotient:								
All cases	0.76	0.75	0.73	0.72	0.81	0.77	0.76	0.72
Percentage variation in metabolism of severe cases[1]	+9	+12	+15	+12	−19	−14	−11	+2

Shaffer[2] has clarified the whole subject of acidosis both in normals and diabetics. He has calculated the respiratory quotients for total glucose and fatty acid by subtracting from the total CO_2 and O_2 the amounts corresponding to the metabolism of the non-carbohydrate quota of protein during the respiration period. He has constructed a table which exhibits these fatty acid: glucose respiratory quotients. Along with these he gives the percentage of calories from glucose and fatty acid and the molecular ratio of the mixture burned. According to his calculations: "*A total respiratory*

[1] Group confined to cases compared with H. and B. standard.
[2] Shaffer: Jour. Biol. Chem., 1921, **49**, 143.

quotient of 0.76 indicates the oxidation of a metabolic mixture made up of approximately equimolecular amounts of ketogenic substances (fatty acids or ketogenic amino-acids), and of antiketogenic derivatives of amino-acids, glycerol, or carbohydrate, expressed in terms of glucose. Expressed in the same terms, a respiratory quotient of 0.73 indicates approximately 2 molecules of ketogenic to 1 of antiketogenic substance in the mixture; while a quotient of 0.8 indicates only 0.5 molecule of ketogenic to 1 of antiketogenic glucose equivalent.

"With these values in mind we may inspect any respiratory data and provided we assume that the latter are truly representative of metabolic reactions, the ketogenic ratio of the subject may be determined. . . .

"After an examination of many experiments by others as well as by ourselves there appears to be no doubt that the mixture in all subjects, *at the threshold of ketonuria* is, according to respiratory data, that which corresponds to *equimolecular* mixtures of ketogenic and antiketogenic substances, *the latter being calculated in terms of glucose equivalents.*"

Shaffer has analyzed the data accumulated for Case No. 740 of our series and has published it as an example of acidosis disappearing during fasting, and has added to our data the calculations of the ketogenic ratio. These are shown in Table 144.

TABLE 144.—SEVERE DIABETIC WITH DECREASING ACIDOSIS ON FASTING (CASE 740).

Date.	Total R. Q.	Ketogenic ratio.	Total hydroxybutyric acid excreted, gm.	Harris and Benedict.[1]	Nitrogen.
April 15–16	0.72	3.2	24.9	− 3	16.5
16–17	0.73	2.1	18.9	− 1	16.2
17–18	0.72	3.2	11.8	− 4	9.6
18–19	0.74	1.9	11.0	− 8	8.1
19–20	0.76	1.0	7.9	−10	6.7
21–22	0.75	1.2	6.5	−14	7.9
24–25	0.74	1.9	5.4	−16	9.1
27–28	0.75	1.4	4.7	−13	7.4
May 1	0.76	1.0	4.1	−19	7.6

The acidosis decreased but did not entirely disappear with the rising quotient, since when a respiratory quotient of 0.76 was reached the total β-oxybutyric acid excreted still amounted to 4.1 grams. Shaffer explains this with the assumption that the actual metabolic quotient of the subject was really below 0.76. This is possible, but perhaps it may be explained by the fact that the 4.1 grams hydroxybutyric acid represented acid for the twenty-four hours immediately preceding the experiment. At the actual moment of the experiment the acidosis might have been absent or nearly so. Shaffer continues:

[1] Added to Shaffer's table by E. P. J.

"It is evident from an analysis of Joslin's data (not included in our table) that the gradual rise of the respiratory quotient, the lowering of the ketogenic ratio which that rise indicates, and the decline of the acidosis, were not caused by any increase in sugar burning power but were caused by the decrease in total metabolism resulting from the fast, and in the amount of ketogenic material (fat and protein) in the metabolic mixture. The metabolism of ketogenic substances was merely slowed down by undernutrition to the point where it no longer markedly overbalanced the already low rate at which the body was able to provide antiketogenic substance for 'neutralization.' This appears to the writer to be the probable explanation of the beneficial effect of fasting and undernutrition in causing a decrease of diabetic acidosis."

The variations in metabolism and the nitrogen values of the day of the observation are added to this table as abstracted by Shaffer. The fall in metabolism with fasting is well shown. It would be easy to ascribe it to the nitrogen alone.

(*g*) **The Respiratory Quotient in Relation to Pulse-rate of Diabetics.**—Like the metabolism, the pulse-rate in diabetes varies with the respiratory quotient. This is evident for the entire period of the research. As the respiratory quotients rise, the pulse-rates successively decrease. With quotients of 0.91 and over, the lowest average pulse-rate (60) was encountered. When the pulse-rate averaged 70, the range in respiratory quotient was 0.64 to 0.69.

(*h*) **The Respiratory Quotient in Relation to the Glycosuria of the Preceding Twenty-four Hours.**—When the sugar in the urine amounted to 26 grams or more in the twenty-four hours, the respiratory quotient was approximately 0.73; when the urine was sugar-free, or nearly sugar-free, the average respiratory quotient was 0.76 to 0.79; but with quantities of urinary sugar of 200 grams or more, the respiratory quotient was sometimes 0.75 or above, indicating that a great excess of carbohydrate in the diet was accompanied by the oxidation of at least a portion of it.

(*i*) **The Respiratory Quotient in Relation to Blood Sugar and Blood Fat.**—It would be easy to give undue importance to the relation brought out between blood sugar and the respiratory quotient. The blood sugar is an index of the severity of the disease, and with increasing severity there is usually an increase in the percentage of sugar. On the other hand, after prolonged inanition there may be a terminal stage in which the blood sugar falls.

With the severe diabetics when the respiratory quotient was low (0.69 to 0.73), the blood sugar averaged 0.27 per cent. When the respiratory quotient was high (0.80 to 0.83) the percentage of blood sugar had fallen to 0.22. When it was still higher, *i. e.*, between 0.84 and 0.94, the average percentage of blood sugar was

even lower, or 0.2. Although certain exceptions to this general relationship can be found in each group, the study of the blood sugar in severe cases of diabetes confirms the conclusions regarding all cases of diabetes in showing that a low respiratory quotient is accompanied by a high percentage of blood sugar, and a high respiratory quotient by a significantly lower, though not normal, percentage of blood sugar.

TABLE 145.—RELATION OF AMOUNT OF SUGAR IN URINE TO RESPIRATORY QUOTIENT OF DIABETICS IN POSTABSORPTIVE EXPERIMENTS.

Sugar in urine of preceding 24 hours, gm.	Before June, 1914.		After June, 1914.		Before and after June, 1914.	
	No. of experimental days.	Average respiratory quotient.	No. of experimental days.	Average respiratory quotient.	No. of experimental days.	Average respiratory quotient.
0 . .	5	0.76	161	0.79	166	0.79
1– 5 . .	4	0.77	30	0.78	34	0.78
6– 25 . .	9	0.74	40	0.76	49	0.75
26– 50 . .	11	0.73	11	0.76	22	0.74
51–100 . .	33	0.73	18	0.76	51	0.74
101–452 . .	38[1]	0.73[1]	5[2]	0.75[2]	43	0.73

These data give no encouragement to the practice sometimes followed of administering carbohydrates to diabetics when the blood sugar is high.

When carbohydrate is burned in the body, the respiratory quotient approaches 1, but when fat is consumed it falls toward 0.71. If the abnormal accumulation of carbohydrate and fat in the blood signifies they are not being properly oxidized, then with a high-blood sugar one would expect a low quotient and with a high-fat content a high quotient and these relations indeed were found.

TABLE 146.—RELATION BETWEEN RESPIRATORY QUOTIENT IN POSTABSORPTIVE EXPERIMENTS AND PERCENTAGE OF SUGAR IN THE BLOOD OF DIABETICS.

Range in respiratory quotient.	Number of experiments with percentage of sugar in the blood ranging from:					Total number of experiments.
	0.05–0.11	0.12–0.20	0.21–0.30	0.31–0.40	0.41–0.43	
0.64–0.69 . .	0	2	1	0	0	3
0.70–0.75 . .	2	23	33	17	2	77
0.76–0.79 . .	2	31	31	3	0	67
0.80–0.83 . .	2	24	19	4	0	49
0.84–0.90 . .	2	13	14	2	0	31
0.91–1.00 . .	0	3	3	0	0	6
All experiments .	8	96	101	26	2	233
Average respiratory quotient .	0.80	0.79	0.78	0.76	0.71	

[1] Range of sugar values in this group before June, 1914, was 102 to 452 grams.
[2] Range of sugar values in this group after June, 1914, was 102 to 170 grams.

When the blood fat was essentially normal (between 0.59 and 0.75 per cent) the average respiratory quotient was 0.77, but when the blood fat was above normal and between 1.26 and 2 per cent in 10 analyses, the average respiratory quotients were 0.88, 0.85 and 0.85. An exception to the general trend is the average quotient for 6 analyses when the fat in the blood was 2.01 per cent or over, for here the respiratory quotient fell again to 0.78.

An increased amount of fat in the blood accompanying a high quotient, therefore, implies that the fat is being transported rather than burned. The questions now arise for investigation whether the increased fat in the blood is due to the intake of fat in the food, whether it comes from the tissues, or whether it is being formed from carbohydrate or even protein. Inconsistencies appear in the table which studies arranged with design should clear away. The investigation of the respiratory quotient when the blood fat is high is a fruitful field for work. As a rule increased fat in the blood signifies acidosis and with acidosis the respiratory quotient is low. Here we meet with high blood fat values without acidosis and with relatively high quotients. The severe diabetic, therefore, during inanition is an anomaly.

TABLE 147.—RELATION OF FAT IN THE BLOOD TO RESPIRATORY QUOTIENT IN POST-ABSORPTIVE EXPERIMENTS WITH DIABETICS (AFTER JUNE, 1914).

Percentage of fat in the blood.	No. of observations.	Average respiratory quotient.
0.59–0.75	16	0.77
0.76–1.00	26	0.78
1.01–1.25	23	0.79
1.26–1.50	5	0.88
1.51–1.75	3	0.85
1.76–2.00	2	0.85
2.01+	6	0.78
All determinations of blood fat	81	0.79

12. **General Factors Influencing the Normal Metabolism.**—Before the presentation of various data obtained with diabetic patients upon their metabolism after the ingestion of food, certain considerations are here recorded upon metabolism in general which will help in their interpretation.

The knowledge acquired regarding metabolism is of such recent origin that the most fundamental facts relating to it are often overlooked. Among these is its extraordinarily labile character. When one considers the varying circumstances which occur in the waking hours of a man, it is inconceivable that the metabolism with any two individuals should be exactly alike. Even in sleep[1] the metabolism varies with the individual. More influences tend to raise

[1] Benedict: Carnegie Inst., Washington, Pub. No. 203, 1915, p. 343.

the metabolism under normal conditions than to depress it. The chief of these are exercise and food.

(*a*) **Factors Increasing Metabolism.**—(1) *Exercise.*—Although reclining in an easy chair[1] may not appreciably increase the heat-production of the human organism over that obtained with the body in a horizontal position, yet the simple maintenance of an upright position will raise the metabolism 10 per cent. This statement is likewise applicable to diabetics. Walking raises the metabolic rate still more, the increase, as demonstrated in the Nutrition Laboratory,[2] varying between 100 and 800 per cent according to the rate of walking. Experiments also conducted in the Nutrition Laboratory upon a professional bicycle rider have shown that under extreme conditions the increase due to muscular effort might amount to more than ten times the normal metabolism, or 1000 per cent.[3] The total metabolism of a normal individual engaged in a sedentary occupation may be estimated as 25 to 30 per cent above the basal level and for the inactive diabetic at 20 per cent above his basal metabolism.

A great opportunity was lost when years ago those interested in the metabolism of diabetics neglected to investigate intensively the effect of exercise. Had this been done the solution of the problem of the formation of carbohydrate out of fat might have been advanced by several years. From the work of Hill[4] we know that during exercise in health the respiratory quotient rises, presumably because carbohydrate is being oxidized and lactic acid formed, the reverse process taking place afterward. With prolonged exercise the respiratory quotient falls and Hill believes this due to the conversion of fat into carbohydrate. Today all know from clinical experience with patients taking insulin that exercise utilizes carbohydrate. Formerly when we tried it with severe diabetics we broke down a disproportionately large quantity of fat. Allen noticed that a dog showing glycosuria with 100 grams of bread became sugar-free with exercise when taking 200 grams of bread. Nehring and Schmall, Mohr, Allen and DuBois, Benedict and I, all noted either better utilization of carbohydrate or a higher respiratory quotient with exercise, but we did not follow it up! Suppose Lavoisier had done the tests! Grafe and Salomon and Richardson and Levine[5] more recently have shown that the effect of exercise upon diabetics was to lower the quotient below the normal level. They consider this depression to be evidence of a decrease in the proportion of

[1] Soderstrom, Meyer and DuBois: Arch. Int. Med., 1916, **17**, 872.
[2] Benedict and Murschhauser: Carnegie Inst., Washington, Pub. No. 231, 1915. Smith: Carnegie Inst., Washington, Pub. No. 309, 1922.
[3] Benedict and Cathcart: Carnegie Inst., Washington, Pub. No. 187, 1913.
[4] Hill: Boston Med. and Surg. Jour., 1924, **191**, 1097.
[5] Richardson and Levine: Jour. Biol. Chem., 1925, **66**, 161.

carbohydrate undergoing metabolism and conclude that fat can be oxidized without preliminary conversion into carbohydrate. Himwich, Loebel and Barr[1] however, point to the greater changes in acid-base equilibrium than in normals, due to a reduction in CO_2 capacity, CO_2 tension and alkalinity. This is explained by a marked increase in lactic acid in the circulating blood without change in the concentration of acetone bodies. In these diabetic individuals the breakdown of carbohydrate to lactic acid was employed as the chemical mechanism of muscular contraction.

Exercise greatly increased the hypoglycemic action of insulin as shown by Lawrence.[2] Experiments upon the effect of insulin and exercise on the percentage of sugar in the blood caught the diagrammatic eye of my friend H. J. John and Fig. 21 is the result. Comment is unnecessary. In his article Lawrence points out the bearing of his experiments upon the conversion of fat into carbohydrate and the dependence of the insulin requirements of the body upon the three food stuffs.

(2) *Increase in Metabolism Due to Ingestion of Food.*—The changes in the metabolism produced by food are not so sensational as those just cited as a result of exercise. They are, however, very considerable and, furthermore, continue for a relatively longer period. This last consideration is one of no mean importance. Whereas, following exercise the metabolism returns to a normal (basal) level in a comparatively few minutes, hours are required before the normal is reached after food. For this reason the total caloric excess above the basal metabolism produced by a meal of 600 to 800 calories may be the equivalent of a climb up the Washington Monument (168 meters high, with a requirement of 80 calories), and the excess of calories following a light breakfast might suffice to carry the subject to the top of the monument on Bunker Hill, 67.1 meters high. The effect of the ingestion of protein upon the metabolism may not cease for twelve or more hours,[3] that of fat continues for a somewhat shorter period, while with a meal of carbohydrate food, the metabolism usually reaches its maximum within two hours, and then rapidly falls.[4]

Two dimensions, as it were, must, therefore, be considered in estimating the effect of food, namely, the average height which the metabolism reaches above the basal metabolism and the length of time during which the increase persists. From these data the

[1] Himwich, Loebel and Barr: Jour. Biol. Chem., 1924, **59**, 265.
[2] Lawrence: Quart. Jour. Med., 1926, **20**, 69.
[3] Benedict and Carpenter: Carnegie Inst., Washington, Pub. No. 261, 1918.
[4] The rate of decrease is to a considerable extent dependent upon the rate of absorption from the stomach. Even with a pure carbohydrate like glucose, this is most variable, as Fitz reported at the American Society for Clinical Investigation, May, 1922.

total increment of heat may be determined. The heat due to basal metabolism subtracted from the total heat obtained in the period

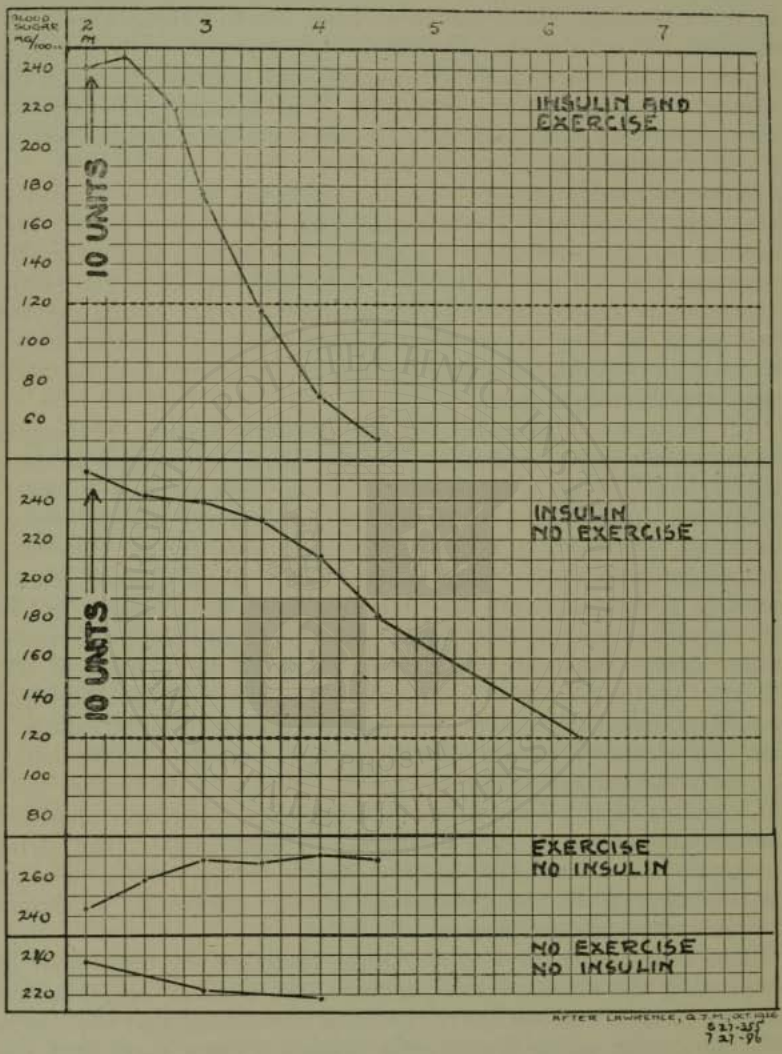


FIG. 21.—Effect of insulin and exercise upon the percentage of sugar in the blood. (Experiments of Lawrence with diagram by John.)

of increment after the ingestion of food gives the *total heat increment*. If this total heat increment is compared with the caloric value of the meal, *i. e.*, fuel value—the resulting percentage

represents the *cost of digestion*. The highest point which the metabolism reaches after the administration of food is known as the *peak effect* of that food, and this same term is sometimes applied to the change in respiratory quotient. For example, the total heat production following the ingestion of 100 grams of levulose by a healthy subject[1] was 379 calories, covering a period of about five and a half hours. The basal metabolism for this length of time was 343 calories and the difference between the two, or 36 calories, represents the *total heat increment*. The energy of the levulose was 379 calories. Dividing the total heat increment of 36 calories by the caloric value of the meal (379 calories), one obtains 9 per cent, which represents the *cost of digestion* of the meal. The metabolism reached its highest point, or 18 per cent above the basal metabolism, two hours after the ingestion of levulose, and this maximum increase therefore represents the *peak* effect of the meal. About one hour after the ingestion of the food, the respiratory quotient attained a maximum of 1.03, or the *peak* effect.

The results obtained in a study[2] of the increase in the metabolism of healthy individuals following the ingestion of different classes of food materials are summarized in Table 148. A number of the experiments, especially those with protein foods, were not continued long enough to obtain the full period of increment. The figures may, therefore, be considered in some cases as below the actual percentage increases.

From these data it would appear that an ordinary sized meal of carbohydrate food may increase the heat production over basal on the average 10 per cent, with an average maximum increase of 16 per cent. As the result of a meal of protein the heat production was increased on the average 12 per cent with an average maximum of 19 per cent, while after a meal of fat the average and maximum increases were 6 and 11 per cent. Beefsteak increased the metabolism on the average 14 per cent, while the average increment following the taking of cream was 6 per cent. Ordinary mixed meals raised the heat production on the average 16 per cent; beefsteak and bread or beefsteak and potato chips gave an average increase of 10 per cent. With milk the increase was 9 per cent.

The estimated cost of digestion for the pure carbohydrates (sugars) ranged from 5 to 7 per cent, for starches from 2 to 7 per cent, for protein foods 13 per cent, for fat 3 per cent, for milk 8 per cent, and for mixed meals 5 per cent.

The mechanical act of eating is in itself an expense. Thus, the

[1] Benedict and Carpenter: Carnegie Inst., Washington, Pub. No. 261, p. 212, 1918, Table 141.

[2] Ibid., 1918, Pub. No. 261.

drinking of more than 500 cc. of cold water may affect the metabolism, which has been known to rise in consequence as much as 16 per cent, though the average increase in 11 observations was but 3 per cent. Chewing may cause a rise of 17 per cent. Beef-tea and coffee increase the metabolism, coffee increasing it considerably.

TABLE 148.—EFFECTS OF FOOD UPON THE METABOLISM IN HEALTH.

Kind of food.	Energy (fuel value) of food.		Period of increment observed in experiment, hours.	Increase in heat production over basal.		Cost of digestion, per cent.
	Average, calories.	Range, calories.		Average, per cent.	Average maximum, per cent.	
Carbohydrate foods	526	280–1562	1½–8	10	16	6
Protein	434	168–1305	2–8	12	19	13
Fat	956	666–1362	3–8	6	11	3
Mixed diets:						
Mixed meals	998	468–1731	3½–4	16	26	5
Beefsteak, bread	431	399– 480	5	10	17	10
Beefsteak and potato chips	518	425– 676	3–4½	10	16	5
Milk	392	358– 444	4–6	9	14	8
Specific foods:						
Carbohydrate:						
Starch:						
Bananas	406	403– 409	3–4	11	19	6
Pop-corn	822	796– 847	8	8	13	7
Rice (boiled)	432	432	4	1	6	2
Sugars:						
Dextrose	354	286– 385	2–5	7	14	5
Levulose	359	280– 384	1½–5½	9	15	7
Sucrose	384	295– 756	1½–6	11	18	6
Lactose	380	374– 385	3–4½	9	14	5
Maltose-dextrose mixture	992	449–1382	3–8	12	19	6
Protein:						
Beefsteak	486	221–1305	2–8	14	21	12
Fat:						
Cream	956	666–1362	3–8	6	11	3

The ingestion of a *large* cupful of *strong* coffee increases the metabolism about 8 per cent for several hours.

(*b*) **Factors Decreasing the Metabolism.**—A decrease in the metabolism is known to take place normally as a result of undernutrition and is considerable. A decrease also occurs during normal sleep. In the experiments upon a fasting man, conducted by the Nutrition Laboratory, the basal metabolism at the end of the thirty-one days of fasting had been lowered to 14 per cent below standard.[1] The actual decrease in calories was 408 calories, or 27 per cent.

[1] Benedict: Carnegie Inst., Washington, Pub. No. 203, 1915.

Subsequent observations by the Nutrition Laboratory upon two groups of students (Squad A and Squad B) in the International Young Men's Christian Association College at Springfield,[1] who were subjected to a loss in body weight of 10.5 per cent for Squad A and 6.5 per cent for Squad B in eighteen weeks and three weeks respectively, showed a decrease in metabolism of 19 per cent for both groups.

The metabolism of a neurasthenic man studied by Magnus-Levy[2] was 33 per cent below standard, an actual fall of 44 per cent. His weight was 30 per cent below normal. Undernutrition with coincident loss of weight, therefore, is a very important factor in the lowering of the metabolism. This has already been considered. (See p. 275.)

(*c*) **Variations in Metabolism Due to Pathological Conditions.**— Under pathological conditions the most notable example of increased metabolism is in hyperthyroidism.[3] Here the increase may reach 100 per cent and is frequently as great as 50 per cent. F. H. Lahey tells me that he has had one case showing a basal metabolism of +136 per cent and the observations were checked. Fever may also cause an increase, as is shown by the report of Carpenter and Benedict[4] on cases of probable mercurial poisoning and by the studies upon typhoid fever patients conducted by Coleman and DuBois.[5] These latter investigators observed that at the height of the fever there was an average increase in the basal metabolism of about 40 per cent above the normal, but in some cases it rose to more than 50 per cent. In malaria Barr and Du Bois[6] found that the heat production increased 100 to 200 per cent during the chill; immediately after the chill it fell to within 20 to 38 per cent of the average basal level. McCann and Barr[7] found the basal metabolism of tuberculous patients may be normal or very slightly above that of normal men of the same size. In 10 cases the variation from average normal was from −3 to +15 per cent. DuBois refers to experiments conducted at the Russell Sage Laboratory which show an increase in metabolism in erysipelas, arthritis, and the fever produced by intravenous injections of protein. Leukemia causes a marked rise in metabolism. This has been observed in lymphatic leukemia by Murphy, Means, and Aub[8] and in myelogenous leukemia by Gunderson.[9]

[1] Benedict, Miles, Roth and Smith: Carnegie Inst., Washington, Pub. No. 280, 1919, p. 228.
[2] Magnus-Levy: Ztschr. f. klin. Med., 1906, **60**, 177.
[3] DuBois, Means and Aub: Arch. Int. Med., 1916, **17**, 915; ibid., 1919, **24**, 645.
[4] Carpenter and Benedict: Am. Jour. Physiol., 1909, **24**, 203.
[5] Coleman and DuBois: Arch. Int. Med., 1915, **15**, 887.
[6] Barr and DuBois: Arch. Int. Med., 1918, **21**, 627.
[7] McCann and Barr: Arch. Int. Med., 1920, **26**, 663.
[8] Murphy, Means and Aub: Arch. Int. Med., 1917, **19**, 890.
[9] Gunderson: Boston Med. and Surg. Jour., 1921, **185**, 785.

A lowering in metabolism occurs chiefly in myxedema, and at times the metabolism may fall to 33 per cent below normal. In chronic anemia, when it is profound, the metabolism may be reduced to 26 per cent below normal.

Following removal of the thyroid gland, the metabolism is lowered. In 1922 Aub[1] pointed out the predominating influence of the thyroid and the adrenal glands upon the total metabolism, considered the mechanism of their action independently, and as probably due to thyroxin and adrenalin, respectively.

Attention has already been directed to the decrease in metabolism of the average diabetic since the introduction of undernutrition in 1914. In a patient under observation at the New England Deaconess Hospital at the close of the Undernutrition Era in 1922 and just prior to his beginning insulin the metabolism reached the lowest level I recall for a diabetic, namely, −43 per cent. This patient, Case No. 866, was 185.9 cm. in height, weighed 90 to 92 pounds, was thirty-nine years of age. His basal metabolism in the course of two weeks varied between 765 calories and 930 calories. (See p. 63.)

(*d*) **Food and the Respiratory Quotient of Normal Individuals.**—A study of the effect of food upon the total metabolism is incomplete unless the influence which it exerts upon the respiratory quotient is also given. The average postabsorptive respiratory quotient of 236 of the 239 individuals upon whom the Harris and Benedict prediction tables are based was 0.83.[2] Presumably the diets of these subjects for the previous day were the usual average diet: namely, carbohydrate 400 to 300 grams, protein 100 to 75 grams, and fat 100 to 50 grams, which when expressed in proportion of calories for each food material would be carbohydrate 58 per cent, protein 14 per cent, fat 28 per cent. The ingestion of additional carbohydrate immediately before a test would raise this quotient, because the respiratory quotient of carbohydrate is 1. Whether the addition of more fat would tend to lower it, since the respiratory quotient of fat is 0.71 is yet to be proved for normals, but for diabetics it seems probable. An increase or decrease in the proportion of protein in the diet would make little change, since the characteristic quotient for protein is 0.81.

The effect upon the respiratory quotient the morning following a hearty evening meal, rich in carbohydrate as compared with one low in carbohydrate, was studied by Benedict, Emmes, and Riche.[3] In a series of experiments with 7 subjects they found that with an

[1] Aub: Jour. Am. Med. Assn., 1922, **79**, 95.

[2] Harris and Benedict: Carnegie Inst., Washington, Pub. No. 279, 1919, pp. 40–47, inclusive. Quotients can be calculated from data for carbon dioxide and oxygen.

[3] Benedict, Emmes and Riche: Am. Jour. Physiol., 1911, **27**, 383.

excessive carbohydrate diet the average respiratory quotient was 0.88, while with a low carbohydrate diet the respiratory quotient was 0.81. It is seldom, however, that such great changes in the diet are encountered as were employed by these experimenters with their subjects.

On the other hand, there is no doubt that Bernstein and Falta were right in emphasizing the importance of standard diets before metabolism tests and in recommending that these be continued for several days. This criterion was fulfilled at the Russell Sage Laboratory in the observations with Cyril K. One of the chief values of the recent work of Wilder, Boothby, and Beeler[1] is that this procedure was carried out in their 44 tests made with Bessie B., a diabetic. (See Table 149.) Between May 19 and May 26, the patient was upon a constant diet of carbohydrate 43 grams, protein 27 grams, fat 151 grams, equivalent to 55 calories per kilogram of body weight. The metabolism at the beginning of this period was −22 per cent as compared with the DuBois standard, the carbon dioxide in the blood 49 and 50 volumes per cent, and the acidosis slight. In the middle of the period the average metabolism had risen to −12 per cent with an increase in acidosis as shown by the carbon dioxide in the blood of 45 volumes per cent. At the conclusion of the period the metabolism was −11 per cent and the acidosis again higher, for the carbon dioxide in the blood was 41 volumes per cent. If the tests after the first two days of dieting were alone considered, the influence of acidosis in raising the metabolism in this patient would have been overlooked.

In the discussion of the series of observations upon food with diabetics one must remember the many opportunities for unusual quotients which have previously been mentioned. (See p. 306). The respiratory quotient of an individual will rise (1) when an additional proportion of carbohydrate is burned in the metabolism; (2) when β-oxybutyric acid and its derivatives are burned, if the basal respiratory quotient is below 0.75; and (3) when the quotient is under 0.81, it will rise when additional protein is oxidized; the respiratory quotient will also rise, even if the carbohydrate is not burned, provided (4) the carbohydrate is changed into fat, because in this process an excess of carbon dioxide is set free and the numerator of the respiratory quotient fraction $\frac{CO_2}{O_2}$ is thereby increased; the conversion of protein to fat (5) will accomplish the same result, though in much smaller degree; it is also conceivable that (6) a rise of the respiratory quotient above 0.81

[1] Wilder, Boothby and Beeler: Loc. cit., p. 230.

would take place if the carbohydrate portion of the protein molecule was burned and the non-carbohydrate portion retained in the body. There are but two possibilities by which the respiratory quotient may rise above 1. These are by the conversion of carbohydrate into fat or of protein into fat.

TABLE 149.—THE ADVANTAGE OF CONSTANT DIETS OF SEVERAL DAYS' DURATION IN METABOLISM EXPERIMENTS. COMPILED FROM WILDER, BOOTHBY AND BEELER.[1]

Date.	Carbohydrate, gm.	Protein, gm.	Fat, gm.	Calories per kg.	Acidosis.				Variation of metabolism from DuBois standard, per cent.
					Urine.		Blood.		
					Acetone bodies as acetone, gm.	Ammonia nitrogen, gm.	Acetone bodies as acetone per 100 cc mgm.	Carbon dioxide, vol., per cent.	
May									
10–14	16	10	83	28	2.0	0.6	19	59	−22
15–18	15	31	109	38	3.2	0.5	26	49	−20[2]
19	43	27	151	55	5.3	0.6	..	..	−22
20	43	27	151	55	3.0	0.6	..	..	−20
21	43	27	151	55	2.4	0.6	..	..	−17
22	43	27	151	..	4.4	0.6	30	50	
23	43	27	151	55	3.5	0.6	..	..	−10
24	43	27	151	55	6.2	0.6	25	45	−12
25	43	27	151	55	6.5	0.8	..	..	−14
26	43	27	151	55	6.5	1.1	..	..	−15
27	0	0	0	0	0.6[3]	0.7	38	41	−11

The respiratory quotient will fall when the percentage of carbohydrate in the diet which is oxidized decreases, and also when there is incomplete oxidation of fat. For further discussion of this question see p. 314.

Finally, great caution must be exercised in the interpretation of respiratory quotients. An uncertain element is introduced into the computations of the respiratory quotient when the carbohydrate ingested is not oxidized immediately but is stored as glycogen to be drawn upon later from time to time for oxidation. The mere storage of carbohydrate, however, would not affect the

[1] Wilder, Boothby and Beeler: Loc. cit., p. 230.

[2] For computing this average, the basal metabolism (−22 per cent) for May 19 is included because the value represents the result for the diet of this period.

[3] This is a decrease of 91 per cent in twenty-four hours and a value lower than that obtained on any day between March 31 and July 12. (I am assured it is correct.)

respiratory quotient. Fat may also be stored and not immediately burned. The storage capacity for protein is most uncertain.

The question of the storage of carbohydrate, protein, and fat in the body, particularly in the liver and muscles, greatly complicates the problem. The liver, which contains about one-half to one-fifth of the glycogen in the entire body, may vary in its content of glycogen from a negligible amount to 20 per cent, even upon a protein diet, and this percentage is as great as after feeding carbohydrate alone. These figures relate to the dog. The liver normally contains less than 6 per cent of fat; in starvation the quantity may amount to 10 per cent. When Pflüger[1] fed a dog for thirty days exclusively on large quantities of fat, at the end of this period the liver contained 45 per cent of fat and no glycogen. The antagonism in the liver between glycogen and fat, formerly supposed to exist, vanishes before Macleod's statement that following the administration of insulin both exist together. The intermediary metabolism of the muscles is not so well understood, but Best, Dale, Hoet, and Marks[2] have shown how readily glucose will be deposited in these structures as glycogen under the influence of insulin. The metabolism of protein is well known to be in large measure affected by the storage of fat in the body. When the fat in a fasting organism is abundant, protein metabolism is spared and the influence upon it of the ingestion of 100 to 300 grams of fat has been shown to be slight. This is, however, in the healthy animal, not in the diabetic. On the contrary, when the store of fat is very, very greatly reduced in the body, protein is drawn upon to excess.

Finally, if carbohydrate and fat are both available to the organism for combustion, the carbohydrate is burned first. Even when the metabolism has been raised by the ingestion of fat, it will be still further raised by the ingestion of carbohydrate.

(*e*) **The Storage of Carbohydrates in Diabetes.**—It is well known that following a period of fasting large quantities of carbohydrate can be administered to a diabetic without immediately appearing in the urine. The best illustration of this is von Noorden's oatmeal treatment. Thus, Case No. 344 (see p. 748) showed a positive carbohydrate balance of 520 grams when undergoing an oatmeal cure under the direction of Prof. von Noorden, although he never became sugar-free after this cure, despite a rigorous diet, save for occasional days. A more spectacular demonstration is the severe diabetic of Klemperer[3] who took 100 grams of glucose in divided portions during twenty-four hours without its appearing in the urine. More impressive are the observations recorded with levulose

[1] Pflüger: Arch. f. d. ges. Physiol., 1907, **119**, 123.
[2] Best, Dale, Hoet, and Marks: Proc. Roy. Soc., 1926, B. **100**, 55.
[3] Klemperer: Therapie der Gegenwart, 1911, **52**, 447.

in which severe diabetics are shown to assimilate practically all the carbohydrate administered. Our severe cases excreted but 12 per cent of the quantities ingested. Here another problem enters into the situation, because the levulose may or may not be stored as carbohydrate, since transformation into fat is quite probable.

Richardson and Ladd[1] have also demonstrated that severe diabetics can store large quantities of carbohydrate.

How large a quantity of carbohydrate it is possible for the body to store is really unknown, but its importance is none the less evident. Unless the amount of stored carbohydrate is known, it is unjustifiable to say that the carbohydrate excreted represents a part of that ingested during the same twenty-four hours. All data with reference to the D : N ratio are confused by our ignorance of stored carbohydrate. The influence of carbohydrate so stored in the body upon carbohydrate assimilation or retention, but not necessarily upon utilization, is also great. Whatever virtue the oatmeal cure possesses, all agree that it depends in major part upon preceding starvation which has tended to exhaust the carbohydrate depots of the body. On the other hand, it is quite possible that the storage of carbohydrate as glycogen in the body may activate the process by which further carbohydrate may be utilized. Roger[2] emphasizes the importance of a storage of glycogen in the liver and the intimate part it takes in the prevention of acidosis. He cites Chevrier as authority for the usefulness of 150 grams of carbohydrate the night before and morning of an operation for the protection of the liver from anesthetics. See Figs. 28 and 29 for illustration of the abnormal storage of glycogen and fat in the diabetic liver and spleen.

(1) *As Glycogen.*—Carbohydrate is stored in the body in various ways, but most of it is supposed to be in the form of glycogen, and this is divided between the liver and muscles. An old estimate of Bunge that the body contained 400 grams carbohydrate is roughly approximated by experiments upon fasting men and professional athletes doing severe work without food. This figure may be taken as a fair average, but there are enormous variations. This statement is based upon glycogen which has been shown to be burned in calorimetric experiments; it does not exclude the possibility of some glycogen still remaining in the body. Experiments of fasting men show that they may burn from 93 to 232 grams of glycogen in the first three days of a fast.[3]

[1] Richardson and Ladd: Jour. Biol. Chem., 1924, **58**, 931.

[2] Roger: Presse Médicale, 1922, **30**, 345.

[3] Benedict: The Influence of Inanition on Metabolism, Carnegie Inst., Washington, Pub. 77, 1907, p. 464; A Study of Prolonged Fasting, Carnegie Inst., Washington Pub. 203, 1915, p. 251.

In diabetic patients the quantity of glycogen is universally considered to be far below this amount, but Frerichs[1] found, upon puncturing the liver of 2 diabetics, a small amount of glycogen in 1 and a considerable amount in the other, and Külz found 10 to 12 grams of glycogen in the liver of a diabetic who had been for a long time on a diabetic diet. Examinations of the tissue removed from the livers of living diabetic patients also show appreciable quantities of glycogen, and it is the experience of pathologists that the organs of diabetic patients contain more than traces of glycogen. It is most unfortunate that no data exist which enable us to determine what this minimum is. Although it might be extremely small at any one moment, a small quantity might be continuously formed and destroyed, and the sum of these small quantities reach a substantial amount in twenty-four hours.

The work of Helly[2] throws light upon the problem. He points out the striking contrast between the constant presence of glycogen in the liver of human diabetes and the very small quantity which is found in the severe diabetes of depancreatized dogs, yet even in the latter the power of the liver to form or deposit glycogen is shown when levulose is administered. If a milder form of diabetes is produced in the dog more glycogen remains in the body and there is a closer resemblance to human diabetes. Whereas with total removal of the pancreas there was only 0.065 per cent of glycogen in the liver; with partial removal there was 0.3 per cent of glycogen, even though 8 to 10 per cent of sugar remained in the urine. By microscopic examination so considerable a quantity as this appeared small. When insulin was given to a depancreatized dog the content of glycogen in the liver was raised to 20 per cent.[3]

2. *As Blood Sugar.*—Sugar is also stored in the body in the form of blood sugar. The normal quantity of sugar in the blood of healthy individuals varies between 0.08 and 0.11 per cent, and for convenience in calculation may be considered 0.1 per cent. This rises quickly after a meal rich in carbohydrates, but soon falls to its former level. The percentage of sugar rapidly increased in the blood of diabetics following a carbohydrate meal, but it does not fall as rapidly as in normals. Thus, in 191 observations upon 72 of our diabetic patients the percentage of blood sugar varied from 0.45 to 0.07.

Certain types of diabetic patients—namely, those with disease of the kidneys—are especially prone to maintain high percentages of sugar in the blood for many days after their urines have become

[1] Cit. Nehring and Schmoll: Ztschr. f. klin. Med., 1897, **31**, 59; Pflüger's Archiv, 1876, **13**, 267.

[2] Helly: Ztschr. f. exp. Path. u. Therap., 1914, **15**, 464.

[3] Banting *et al.*: Trans. Roy. Soc. Canada, Section V, 1922, **16**, 39.

sugar-free. Various writers have also noted this in insulin-treated patients, but it has not occurred in my standard patient. Rabinowitch[1] writes the following:

"Since the institution of insulin treatment of diabetics, I have met with 14 cases which presented normal thresholds prior to the institution of insulin treatment, excreting sugar in the urine, with blood sugars ranging between 0.16 and 0.18 per cent. Following insulin treatment, these individuals were apparently taking much more food than they were allowed, and when they reported to the clinic had blood sugars ranging between 0.23 and 0.31 per cent with no sugar in the urine. These raised thresholds are known to have developed anywhere from one week to eighteen months after insulin treatment. In 5 of these cases there is an accompanying polyuria, these subjects excreting 2500 to 4000 cc. of urine a day. They all look very well, appear to be well-nourished, and feel well. I have investigated the kidney function in each of these cases and in no case have I been able to note definitely any impairment in kidney function as far as excretion of nitrogenous substances is concerned. The water test in 3 cases suggested impairment in water excretion, and this is corroborated by the fact that these individuals have what we now recognize as insulin edema.

"It appears to me that even if this condition is not uncommon, it should be recognized by the practitioner, since I cannot help but feel that individuals with marked hyperglycemia are 'active' diabetics and exposed to all the complications and dangers of this disease whether they excrete sugar in the urine or not. Since we know that there are other conditions which cause high thresholds, such as chronic nephritis, and diabetes of very long standing, I think that I have been careful to exclude these conditions. None of these individuals have shown albuminuria, and 5 of them are juvenile diabetics all under the age of fifteen years."

It is impracticable to consider that the percentage of blood sugar is maintained independently of the sugar in other tissues in the body save for short periods, because: (1) the percentage is so unstable; (2) there is no constant relation between the sugar in the blood serum and the sugar in the total blood; (3) the capacity of the blood for storage of sugar is so slight. Confirmation of the above statements has been afforded by the ingenious experiments of Woodyatt and his co-workers later to be described. (See page 492). If we assume an individual of 70 kilograms body weight and consider that 7 per cent of his weight is made up of blood, we have 4.9 kilograms of blood of which the sugar content is 0.1 per cent. This would amount to 4.9 grams, even taking the highest for the normal individual.

[1] Rabinowitch: Personal communication.

Fitz and Bock[1] determined the total sugar in the blood of normal individuals. It varied, but did not exceed 7.5 grams. With 9 diabetics the highest blood-sugar content was 15 grams and the highest plasma sugar was 10.78 grams, and should we take a high figure such as that encountered in some diabetics after the administration of food—namely, 0.45 per cent—the total quantity of sugar stored in the blood could not be far from 22 grams. Falta[2] has called attention to the slow return of the blood sugar of diabetic patients after a carbohydrate meal to the former sugar level. Kleiner and Meltzer[3] have also beautifully shown this same difference to exist between normal and depancreatized dogs. Whereas the sugar in the blood of normal dogs increases fourfold, namely, from 0.2 per cent to 0.79 per cent, following the injection of 4 grams of dextrose per kilogram body weight, and of depancreatized dogs threefold, from 0.38 per cent before to 1.19 per cent after the injection, the blood sugar of the former returned nearly to normal at the end of an hour and a half, while diabetic dogs then showed 0.86 per cent. It is significant that in these experiments the quantities of sugar excreted in the urine were practically the same.

3. *Other Possible Storehouses for Carbohydrate.*—The small amount of glycogen in the body and the still smaller quantity of blood sugar represent an amount of carbohydrate far too low to account for the phenomena above described in diabetes. Other sources for storage of sugar in the body must be sought, and this has been emphasized by Ivar Bang.[4] If we should assume that the percentage of sugar was the same for all the fluids in the body as in the blood, certain amounts of sugar might be stored in this manner. While such an assumption is not wholly justifiable, it has some basis, for we know that sugar exists in the spinal fluid of diabetes as well as in other fluids. In normal individuals Dr. Jacobsen affirms that he has not found it to follow the blood so closely, but that the opposite was true in his cases of diabetes mellitus. Hopkins[5] has observed in diabetic patients that the reducing substances in the spinal fluid were but slightly less than the blood sugar of the same individuals. These varied from a minimum of 0.074 to a maximum of 0.623 for the spinal fluid and the corresponding values for the blood were 0.077 and 0.66. Notable percentages of sugar, not very different from those in the blood, have been found in pleuritic and ascitic fluids, and Husband[6] found even 0.7 per cent in the amniotic fluid. Yet granted that the assumption of uniform dis-

[1] Fitz and Bock: Jour. Biol. Chem., 1921, **48**, 313.
[2] Falta: Med. Klinik., 1914, **10**, 9.
[3] Kleiner and Meltzer: Proc. Soc. for Exp. Biol. and Med., 1914, **12**, 58.
[4] Ivar Bang: Wiesbaden, 1913.
[5] Hopkins: Am. Jour. Med. Sci., 1915, **150**, 837.
[6] Husband: Loc. cit., Naunyn, p. 190.

tribution of sugar in the fluids of the body is correct, we cannot increase our storage capacity very much in this way. For example, assuming the total quantity of fluid in the body as 60 per cent of the body weight of 70 kilograms, we have 42 kilograms of body fluid from which we must deduct 4.9 kilograms already reckoned as blood. This leaves us a remainder of 37.1 kilograms of fluid in the body, and using the high figure (0.45 per cent) for blood sugar, the quantity of sugar in this mass of fluid would be only 167 grams, or 37.1 grams with a normal value for the blood sugar. This is not enough, relatively, to explain Kleiner and Meltzer's experiment and far less those of Woodyatt, and it suggests that a portion of the sugar must have been transformed into some other material, perhaps glycogen.

(*f*) **The Ingestion of Carbohydrate and the Respiratory Quotients of Normals.**—Before taking up the consideration of the effect of carbohydrate upon diabetics, it will be advantageous to note the influence rather more specifically of carbohydrate upon normal individuals. For this purpose Benedict and Carpenter[1] studied the effect of various sugars upon the respiratory quotient when given to healthy subjects. The amount of carbohydrate administered was 100 grams, or on the average 1.6 grams per kilogram body weight. The average maximum increase in the respiratory quotient for the series of experiments with each sugar follows: The increase in the respiratory quotient with levulose was 0.18, and with sucrose 0.21, in contradistinction to the increase for lactose 0.14, and dextrose 0.12. Such figures suggest that levulose, derived by inversion of the sucrose molecule, may be responsible for the high quotient obtained with sucrose. The actual quotients obtained both with levulose and sucrose rose above 1, this in each instance rising much higher than those obtained with dextrose and lactose. Almost invariably, four hours elapsed before the quotient returned to the basal value, and in some of these experiments it had not returned in six hours. Both Dürig[2] and Lusk[3] have also noted the greater increase in metabolism after levulose than after glucose.

Benedict and Carpenter state: "It is clear that there is a specific property of levulose that is markedly different from dextrose in its effect on the metabolism, both quantitatively and (as is now seen) qualitatively. To what extent this is determined by direct and rapid combustion, intermediary processes in transformation to glycogen or fat, or to the stimulating action of intermediary products may not at present be stated with surety."[4]

[1] Benedict and Carpenter: Carnegie Inst., Washington, 1018, Pub., No. 261, p. 256, Table 183.

[2] Tögel, Brezina and Dürig: Biochem. Ztschr., 1913, **50**, 296.

[3] Lusk: Jour. Biol. Chem., 1915, **20**, 555.

[4] Benedict and Carpenter: Carnegie Inst., Washington, 1928, Pub. No. 261, p. 243.

It has been pointed out that a rise in respiratory quotient may be due to the substitution of the combustion of carbohydrate for that of protein and fat, and second to the formation of fat from carbohydrate as a result of excessive carbohydrate feeding. The rapid ingestion of 100 grams of carbohydrate makes immediately available 400 calories with which to offset a basal requirement of perhaps 70 calories per hour. The taking of this moderate quantity of carbohydrate would, therefore, logically suffice for the basal requirement during a period of five or six hours. In normal individuals, therefore, whether carbohydrate is oxidized or changed to fat, additional carbon dioxide is being produced and the quotient should be raised for about five hours. If this does not take place, one is forced to conclude that the carbohydrate is being stored as glycogen or, what is equally important, the carbohydrate is being excreted. The only other alternative for an increase in carbon dioxide would be an increase in the total intake of food, but in this event the respiratory quotient would remain the same.

From what has been said in the foregoing pages concerning the administration of food to *normal* individuals and the many possibilities which must be considered in the interpretation of results, it is evident that the problem will become far more intricate when it is desired to learn what takes place when food is given to a patient with so complicated a disease as diabetes. That investigator is over-sanguine who expects to unravel more than a few of the tangled threads by any one series of experiments.

13. **The Ingestion of Levulose by Diabetics.**—Minkowski[1] discovered that levulose when given to a depancreatized dog appeared only in part in the urine and that after the administration of levulose glycogen was stored in the liver in varying quantities. Hédon[2] was unable to confirm the statement so far as it relates to glycogen. Minkowski also found that it diminished the protein metabolism in a diabetic dog, but Mandel and Lusk,[3] as well as von Noorden,[4] were unable to confirm this with a diabetic man. On the other hand, Verza[5] rdemonstrated that levulose, when given to a depancreatized dog, raised the respiratory quotient for a considerable period after glucose had failed to do so, though eventually it, too, lost the power.

Tögel, Brezina and Dürig[6] observed that levulose increased the metabolism to a greater degree than glucose, that the increase began earlier, and in their opinion, led more to the formation of fat than glucose. With a patient to whom they gave 30 grams of levulose,

[1] Minkowski: Arch. f. exp. Path. u. Pharm., 1890, **26**, 371, or 1893, **31**, 85.
[2] Hédon: Arch. de Med. Exp. et d'anat. Path., 1891, **3**, 44.
[3] Lusk: Science of Nutrition, Philadelphia, 3d Edition, 1917, p. 485.
[4] Cited by Lusk, loc. cit., p. 486.
[5] Verzar: Biochem. Ztschr., 1914, **66**, 75.
[6] Tögel: Biochem. Ztschr., 1913, **50**, 298.

in hourly doses, the respiratory quotient was kept at 1 for a long time. They also observed that the respiratory quotient fell for the first few minutes after carbohydrate was given. Külz[1] was apparently the first clinician to advocate seriously the therapeutic use of levulose in diabetes.

Lusk[2] used the oxygen as well as the carbon dioxide in the study of the effect of 50 grams of various sugars, glucose, sucrose and levulose, which he gave to a dog. He noted increases in metabolism, in the order named, of 30 per cent, 34 per cent, and 37 per cent, but only with levulose did any considerable increase persist throughout the fifth and subsequent hours. The respiratory quotients rose to 1, 1.02, and 1.02, respectively. There was no increase in the metabolism and respiratory quotient with lactose and but little with galactose. Levulose (2.8 grams) appeared in the urine as such in the levulose experiment and 0.25 gram appeared as sucrose after the sucrose experiment, but the urine was sugar-free following glucose. In the light of Folin and Berglund's[3] investigations upon blood sugar (see p. 352), the question arises whether the particular dog used in Lusk's investigation might not have had a low levulose threshold.

Bernstein and Falta[4] gave 100 grams of levulose on three successive days to a diabetic patient. No rise in respiratory quotient is recorded, but the tests made were postabsorptive upon the mornings *after* the levulose was given, too late a period to show results.

The most extensive investigations with levulose have been made by Johansson. In 1904 he, with Billström and Heijl,[5] gave 100 grams of dextrose, sucrose and levulose to normal individuals and determined the rise in carbon dioxide expelled as compared with basal values for succeeding hours. They observed that glucose increased the carbon dioxide 7 per cent, sucrose 14 per cent and levulose (93 grams) 15 per cent. They noted that the rapidity of oxidation of levulose was greater and the rapidity of storage as glycogen less than for glucose.

In a subsequent article Johansson[6] confirmed the results just cited. Incidentally, he noted that the increase in carbon dioxide varied with the rapidity of absorption of the sugars from the gastrointestinal tract, and thought he demonstrated quite definitely that the increase in carbon dioxide varied with the amount of glycogen

[1] Külz: Diabetes Mellitus, Marburg, 1874, p. 130. For a summary of the earlier literature see von Noorden, "Metabolism and Practical Medicine," Chicago, 1907, **3**, 635.
[2] Lusk: Jour. Biol. Chem., 1915, **20**, 555.
[3] Folin and Berglund: Jour. Biol. Chem., 1922, **51**, 213.
[4] Bernstein and Falta: Deutsch. Arch. f. klin. Med., 1916, **121**, 95.
[5] Johansson, Billström and Heijl: Skand. Arch. f. Physiol., 1904, **16**, 263.
[6] Johansson: Skand. Arch. f. Physiol., 1908, **21**, 1.

stored in the body at the beginning of the experiment. Levulose increased the excretion of carbon dioxide twice as much as glucose.

He performed several experiments with diabetic patients. In some instances the ingestion of sugar increased the carbon dioxide and in others did not, or increased it to a less extent than with normals. In one diabetic dextrose brought about an increase of 7 per cent in the carbon dioxide elimination, whereas levulose increased the carbon dioxide elimination 13 per cent. In other words, the same relation between glucose and levulose was obtained with this diabetic as with normals.

Loeffler[1] gave 100 grams of levulose to a diabetic patient and at an interval of seven hours repeated the dose. He observed an increase in the metabolism with an increase in the respiratory quotient, both of which were greater after the second feeding. The increases were not more marked than with glucose but less of the levulose was excreted in the urine.

Bodansky[2] used levulose in determining the carbohydrate tolerance in derangements of the liver due to chloroform and phosphorus poisoning and considers it of great value in measuring the degree of liver involvement. Within six to fourteen days after poisoning with chloroform the tolerance for levulose in dogs had returned to normal. Cori and Cori[3] discovered that glucose was absorbed twice as fast as levulose from the gastro-intestinal tract, but that they were on a par as glycogen formers. On the other hand, the liver retained only 17 per cent of the glucose absorbed as glycogen in contrast to 39 per cent of the levulose. Large doses of insulin would suppress the formation of glycogen from either.

Pollak[4] found that glycogen deposited in the liver of rabbits by feeding levulose disappeared more slowly as a result of an injection of epinephrin than when it had been deposited by glucose.

Fifty-one tests with levulose were carried out with diabetic patients at the Nutrition Laboratory and New England Deaconess Hospital between March 31, 1911, and June 25, 1917, only 3 of these being previous to January 11, 1916. Since that date 17 other tests have been made.

At the time of taking the food the patients were in the post-absorptive state in all instances, except that in 1 case 90 grams of oil had been taken earlier in the day. The total quantity of levulose ingested varied between 28 and 100 grams, and per kilogram body weight between 0.9 gram and 2.5 grams.

(*a*) **Utilization.**—The quantities of levulose ingested were well utilized by the patients. In the two experiments with the mild

[1] Loeffler: Ztschr. f. klin. Med., 1919, **87**, 309.
[2] Bodansky: Jour. Am. Med. Assn., 1924, **82**, 578.
[3] Cori: Jour. Biol. Chem., 1926, **70**, 577.
[4] Pollak: Arch. f. Exp. Path. u. Pharm., 1909, **61**, 149.

cases no sugar appeared in the urine after the administration of 1 gram of levulose per kilogram body weight. Almost equally good results were obtained with the 5 moderate cases who received, on the average, 1.2 grams of levulose per kilogram body weight. In the severe group there were 41 experiments with 19 cases. The urines remained sugar-free for the twenty-four hour period in only 9 of these 41 experiments. The average quantity of levulose given in the various experiments with the severe cases was 1.55 grams per kilogram body weight, and 88 per cent of this carbohydrate was assimilated. Thus it is seen that the levulose was nearly all utilized and, if not oxidized, must have been retained in the body in some form. These results help to explain how certain mild cases of diabetes may be able to take foods rich in levulose, such as certain varieties of honey and raisins, with impunity.

(*b*) **Effect Upon the Metabolism.**—The administration of levulose to this series of diabetic patients increased the metabolism in 51 observations on the average by 17 per cent. An increase in the metabolism occurred in each experiment, the least increase being 5 per cent and the greatest increase 32 per cent. This rise in metabolism of the diabetic patients is greater than the rise (9 per cent) found in the Nutrition Laboratory with normal subjects under similar conditions, and furthermore it persisted at a higher level for a greater period of time. DuBois points out that in order to make comparisons with normals the latter should live on the same diet as the diabetic subject for several days preceding the test.

In seeking for an explanation of the wide variation in the response of the diabetics to levulose, it was found that it was in part due to the difference in the quantities of levulose given per kilogram body weight. With the lowest amount of levulose, namely, 0.9 to 1.25 grams per kilogram body weight, the average rise in metabolism was 14 per cent, but when 1.8 to 2.5 grams per kilogram body weight were taken by the patient, the average rise in metabolism was 20 per cent.

For the severe cases of diabetes the response to levulose was also directly proportional to the quantities given. With the largest quantity of levulose, 2.5 grams per kilogram body weight, in 9 out of 18 experiments the increase of metabolism varied between 21 and 32 per cent. Thus the severe cases reacted more energetically with a rise in metabolism to levulose than did the normals, and also more than did the moderate or mild diabetics.

Acidosis is not a factor in the effect which the administration of levulose produces upon the basal metabolism of diabetic patients. (See Table 150.) This suggests that acidosis itself does not exert as deleterious an influence upon the metabolism of carbohydrate, or at least of levulose, as has generally been thought, and that some

other method must be sought to explain the harmful effect of acidosis clinically. Yet a contrary view is suggested by the respiratory quotient which failed to rise, in fact fell to a negligible extent, when the acidosis was extreme.

TABLE 150.—EFFECT OF ACIDOSIS UPON THE METABOLISM OF DIABETICS AFTER THE ADMINISTRATION OF LEVULOSE.

Acidosis.	Levulose per kilogram of body weight, gm.	No. of observations.	Increase in heat production, per cent.	Respiratory quotient.				
				Basal.	After levulose.	Observations showing.		
						Increase.	Decrease.	No change
+++	1.95	5	17	0.74	0.73	0	4	1
++	1.55	13	19	0.75	0.78	10	2	1
+	1.45	13	15	0.78	0.80	9	3	1
0	1.50	20	16	0.82	0.86	16	2	2
Average	1.55	51	17	0.79	0.81			

(*c*) **Effect Upon the Respiratory Quotient.**—The wide variation in basal respiratory quotients of the patients who took the levulose afforded opportunity to study its effect under these varying conditions. So far as the observations in this series went, the rise in respiratory quotient after levulose was independent of whether the basal quotient was low or high. Likewise, the increase in heat production over basal after the ingestion of levulose was practically the same at all quotient levels. This is contrary to an analogous line of investigation pursued by Staub. He showed in his work on the blood sugar that a protein fat diet represented by a low respiratory quotient presented an unfavorable substratum for the action of carbohydrate, since the storage of glycogen in the body was depleted. Of course it is possible that in the present series of experiments the amount of glucose formed from levulose was so great that it not only sufficiently filled the reservoirs but afforded sufficient for oxidation, too, but if this were the case one would not expect a rise in the respiratory quotient with small quantities of levulose, but such did take place. All these difficulties are avoided if one assumes that the levulose is first transformed into fat, because in that event the quotient would rise to an equal degree independent of the basal respiratory quotient.

Even if the levulose were not transformed into fat, but burned directly without transformation into glycogen, the rise in respiratory quotient would be explained. An argument against this immediate oxidation, however, is the general depletion of the body in

levulose or rather the great capacity which exists in the body for storing levulose, which makes immediate oxidation unnecessary. Apparently, however, immediate oxidation or change into fat does take place even though the capacity for storing more levulose is present.

The average respiratory quotient in the basal control experiments with the diabetics preceding the ingestion of levulose was 0.79 and for the interval during which the metabolism was tested after the ingestion of levulose was 0.81, a rise of but 0.02.

TABLE 151.—THE AVERAGE RESPIRATORY QUOTIENT AND THE PERCENTAGE INCREASE IN HEAT-PRODUCTION BEFORE AND AFTER INGESTION OF LEVULOSE ARRANGED IN SUCCESSIVE PERIODS OF TIME.

Kind of experiments.	Average respiratory quotient in,								
	2d half hour.	3d half hour.	4th half hour.	5th half hour.	6th half hour.	7th half hour.	8th half hour.	9th half hour.	10th half hour.
Diabetics:									
Basal[1] . . .	0.79	0.79	0.79	0.79	0.76	0.76			
After levulose .	0.84[2]	0.83[3]	0.81[3]	0.79[3]	0.74[4]	0.72[5]	0.70[6]	0.72[6]	0.69[6]
Percentage increase in heat production .	16	16	18	18	16	9	13	10	10
Normals:									
Basal experiment averages . .	0.88	0.87	0.86	0.85	0.85	0.82	0.86	0.85	0.83
After levulose .	1.04	1.00	0.98	0.97	0.94	0.86	0.93	0.90	0.84
Percentage increase in heat production .	12	14	13	11	7	−2	5	3	1

The slight increase in the respiratory quotient after levulose appeared peculiar. This is explained in part because of the different quantities of levulose given per kilogram body weight. When these were investigated, it was found that when the quantity of levulose ingested was below 1.25 grams, the quotient rose 0.02; when between 1.3 and 1.75 grams, it rose 0.03; and when 1.8 grams or more, it rose 0.04. In fact, the normal individuals in the Nutrition Laboratory showed analogous phenomena. The important factor, however, in the elucidation of this apparently slight increase in quotient is that the *quotients above mentioned were average quotients for the entire duration of the experiments and not for individual periods*

[1] Basal experiments secured preceding 44 of the 51 levulose experiments.
[2] Drawn from 45 experiments.
[3] Drawn from 47 to 51 experiments.
[4] Drawn from 7 experiments.
[5] Based on 2 experiments.
[6] Individual quotients. Case No. 1196.

immediately following the ingestion of levulose. Our data do not show what took place for the first thirty or thirty-five minutes, but they do indicate the results in subsequent half hour periods. In the second half hour these are shown in Table 151, and it will be noted that the chief rise in the respiratory quotient took place in the second[1] half hour and then declined, reaching the basal level in the fifth half hour and thereafter falling below it in subsequent periods, a phenomenon not distinctive for levulose, because noted also by others for glucose.[2] With normals the basal level was not quite reached even at the end of the tenth half hour. The maximum rise followed by a steady fall in the respiratory quotient after the ingestion of levulose is the best proof of its utilization by the body.

The increase in heat production after levulose persisted not only for six half hours, which is the customary length of duration of the increase in heat-production with normals under similar conditions, but continued even until the tenth half hour. In considering the action of levulose with diabetics, therefore, one must bear in mind its prolonged effect in raising the metabolism for even five hours.

The metabolism of Case No. 1196 after levulose rose 41 per cent in the second half hour and 40 per cent in the third half hour. In the subsequent three half hours the increases were, respectively, 20, 36, and 25 per cent. Even to the tenth half hour the metabolism was 10 per cent above the average basal metabolism for this day. An increase in heat production of 41 per cent after the ingestion of carbohydrate is an anomaly in health and hitherto unreported in diabetes.

1. *High Respiratory Quotients Obtained after the Administration of Levulose and Their Explanation.*—Two diabetic patients showed extraordinary increases in the respiratory quotient after levulose, and with each of these patients duplicate experiments on subsequent days confirmed the observations noted. Case No. 1213 received 1.9 grams levulose per kilogram body weight when the basal respiratory quotient was 0.87, and the resulting quotients, beginning with the second half hour, were 0.98, 1.01, 1.04, 0.86. Case No. 1233 with a basal quotient of 0.86 gave a quotient in the second half hour of 1 and in succeeding half hours 0.96, 0.93, 0.90, and upon a subsequent day, with a basal quotient of 0.87, gave a quotient of 0.93 in the second half hour and quotients of 1.08, 0.99, and 0.82 on subsequent half hours. With the first case there was a third experiment in which levulose and fat, each in quantities of 1.85 grams per kilogram body weight, were administered. Here, too, the respiratory quotient rose to above 1, and, in fact, was maintained at a higher

[1] In Tables 152 and 153 this is more clearly shown than in Table 151.

[2] Wilder, Boothby, Barboka, Kitchen and Adams: Jour. Metab. Res., 1922, 2, 701.

level throughout the four half hour periods than in any of the other experiments.

TABLE 152.—THE AVERAGE RESPIRATORY QUOTIENT AND THE PERCENTAGE INCREASE IN HEAT PRODUCTION BEFORE AND AFTER THE INGESTION OF LEVULOSE IN EXPERIMENTS CONTINUING BEYOND THE FIFTH HALF-HOUR.

Kind of experiments.	Average respiratory quotients, basal and for each half-hour after levulose.[1]								
	2d half hour.	3d half hour.	4th half hour.	5th half hour.	6th half hour.	7th half hour.	8th half hour.	9th half hour.	10th half hour.
Diabetics:	4	6	8	8	7	2	1	1	1
Basal, experiment averages . .	0.74	0.77	0.76	0.76	0.76	0.72	0.80	0.80	0.80
After levulose .	0.83	0.83	0.79	0.74	0.74	0.72	0.70	0.72	0.69
Percentage increase in heat production .	29	18	19	20	16	9	13	10	10
Case No. 1196. Dec. 15–16, 1916:									
Basal in half-hours . . .	0.83	0.81	0.77						
After levulose .	0.91	0.85	0.91	0.69	0.74	....	0.70	0.72	0.69
Percentage increase in heat production .	41	40	20	36	25	....	13	10	10

TABLE 153.—METABOLISM AND CLINICAL STATISTICS OF FIVE SEVERE DIABETICS SHOWING HIGH RESPIRATORY QUOTIENTS AFTER LEVULOSE.

Case No.	Date	Variation in weight from normal standard.	Urinary nitrogen per kilogram per 24 hours.	Blood sugar.	Average respiratory quotient in basal experiment.	Respiratory quotient for each half-hour after levulose.				Average respiratory quotient after levulose.	Variation of basal metabolism from H & B standard.
						2d.	3d.	4th.	5th.		
		%	gm.	%							
755	May 7– 8, 1917	−20	0.135	0.14	0.81	0.88	0.81	0.79	0.83	0.83	−23
	" 14–15, 1917	−21	0.110	0.12	0.81	0.90	0.84	0.82	0.83	0.85	−18
	" 21–22, 1917	−22	.....	0.10	0.81	0.92	0.88	0.85	0.78	0.86	−17
1049	May 19–20, 1916	−26	0.185	0.21	0.80	0.82	0.86	0.80	0.72	0.80	−20
	" 27–28, 1916	−30	.....	0.22	0.82	0.91	0.94	0.85	0.81	0.88	−18
1196	Dec. 14–15, 1916	−27	0.185	0.15	0.76	0.88	0.88	0.77	0.72	0.81	−19
	" 15–16, 1916	−23	0.115	....	0.80	0.91	0.85	0.91	0.69	0.78	−27
	" 16–17, 1916	−23	0.125	0.37	0.72	0.92	0.93	0.83	0.71	0.83	−22
1213	Feb. 7– 8, 1917	−45	0.185	0.21	0.85	0.95	0.90	0.80	0.74	0.85	
	" 14–15, 1917	−45	0.120	0.23	0.80	0.94	0.83	1.02	0.73	0.88	
	" 21–22, 1917	−45	0.150	0.15	0.87	0.98	1.01	1.04	0.86	0.97	
	" 28–Mar. 1,	−42	0.240	0.28	0.91	0.96	0.95	0.87	0.91	0.92	
	Mar. 28–29, 1917	−43	0.140	0.19	0.91	0.90	0.82	0.90	0.93	0.89	
1233	Feb. 19–20, 1917	−22	0.210	0.13	0.86	1.00	0.96	0.93	0.90	0.95	−33
	" 26–27, 1917	−22	0.090	0.14	0.87	0.93	1.08	0.99	0.82	0.95	−28

[1] The figures in the upper row of the table represent number of observations.

The patients with the highest respiratory quotients have various points in common. Paradoxical as it may seem, the case most below standard weight, Case No. 1213, had the highest basal respiratory quotients. Three other patients also had very high quotients. All the 5 cases were considered severe cases of diabetes, all were free from severe acidosis, the average loss in weight below the reported maximum weights was 31 per cent, while the average loss in weight below standard weight was 30 per cent. Excluding the one girl diabetic for whose basal metabolism there are not entirely satisfactory comparisons, the remaining 4 of the 5 cases agreed in having a low basal metabolism. The values for blood sugar were also distinctly low for diabetics, and in only 6 of 15 analyses were distinctly above normal. Save with 1 patient, sugar was absent from the urine.

It is impracticable to explain the exceptionally high quotients above cited in any other way than by a conversion of carbohydrate to fat, strange as this may seem to be in diabetes. Morgulis and Pratt[1] demonstrated in a dog, extremely reduced in weight as a result of partial extirpation of the pancreas, that a change of carbohydrate to fat could go on undisturbed, as shown by the respiratory quotient of 1.06. Perhaps this result took place all the more readily because the dog was emaciated. It is certainly significant that the Russian investigators whom they cite obtained similar results with dogs which had first been subjected to a fast for several days. It would be desirable to observe whether in the presence of undernutrition carbohydrate given in temporary excess might be transformed to fat with especial readiness, and, particularly, if levulose were the carbohydrate used. If this were the case, Morgulis and Pratt's emaciated "Flora" would help explain the high quotients obtained with emaciated diabetics after levulose administration.

The average rise in the respiratory quotient for 8 cases receiving levulose on three days, though in only 1 instance on successive days, in the first levulose experiment amounted to 0.03 on the first day, 0.04 on the second, and 0.08 on the third. This indicates a progressive gain in tolerance for carbohydrate while under treatment. A further increase is to be seen with 1 of the 2 cases receiving levulose for a fourth time, Case No. 755, showing a progressive rise in the quotient of that case of 0.01, 0.02, 0.04 and 0.07. Hitherto reports have not come to my attention of demonstration of improvement in toleration of carbohydrate with diabetics by observations of the respiratory quotient subsequent to test meals. Their occurrence with these 8 cases of diabetes illustrate the inherent possibilities for improvement in the disease which are not widely enough recognized, but also another means by which such improvement can be measured.

[1] Morgulis and Pratt: Am. Jour. Physiol., 1913, **32**, 200.

(*d*) **Levulose, Respiratory Quotient and Acidosis.**—When the acidosis was absent, the increase in the respiratory quotient above basal within a period of two hours was 0.05 with moderate acidosis from 0.03 to 0.05, and there was no increase when acidosis was severe. Although the total metabolism after levulose was apparently unaffected by the presence or absence of acidosis, it is evident that acidosis had a very definite influence upon the change in respiratory quotient.

(*e*) **Effect of Levulose Upon the Blood Sugar.**—Folin and Berglund[1] noted that levulose produced no hyperglycemia in a normal individual to whom they gave 200 grams. Unfortunately we have few data upon the change in the blood sugar soon after the administration of levulose. For 30 experiments with 17 of the subjects the blood sugar was determined early in the morning of the experimental day before levulose was given and again twenty-four hours later. On both days the blood sugar averaged 0.19 per cent. Eight observations were made upon the percentage of the blood sugar within two and a half to four hours after levulose was given. Before administration the average per cent of sugar in the blood was 0.23 and two and a half to four hours after it was given was 0.3 per cent. In 2 instances the blood sugar percentage returned to approximately the basal value during this period. In several the rise in blood sugar was 0.1 per cent or more and in 1 experiment 0.21 per cent. The increases in blood sugar after levulose with diabetics are in marked contrast to what Folin and Berglund report with normal individuals.

The fact that there may be no hyperglycemia after the administration of levulose to normals as demonstrated by Folin and Berglund can be explained by a transformation of the levulose into fat. This is in line with the unusually high respiratory quotient found with normal individuals and diabetics after its administration. If the levulose were transformed into glycogen, the respiratory quotient would not rise, and if into glucose and was burned, it would give an increase in the blood sugar which they have shown does not take place normally. The possibility should be entertained that the increased metabolism following the administration of levulose, which continues after the respiratory quotient has fallen to the basal value, might be due to the levulose continuing to be burned as fat; and for this theory there is some support because, after this period the respiratory quotient falls even below the basal value.

14. **The Ingestion of Orange Juice, Dextrose, and Sucrose and the Metabolism of Diabetics.**—(*a*) The effect of orange juice was determined in several experiments. The quantity of carbohydrate in orange juice was accepted arbitrarily as 10 per cent. There are

[1] Folin and Berglund: Jour. Biol. Chem., 1922, **51**, 213.

three different sugars found in orange juice—sucrose, dextrose and levulose. Sucrose usually makes up a little over one-half of the total sugar. After the fruit is removed from the tree, there is a gradual decrease in the amount of sucrose with a corresponding increase in the other two sugars, indicating that sucrose is changed into the other two. One group of analyses of California oranges shows variation in content of sucrose, 4.93 to 5.35 per cent, of invert sugar (dextrose and levulose) 4.36 to 6.8 per cent.

Acid is present in oranges almost entirely as citric acid. In the group of analyses above cited it varied between 1.26 and 1.51 per cent. Since citric acid is oxidized in the body, it is desirable to remember that its respiratory quotient is 1.33. Fortunately its percentage and quantity in orange juice is so low as not to interfere with our experiments.

In the 4 experiments with orange juice the average amount of carbohydrate per kilogram body weight administered was estimated at 1.2 grams. The increase in heat production varied from 1 to 21 per cent, an average of 12 per cent. The increased respiratory quotient was distinct, and although the average increase was but 0.03, the *peak* increase was considerable and the average maximum increase above the basal, 0.09.

(*b*) In a single experiment with dextrose the increase in heat production was less than after orange juice and the increase in respiratory quotient distinctly less.

(*c*) A single experiment with sucrose in a mild case of diabetes gave an increase in metabolism of 3 per cent, but the respiratory quotient behaved like that of a normal individual, rising on an average to 1.02 per cent and as a maximum to 1.05. As in the levulose experiments, here, too, the suggestion is near that with the burning of the sucrose some transformation of carbohydrate to fat may have taken place.

15. **The Effect of the Ingestion of Levulose and Fat on the Metabolism of Diabetics.**—Eight observations upon 4 severe cases of diabetes free from acidosis were obtained after the patients had taken levulose and fat. As a result the metabolism rose on an average of 16 per cent. Comparing this increase with that observed when levulose was given alone to these 4 patients (19 per cent), it will be seen that despite the addition of fat, the metabolism rose slightly less during the actual period of experimentation. The average basal respiratory quotient in the 8 experiments was 0.83, and during the test this was increased on the average to 0.88, which corresponds closely with the values observed when levulose was given alone. The average maximum quotient was 0.92, thus indicating that even the peak effects of these levulose and fat meals correspond with the levulose meals without fat.

TABLE 154.—EFFECT OF INGESTION OF CARBOHYDRATE, FAT AND OLIVE OIL BY DIABETICS.

Variety of food given in experiment and Case No.	Total calories in meal per kilogram body weight of subject.	Increase in heat production over basal per cent.	Respiratory quotient. Basal.	Respiratory quotient. After carbohydrate and fat. Average maximum.
Levulose and fat:				
610	11	23	0.84	0.82	0.84
"	10	12	0.82	0.84	0.88
"	10	19	0.83	0.83	0.86
"	10	16	0.85	0.85	0.88
1213	24	14	0.84	1.01	1.08
"	24	17	0.84	0.92	0.97
1233	19	16	0.85	0.93	0.97
1259	13	13	0.80	0.80	0.84
Average	15	16	0.83	0.88	0.92
Orange and fat:					
1213	16	15	0.91	0.88	0.95
1233	10	9	0.86	0.84	0.89
"	8	8	0.87	0.86	0.89
Average	11	11	0.88	0.86	0.91
Olive oil					
1213	17	0	0.91	0.86	0.94

These experiments show beautifully the selective action of the body for carbohydrate when carbohydrate and fat are ingested simultaneously, the respiratory quotient rising as high when the two food elements were given as when carbohydrate was given alone; in one instance the respiratory quotient rose even above unity. On the other hand, there was no increase in the metabolism over those experiments in which levulose was given alone, although the blood must have contained a far greater number of food molecules. In these experiments only good effects, so far as the metabolism and respiratory quotient were concerned, came from the addition of the fat to the levulose, and the patients obtained additional calories.

These data regarding the levulose and fat experiments are of service in another direction in that they offer a comparison of the effect of variation in the number of calories given in the food at one time per kilogram body weight. If one examines the table from this point of view, it will be seen that when the number of calories was lowest, *i. e.*, 10 calories per kilogram body weight, the increase in metabolism varied between 12 and 19 per cent, and when the number of calories was over twice as large per kilogram body weight, the increases in the metabolism were 14 and 17 per cent. A variation in the number of calories per kilogram body weight caused no change in the metabolism. Attention is again called to the large number of calories per kilogram body weight given in a brief period. In the course of a few minutes 1 patient (Case No. 1213) received 24 calories per kilogram body weight, a quantity sufficient to supply the basal needs of the body for twenty-four hours.

Corresponding to these experiments with levulose and fat, 3 experiments with 2 of the same patients were made after the ingestion of orange juice and fat. The comparative results are strikingly similar. The average increase in metabolism was 11 per cent, and this is essentially the same as when orange juice was given alone. In these 3 experiments the respiratory quotient did not show a rise save for the maxima, which were on the average 0.03 above the basal level. The total amount of carbohydrate given was but 30 to 40 grams, corresponding to 0.65 to 1.25 grams per kilogram body weight.

A single experiment was made with Case No. 1213 after 60 grams of olive oil had been given, or 1.85 grams per kilogram body weight. No change was noted in the metabolism as a result of the oil, thus supporting the results already noted when fat was added to levulose or orange juice. This lack of increase in the metabolism is the more noteworthy because the patient received 17 calories per kilogram body weight in the course of one or two moments, a quantity of food sufficient to supply the basal needs for eighteen hours. The average respiratory quotient *fell* 0.05, though in the first period there was a rise of 0.03 with successive decreases thereafter.

16. **The Ingestion of Protein in Diabetes.**—Small quantities of protein raise the metabolism of diabetics in a striking manner as in the case of normals. Diabetic patients are often so thin that trifling quantities of protein really amount to more than one would think, because they are relatively large per kilogram body weight. Thus the increase in heat production when the protein per kilogram body weight amounted to from 1.55 grams to 1.70 grams varied between 20 and 32 per cent. It is noteworthy that the average respiratory quotient in the protein experiments was essentially unchanged following the ingestion of the protein. The administration of moderate quantities of fat with the protein in another series of 10 experiments brought about similar results. Thus, the average increase in metabolism was 23 per cent. In fact, these experiments with protein and fat bear the same relation to the experiments with protein as do the experiments with carbohydrate (levulose or orange juice) and fat to the experiments with pure carbohydrate. In other words, so far as the limits of these experiments go, there appears to be no tendency for fat to increase the metabolism, either when given with carbohydrate or with protein. The ingestion of fat in these experiments, therefore, produced as little effect on the metabolism as the oxidation of body fat did in the experiments with the overweight normals and diabetics.

In comparison with the protein experiments just cited is another group of experiments after the ingestion of beefsteak, during the years 1908 and 1918, when the basal metabolism of the cases thus

studied averaged 17 per cent *above* standard in contrast to the protein experiments above mentioned in which the average basal metabolism was 17 per cent *below* standard. The observation showed that the increase was similar, being 16 per cent.

TABLE 155.—EFFECT OF INGESTION OF PROTEIN AND FAT BY DIABETICS.

Body weight (naked) kg.	Food ingested. Protein, gm.	Fat, gm.	Increase in heat production over basal, per cent.	Basal respiratory quotient.	Average respiratory quotient in experiment.
39.6	13	..	20	0.80	0.81
36.4	18	16	23	0.82	0.81
49.7	75	54	16	0.71	0.71

A study was made of the increases in heat production in the various food experiments at different levels of basal metabolism. Although it might be supposed that the stimulus of food would be less on an already stimulated body metabolism (*i. e.*, with acidosis and high metabolic state) it would appear from these results that there is no especial relation between the level of the basal metabolism and the degree of reaction of the body to food.

17. **Oatmeal and the Metabolism of Diabetics.**—The effect of oatmeal taken alone and with fat and in divided portions through the day was likewise investigated. When oatmeal was combined with fat, the increase in the metabolism of a series of moderate and severe diabetics amounted to 18 to 26 per cent if the observations were confined to the two or three hours following the ingestion of the food. No change in respiratory quotient was observed.

TABLE 156.—METABOLISM AFTER INGESTION OF OATMEAL AND OATMEAL WITH FAT IN EXPERIMENTS WITH DIABETICS.

Diet and No. of observations.	Body weight (naked) kg.	Time elapsed since eating, hrs.	Food ingested. C. gm.	P. gm.	F. gm.	Metabolism. Increase in heat production over basal, per cent.	Respiratory quotient. Average of experiment.	Basal.
Oatmeal 3	51.5	¼–4	48	12	5	3	0.77	0.76
Oatmeal with fat 7	54.6	1¼–3¼	83	23	53	22	0.75	0.74
Oatmeal day 6	58.0	1¼–2	57	13	44	17	0.71	0.71

The effect of oatmeal divided in 1 to 7 meals was studied. After the first meal there was an average rise of the metabolism in 9 experiments of 14 per cent. The rise, in general, varied according to the quantity of all the food given. After the second feeding an increase in metabolism above basal was noted, amounting to 19 per cent. After the third meal the rise in metabolism amounted to 24 per cent and in 2 observations the increases in metabolism were

as great as 37 and 40 per cent. The respiratory quotient as after the first and second meals was unaffected. After the fourth meal in 5 experiments the average rise in metabolism was maintained at 20 per cent. As a result of four successive meals of oatmeal and fat (1) there was no clear tendency to a rise in quotient; (2) very low quotients were secured on two successive days and are supported by similar quotients; (3) they were secured after the patient had taken 220 and 260 grams of fat, respectively; (4) these made with carbohydrate and protein total calories equivalent to 56 and 67 calories per kilogram body weight in the preceding seven and a half and nine and three-quarter hours, although the patient was taking no active exercise; (5) the rise in metabolism varied from 14 to 40 per cent.

Following the fifth meal the average rise in metabolism was 26 per cent. The respiratory quotient fell notably in this series and is chiefly to be explained by the single experiment with Case No. 591, discussed under low respiratory quotients. (See p. 316). This subject was an ideal one, a severe diabetic with severe acidosis. He was given carbohydrate 35, protein 10, and fat 55 at each of five successive meals. The rise in this patient's metabolism after the third oatmeal feeding was 40 per cent and after the fifth meal 42 per cent. The respiratory quotient fell to 0.58. The rise in metabolism appears hardly explainable by the protein given but rather by the acidosis. See p. 296, as well as my Carnegie Monograph, p. 174, for further discussion of this case.

There was a single experiment after the sixth feeding of oatmeal and but one after a seventh feeding. The rise in metabolism was essentially the same: that is, 13 and 14 per cent, respectively, with an increase in the respiratory quotient in both of 0.03.

The effect of glycerol, calcium hexose phosphate, and calcium glycero-phosphate has been studied by McCann and Hannon.[1]

With alcohol Allen and DuBois[2] found the results undecisive. Richardson and Mason[3] on the other hand gave considerable amounts of food and the increase in metabolism was negligible.

18. **The Effect of Mixed Meals of the Diabetic Diet Upon the Metabolism of Diabetics.**—A series of observations was made following the ingestion of routine diabetic mixed meals at the New England Deaconess Hospital. The increase in the metabolism after the first meal of the day was 15 per cent. This represents a period of approximately two hours beginning between one and two hours after the meal. If the metabolism observations were begun earlier after the ingestion of food, the metabolism would probably have

[1] McCann and Hannon: Johns Hopk. Hosp. Bull., 1923, **34**, 73.
[2] Allen and DuBois: Arch. Int. Med., 1916, **17**, 1010.
[3] Richardson and Mason: Jour. Biol. Chem., 1923, **57**, 587.

risen to a higher level, and if continued longer the metabolism would have gradually diminished and the figures would have been reduced. In these observations it was again notable that acidosis did not prevent a rise in metabolism after food. The increase in metabolism varied chiefly with the quantity of protein, and also was associated with the calories per kilogram body weight. When the metabolism was determined after the second meal of the day, the average increase was found to be 25 per cent. This corresponds with the quantity of protein administered and would appear to be directly connected with it, because the caloric value of the meal was decidedly lower than that given in the previous series of experiments. When the metabolism was determined after two and three meals the average increase was found to be, respectively, 19 and 28 per cent. In all of these experiments after meals the change in respiratory quotient was negligible.

19. **The Influence of Insulin Upon the Respiratory Quotient and the Total Metabolism.**—The administration of insulin to normal animals and individuals as well as to animals made diabetic and to diabetic individuals tends to raise the respiratory quotient and as a rule to increase slightly the total metabolism. The rise in respiratory quotient by no means can be attributed entirely to the combustion of carbohydrate because it may be associated with the oxidation of ketone bodies, the release of alkali coincident with the disappearance of the ketone derivatives from the circulation and in consequence the blowing out of CO_2 from the lungs, and finally the possibility of the conversion of the carbohydrate into fat. So, too, with the increase in metabolism this is not so great as to account for the combustion of all the sugar and its disappearance from the blood so that in this way one receives evidence that this disappearance of sugar is accompanied either by its deposition in the body as glycogen or by its conversion into some other product.

The early work upon the respiratory change in normal animals by Dixon and Pember[1] showed the respiratory quotient before insulin was 0.86 and it rose to 1.16 within an hour and a half, and that the total metabolism rose from 15 to 26 calories per hour. In general these values varied with the decrease of sugar in the blood and indeed might be considered dependent upon its fall, because the effect was prevented when sufficient glucose was injected into the animal to prevent hypoglycemia. Insulin, therefore, promoted a relative increase in the share which carbohydrate took in the total metabolism. The effect of insulin may be indirect as Boothby and Rowntree and Cannon, MacIver, and Bliss[2] suggest, because it is known that epinephrin has a stimulating influence on metabolism

[1] See Macleod, Loc. cit., p. 257.
[2] Macleod: Loc. cit., p. 257.

and it is generally considered that the action of the adrenals comes into play when the marked hypoglycemia occurs.

In this connection it is interesting to note that Porges and Salomon as well as others have found that the respiratory exchange of hepatectomized preparations is always about unity, indicating that in the absence of this viscus the muscles can burn carbohydrate only, a fact which indicates, as we have seen elsewhere, that the muscles are restricted to the use of carbohydrate and that fats and proteins are unavailable until after they have been transformed into this or some related substance.[1]

The observations of various clinics on diabetics have shown increases in respiratory quotients. At times the results are not striking. There can be no doubt that the respiratory quotient becomes raised soon after the injection of insulin in normal animals.

D. THE NATURE OF DIABETIC ACIDOSIS AND ITS RELATION TO COMA.

1. **Acidosis in Normal Individuals.**—If a healthy individual lives for three successive days upon a carbohydrate-free diet, the urine voided upon the subsequent morning will show the presence of diacetic acid and acetone. This is evidence of the intoxication which was termed by Naunyn "acidosis." Experiments and debates have taken place all these years to prove *pro* or *con* that the acid responsible for the condition was β-oxybutyric acid and its derivatives or a group of acids. This acid is by far the more abundant and important, although in certain states of diabetic acidosis Bock[2] and Fitz and their co-workers believe another organic acid is sometimes present, too, the nature of which is as yet unknown.

Acidosis is still more simply produced in normal individuals by fasting, but it is of a milder type. Thus Benedict's subject at the Nutrition Laboratory constantly showed an acidosis during his fast of thirty-one days. When the fasting subject is obese, Folin and Denis[3] found the acidosis still more marked. (See Table 159, page 364.)

Exercise, even without fasting, leads to acidosis and the extent of it varies with the strenuousness of the exercise.[4]

Examples of acidosis due to a non-carbohydrate (fat-protein) diet, to fasting in an obese subject, and to exercise are shown in Tables 157, 158, 159 and 160. (See pages 360, 362, 364 and 365.)

[1] Macleod: Loc. cit., p. 257.
[2] Bock, Field, and Adair: Jour. Metab. Research, 1923, **4**, 27.
[3] Folin and Denis: Jour. Biol. Chem., 1915, **21**, 183.
[4] Landergren: Nord. med. Ark., 1910, **2**, 1; Barach (reprint) Physiological and Pathological Effects of Severe Exertion (The Marathon Race) from the Dept. of Phys. Research of the Pittsburgh Athletic Assn.

TABLE 157.—ACIDOSIS OF A NORMAL INDIVIDUAL UPON A FAT-PROTEIN DIET.

Day.	Acetone.	β-oxybutyric.
1	0.062	0.84
2	0.660	0.73
3	2.550	3.56
4	3.110	14.70

Prerequisite for the acidosis in all these states is the diminution of the combustion of carbohydrate in the body no matter whether caused by withholding food or the exhaustion of glycogen stores or its excretion unburned as in diabetes. Zeller[1] first and later Benedict's experiment showed that so soon as the percentage of carbohydrate in the combined carbohydrate and fat metabolized fell below 10 or 12 per cent, acidosis was marked. My experiment upon the healthy nurse, Miss L., (see p. 302) showed it did not begin to subside until the equivalent of 15 per cent of the total metabolism was taken in the form of carbohydrate just as Ladd and Palmer[2] showed the same phenomenon for diabetics.

"Fat burns in the flame of carbohydrate,[3] but without it it smokes."[4] This metaphor has been of great assistance in the study of acidosis. One conception of fat metabolism is based on the assumption that the normal katabolism of the fat molecule proceeds via the ketone acids route, but that in diabetes, because of lack of insulin, is halted in the ketone stage. As a result β-oxybutyric acid and its derivatives collect in the body and appear in the urine along with sugar which, too, is a product of the breakdown of fat. Therefore, if we must have a metaphor, it would be more accurate to say that β-oxybutyric acid and glucose are the inseparable Siamese twins, the anomalous offspring of the marriage of their healthy mother, fat, with their defective father, insulin. Carpenter[5] has investigated the metabolism of steers during fasting and found that like the dog and the cat, they exhibited no tendency toward ketosis during fasting. Apparently the ketogenic-anti-ketogenic ratio holds for man but not for these animals. The respiratory quotient of the steers fell as rapidly to a fasting value as with man, consequently absence of ketosis was not due to the fact that the proportion of katabolized carbohydrate to fat was high or that the animals were not burning fat. This suggests the possibility that the ratio of carbohydrate to fat is not necessarily the cause of ketosis, but that it is due to some other factor, man being one of the animals which exhibited this condition when subjected to high fat metabolism such as occurs with a carbohydrate-free diet or during fasting.

[1] Zeller: Arch. f. Physiol., 1914, p. 213.
[2] Ladd and Palmer: Proc. Soc. Exp. Biol. Chem., 1921, **47**, 433; also Am. Jour. Med. Sci., 1923, **166**, 157.
[3] Rosenfield: Deutsch. Med. Wchnschr., 1885, **11**, 683.
[4] Woodyatt: Jour. Am. Med. Assn., 1916, **66**, 1.
[5] Carpenter: Proc. Nat'l. Acad. Sciences, 1925, **11**, 155.

Signs and symptoms in man, however, disappear as if by magic when the subject begins to take and burn carbohydrate. Conversely, if carbohydrate is withheld and excessive fat administered or through exercise drawn upon for energy, the acidosis is intensified. This is beautifully shown in diabetes by the falling respiratory quotient and the rising acidosis as recorded in Table 143. As the metabolism of fat replaced the metabolism of carbohydrate the ketone bodies appeared and hence it was natural to look for their source in fat.

The acid or ketone bodies which have been demonstrated to be present in the acidosis of fasting and, as will be seen later, of diabetes are represented by three bodies: β-oxybutyric acid ($CH_3.CHOH.-CH_2COOH$), diacetic acid ($CH_3.CO.CH_2COOH$), and acetone ($CH_3.CO.CH_3$) all of which are excreted in the urine, and the latter in the breath as well.

(*a*) **The Source of the Acid Bodies.**—The source of these bodies is in the organic acids found chiefly in fat, but also in protein, though not at all in carbohydrate. They develop as readily from body fat and protein as from exogenous fat and protein, so far as is known. Each molecule of a higher fatty acid, as it is broken down to a lower, provided it has an even number of carbon atoms, leads to the production of one molecule of β-oxybutyric acid. As a matter of fact, the only fatty acids which are present in the body are those containing an even number of carbon atoms. It has been extimated by Magnus-Levy that out of 100 grams of fat, 36 grams of hydroxybutyric acid may be produced.[1]

The oxidation of fat in the body takes place at the β-carbon atom and proceeds until all the methyl radicles have been oxidized. In diabetes this proceeds until three methyl radicles are left and only one of these, namely, that in the β group, is partially oxidized. Aceto-acetic acid probably appears first, β-oxybutyric acid and acetone from it by reduction and oxidation, respectively. According to Geelmuyden, the ketone bodies represent intermediary bodies in the conversion of fat into carbohydrate. Macleod and Campbell[2] say: "With Chaikoff and Markowitz the exact time relationships of the changes caused by insulin on the sugar, the ketone bodies, the phosphoric acid, and fat of the blood have been determined on diabetic dogs. Sugar, ketone bodies, and phosphoric acid all come down at the same time and at strictly parallel rates. During recovery the phosphoric acid rises most rapidly. Fat does not fall at the same time. Sugar and ketones were much higher in a fat than in a thin depancreatized dog."

Starting with the assumption mentioned in the second paragraph

[1] Magnus-Levy: Spez. Path. u. Therap. inn. Krank., Kraus u. Brugsch, Berlin, 1913, **1**, 30.

[2] Macleod and Campbell: Medicine Monographs, vol. **6**, Williams and Wilkins, Baltimore, p. 25.

TABLE 158.—TABULAR PRESENTATION OF METABOLISM RESULTS OBTAINED IN AN EXPERIMENT WITH A MAN FASTING FOR THIRTY-ONE DAYS AT THE NUTRITION LABORATORY OF THE CARNEGIE INSTITUTION OF WASHINGTON IN BOSTON. AGE, THIRTY-NINE YEARS, ELEVEN MONTHS. HEIGHT, 170.7 CMS.

Observations.	April 10–11.	April 11–12.	April 12–13.	April 13–14.	April 14–15. 1	April 15–16. 2	April 16–17. 3	April 17–18. 4	April 18–19. 5	April 19–20. 6	April 20–21. 7	April 21–22. 8	April 22–23. 9	April 23–24. 10	April 24–25. 11	April 25–26. 12	April 26–27. 13	April 27–28. 14	April 28–29. 15	April 29–30. 16
Body weight naked, kg.	60.13	60.53	60.95	60.64	59.60	58.68	57.79	57.03	56.37	55.89	55.5	55.08	54.63	54.13	53.88	53.56	53.45	53.15	52.84	52.29
Insensible perspiration per day, gms.	..	..	..	..	1086	1188	1059	779	727	606	603	569	578	672	573	691	436	540	442	578
Pulse-rate, night	82	76	78	70	68	66	62	65	63	60	59	61	59	57	57	58	56	53	53	53
morning	72	73	72	73	74	73	70	68	67	64	64	65	63	63	61	61	59	58	57	58
Blood-pressure, lying: systolic, mm.	122	123	124	..	..	134	113	111	113	112	112	111	110	108	..	103	106	104	102	94
diastolic, mm.	90	92	93	..	..	100	80	85	85	82	85	80	81	82	..	78	80	80	76	75
Alveolar CO_2 tension, mm.	31.7	36.0	36.5	37.5	32.8	31.3	32.1	31.9	31.4	31.6	32.3	28.7	32.1	31.5	..	..	28.4	29.1	28.9	27.5
Volume of urine per day, cc	1485	1521	1528	1441	660	468	565	713	667	610	524	587	607	565	564	517	561	647	758	889
Total nitrogen in urine: gms.	17.02	15.92	14.48	11.54	7.10	8.40	11.34	11.87	10.41	10.18	9.79	10.27	10.74	10.05	10.25	10.13	10.35	10.43	8.46	9.58
Per kilo body weight (Kjeldahl) gms.	0.283	0.264	0.238	0.19	0.118	0.142	0.195	0.207	0.184	0.181	0.176	0.186	0.196	0.185	0.19	0.189	0.193	0.196	0.16	0.182
Ammonia-N, Folin method, original, gms.	..	0.67	0.65	0.59	0.41	0.60	0.95	1.4	1.6	1.67	1.52	1.62	1.7	1.57	1.56	1.47	1.51	1.57	1.43	1.91
Chlorine (Cl) in urine, gms.	..	..	..	..	3.77	1.02	0.79	0.59	0.41	0.4	0.55	0.32	0.31	0.28	0.36	0.31	0.32	0.26	0.16	0.14
β-oxybutyric acid (determined), gms.	..	..	..	..	..	0.5	2.1	3.5	2.1	3.5	2.8	1.6	3.5	3.5	1.4	2.4	4.2	4.7	1.6	5.2
Respiratory quotient: night	0.81	0.88	0.86	0.81	0.78	0.75	0.73	0.74	0.75	0.68	0.71	0.73	0.75	0.72	0.72	0.73	0.74	0.72	0.71	0.71
CO_2 produced per 24 hrs. (partly estimated), liters	..	..	..	..	286.3	281.1	271.8	255.2	252.4	237.9	237.9	235.1	233.3	222.9	218.1	220.8	212.1	214.5	204.2	201.5
O_2 consumed per 24 hrs. (partly estimated), liters	..	..	..	..	374.7	373.8	363.8	349.8	344.9	330.6	331.1	323.2	317.8	306.8	297.8	303.2	290.5	299.9	286.3	283.8
Carbohydrate katabolized per 24 hs., gms.	..	..	..	..	68.8	42.1	38.5	4.3	15.1	..	..	4.0	13.5	3.8	3.8	3.8	3.5			
Fat katabolized per 24 hrs., gms.	..	..	..	..	135	142	130	136	133	133	134	127	119	120	115	118	111	117	116	112
Protein katabolized per 24 hrs., gms.	..	..	..	..	42.6	50.4	68.0	71.2	62.5	61.1	58.7	61.6	64.4	60.3	61.5	60.8	62.1	62.6	50.8	57.5
Flesh equivalent of protein, gms.	..	..	..	..	213	252	340	356	312	306	294	308	322	302	308	304	311	313	254	287
Loss of preformed water from body:																				
Not combined with fat and flesh, gms.	..	..	..	..	585	448	350	225	166	11	−65	−47	−34	48	−202	−128	−339	−154	−80	155
Total loss, gms.	..	..	..	..	769	664	635	524	429	268	183	212	236	301	56	127	−80	108	135	396
Total calories, computed per 24 hrs.	..	..	..	..	1769	1756	1702	1626	1609	1537	1540	1503	1481	1426	1385	1410	1349	1394	1331	1319
Calories per kilo, per 24 hrs.	..	..	..	..	29.4	29.7	29.2	28.3	28.4	27.4	27.6	27.2	27.0	26.2	25.6	26.2	25.2	26.2	25.1	25.1
Total energy loss per 24 hrs., calories	..	..	..	..	1834	1845	1820	1760	1732	1653	1644	1619	1605	1537	1495	1515	1463	1505	1426	1442
Heat prduction per 24 hrs.:[1]																				
Computed from gaseous met.	1577	1541	1572	1526	1615	1555	1524	1433	1394	1349	1380	1378	1289	1277	1262	1262	1291	1222	1202	1226
Predicted from H. & B. — cal.	1478	1483	1490	1485	1471	1459	1446	1435	1427	1420	1415	1409	1402	1395	1393	1389	1387	1383	1378	1371
= % H. & B.	+7	+4	+6	+3	+10	+7	+5	0	−2	−5	−2	−2	−8	−8	−9	−9	−7	−12	−13	−11

Beginning of Fast

Observations.	Apr. 30 May 1. 17	May 1–2. 18	May 2–3. 19	May 3–4. 20	May 4–5. 21	May 5–6. 22	May 6–7. 23	May 7–8. 24	May 8–9. 25	May 9–10. 26	May 10–11. 27	May 11–12. 28	May 12–13. 29	May 13–14. 30	May 14–15. 31	May 15–16.	May 16–17.	May 17–18.
Body weight naked, kg.	51.79	51.50	51.11	50.93	50.49	50.13	49.96	49.62	49.33	49.02	48.70	48.46	48.10	47.69	47.39	47.05	47.12	48.17
Insensible perspiration per day, gms.	509	521	550	371	623	465	504	480	468	473	557	477	554	530	625			
Pulse-rate, night	52	52	52	52	54	53	56	55	55	56	57	59	58	58	57	68	64	90
morning[1]	57	56	57	58	59	59	58	59	60	61	62	61	63	59	60			
Blood-pressure, lying: systolic, mm.	101	104	96	100	98	97	97	98	99	106	100	98	103	98	101*	92	98	124
diastolic, mm.	78	79	75	77	75	73	75	80	75	79	78	75	82	79	80*	74	82	102
Alveolar CO_2 tension, mm.	28.5	28.7	27.6	26.9	28.7	27.9	27.8	26.8	27.3	28.1	27.5	27.9	28.1	27.8	31.8*	32.0	35.1	
Volume of urine per day, cc	848	657	728	699	708	785	556	750	713	728	653	655	697	771	566	414	1262	241 (22 hr)
Total nitrogen in urine, gms.	8.81	8.27	8.37	7.69	7.93	7.75	7.31	8.15	7.81	7.88	8.07	7.62	7.54	7.83	6.94	4.83	3.81	2.75 (22 hr)
Per kilo body weight (Kjeldahl), gms.	0.169	0.160	0.163	0.151	0.156	0.154	0.146	0.164	0.158	0.160	0.165	0.157	0.156	0.163	0.146	0.102	0.08	0.58 (22 hr)
Ammonia-N, Folin method, original, gms.	1.90	1.80	1.76	1.58	1.57	1.51	1.49	1.52	1.51	1.42	1.36	1.28	1.32	1.32	1.25	0.68	0.36	0.35 (22 hr)
Chlorine (Cl) in urine, gms.	0.12	0.15	0.16	0.15	0.18	0.21	0.18	0.10	0.18	0.16	0.16	0.14	0.12	0.14	0.13	0.23	0.26	0.18 (22 hr)
β-oxybutyric acid (determined), gms.	3.6	4.4	7.0	4.4	5.0	3.1	6.0	6.9	4.4	6.1	4.0	4.9	5.6	5.4	4.5	0.8	0.5	0.5 (22 hr)
Respiratory quotient; night	0.72	0.72	0.71	0.71	0.73	0.72	0.72	0.69	0.72	0.70	0.72	0.71	0.72	0.72	0.72	..	0.80	0.97
CO_2 produced per 24 hrs. (partly estimated), liters	199.0	192.5	191.1	191.1	196.5	189.1	189.1	190.9	193.2	190.3	193.3	198.0	192.0	189.6	195.5			
O_2 consumed per 24 hrs. (partly estimated); liters	279.5	270.5	271.2	269.1	274.4	265.5	264.2	269.7	269.0	267.8	269.9	276.9	268.0	266.3	275.0			
Carbohydrate katabolized per 24 hrs., gms.	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...			
Fat katabolized per 24 hrs., gms.	112	109	109	110	112	108	109	109	109	109	109	114	110	108	115			
Protein katabolized per 24 hrs., gms.	52.9	49.6	50.2	46.1	47.6	46.5	43.9	48.9	46.9	47.3	48.4	45.7	45.2	47.0	41.6			
Flesh equivalent of protein, gms.	265	248	251	231	238	233	220	245	235	237	242	229	226	235	208			
Loss of preformed water from body:																		
Not combined with fat and flesh, gms.	67	−91	7	−180	69	−2	−179	−34	−73	−55	−52	−122	4	49	−43			
Total loss, gms.	290	118	219	15	270	195	8	173	126	145	153	72	196	248	135			
Total calories, computed per 24 hrs.	1300	1257	1261	1252	1276	1235	1230	1254	1251	1246	1255	1289	1247	1239	1281			
Calories per kilo per 24 hrs.	25.0	24.3	24.6	24.5	25.2	24.5	24.6	25.2	25.3	25.3	25.7	26.5	25.8	25.9	26.9			
Total energy loss per 24 hrs., calories	1417	1361	1366	1343	1371	1328	1318	1349	1342	1336	1345	1374	1334	1326	1361			
Heat production per 24 hrs.:[1]																		
Computed from gaseous met.	1226	1159	1183	1157	1162	1142	1116	1126	1128	1133	1164	1118	1142	1109	1118			
Predicted from H. & B., cals.	1364	1360	1354	1351	1346	1340	1339	1334	1329	1325	1321	1318	1313	1307	1303			
± % H. & B.	−10	−15	−13	−14	−14	−15	−17	−16	−15	−14	−12	−15	−13	−15	−14			

End of Fast.

The above is a partial presentation of metabolism results obtained with subject L. during four days prefasting period, thirty-one days fasting, and three days postfasting period. In order to bring together comparative data for every day of the fast, it has been necessary to place in each column results which represent in the aggregate a total of thirty-six hours, each single result, however, being either taken at the end of twenty-four hours or representing a total for twenty-four hours. The results recorded on the thirty-first day, to which an asterisk has been affixed, were as a matter of fact, obtained a short time after the first food had been taken. In no series of derived tables is it possible to draw complete comparisons of the various factors of metabolism, and this can be done satisfactorily only when all of the data are grouped together. All of the data obtained with this subject have therefore been summarized in one large table. From Publication No. 203 of the Carnegie Institution of Washington.

[1] Observations on morning following each designated day.

above, Shaffer[1] has computed the ketogenic-antiketogenic derivative from fat, protein and carbohydrate. Taking 874 as the molecular weight of the mixed body fat one may calculate that 1 gram of such mixed fat can give rise to $\frac{1}{874} \times 3$ (molecules of fatty acid in 1 molecule fat) = 0.00343 gram molecule of ketogenic fatty acid × 102 (molecular weight of aceto-acetic acid) = 0.35 gram of aceto-acetic acid. Notable quantities of β-oxybutyric acid, however, can also be formed from protein, since leucine, phenylalanine, and tyrosine have been found to be convertible into acetone bodies. Each gram of urinary nitrogen according to Shaffer is equivalent approximately to 0.01 gram molecule of ketogenic substance, or if multiplied by 102 to 1.02 grams of aceto-acetic acid. It is interesting that those amino-acids of the protein molecule which lead to the production of β-oxybutyric acid do not produce sugar, and conversely, that those which lead to the formation of sugar produce no β-oxybutyric acid.

To offset these ketogenic factors are the antiketogenic derivatives of the diet. These are the carbohydrates *par excellence*. Shaffer writes "until the active derivative of glucose is known we may assume that 1 molecule of monosaccharide is equivalent to 1 molecule of the active derivative, and on this basis the antiketogenic value of carbohydrate in terms of molecules of glucose. Each gram of glucose would thus be equivalent to $\frac{1}{180}$ = 0.00556 gram molecule; and each gram of starch to $\frac{1}{162}$ = 0.00618 gram molecule.

TABLE 159.—THE ACIDOSIS OF A FAT WOMAN DURING THREE PERIODS OF FASTING (FOLIN AND DENIS).

Day.	Acetone, gms.	Diacetic acid, gms.	β-oxybutyric acid, gms.	NH_3N, gms.	Titrated acidity, c.c.	Acetone in expired air per hr., mgms.	Remarks.
1	0.04	0.27	0	0.41	230	0	Feeling well.
2	0.08	1.42	2.90	0.73	250	5.2	Slight headache.
3	0.10	1.57	17.94	1.87	508	24.0	Severe headache.
4	0.88	2.46	18.47	2.50	695	49.5	Headache, nausea, and dizziness.
15	0	0	0	0.31	180	0	Feeling well.
16	0.02	0	0	0.37	290	0	Feeling well.
17	0.03	1.17	0.17	0.53	335	30.0	Feeling well.
18	0.35	1.16	5.44	1.01	595	32.0	Slight headache, nausea.
19	0.40	1.15	13.54	1.50	655	45.0	Headache, nausea, and dizziness.
24	0	0	0	0.50	145	0	Feeling well.
25	0	0	0	0.37	160	0	Feeling well.
26	0.04	0.37	0.18	0.51	210	66.0	Feeling well.
27	0.20	1.36	17.34	0.81	300	24.0	Headache, nausea.

[1] Shaffer: Jour. Biol. Chem., 1921, **47**, 456.

TABLE 160.—CHANGES IN CO_2-COMBINING CAPACITY, CO_2 TENSION, AND REACTION OF ARTERIAL BLOOD AFTER EXERCISE. BARR, HIMWICH, AND GREEN.[1]

Subject.	Date.	Amount of work.	CO_2 capacity at 40 mm.			CO_2 tension of arterial blood.			pH.		
			Before.	After.	Difference.	Before.	After.	Difference.	Before.	After.	Difference.
(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)	(12)
	1922	kgm.	vol. per cent.	vol. per cent.	vol. per cent.	mm. Hg.	mm. Hg.	mm. Hg.			
M. L.	Apr. 7	3,285	46.2	31.9	14.3	47.5	44.5	3.0	7.28	7.11	0.17
N. P. L.	Nov. 15	3,595	46.3	34.7	11.6	43.2	40.2	3.0	7.30	7.17	0.13
J. McL.	" 30	3,605	48.4	32.6	15.8	45.2	39.5	5.7	7.30	7.15	0.15
P. R.	Dec. 10	3,695	45.0	26.2	18.8	41.3	40.0	1.3	7.29	7.04	0.25
J. E.	Nov. 2	3,700	42.7	27.9	14.8	42.0	30.5?	11.5?	7.28	7.12?	0.16?
H. B. R.	Apr. 12	3,500?	46.8	35.7	11.1	43.0	36.5	6.5	7.30	7.22	0.08
D. P. B.[2]	Aug. 8	3,770	49.2	32.9	16.3	36.5	23.0	13.5	7.36	7.27	0.09
H. E. H.	Mar. 29	3,055	48.4	40.9	7.5	46.0	40.7	5.3	7.29	7.25	0.04
H. E. H.[2]	Aug. 25	3,545	47.9	39.3	8.6	46.5	44.0	2.5	7.28	7.21	0.07
H. E. H.	Apr. 5	3,954	50.2	32.5	17.7	49.0	38.3	10.7	7.29	7.15	0.14

Protein is assumed by Shaffer to be converted into glucose by the diabetic according to the D : N ratio to the extent of approximately 3.6 grams for each gram of nitrogen. . . . One gram of urine nitrogen would then correspond to $\frac{3.6}{180} = 0.02$ gram molecule of glucose.

A third probable source of antiketogenic substance is the glycerol of fat, though the evidence is perhaps not conclusive. Thomas[3] assumed that 40 per cent turned to carbohydrate and burned as such. Its antiketogenic value, calculated in terms of glucose, is as follows: One gram of fat $= \frac{1}{874} = 0.00114$ grams molecule fat $\div 2$ $= 0.00057$ gram molecule of glucose from glycerol.

The above calculations are summarized below:

Ketogenic substance expressed as gram molecules of precursors of aceto-acetic acid.

(*a*) 1 gram of fat $= \frac{3 \times 1}{874} =$ 0.00343 mol.

(*b*) 1 gram of urine nitrogen $=$ 0.01 mol.

Antiketogenic substance expressed as gram-molecular equivalents of glucose.

(*c*) 1 gram of urine nitrogen $= \frac{3.6}{180} =$ 0.02 mol.

(*d*) 1 gram of glucose from carbohydrate $= \frac{1}{180} = 0.00556$ mol.

(*e*) 1 gram of fat $= \frac{1}{874} \div 2 =$ 0.00057 mol.

[1] Barr, Himwich and Green: Jour. Biol. Chem., 1923, **55**, 495.

[2] Sodium fluoride, 0.1 per cent, used to protect blood against acid changes.

[3] Thomas, H. M.: Johns Hopkins Bulletin, 1924, **35**, 201.

The sum of the values of (*a*) and (*b*) divided by the sum of the values of (*c*), (*d*) and (*e*) gives the ratio of ketogenic to antiketogenic substance for the mixture metabolisms, and if the general conception is correct, this ratio should determine whether or not the subject will form and excrete acetone bodies."[1]

The first ratio of Shaffer[2] was based on the principle that 1 molecule of glucose would be ketolytic for 1 molecule of fat, but later he concluded that each molecule of glucose is ketolytic for 2 molecules of aceto-acetic acid if there is a large excess of keto molecules. If one wishes to be on the safe side, however, it is better to adhere to the original ratio. The ratio of Woodyatt is described on page 524. DuBois[3] gives a clear concise statement of the whole question with literature. In general the work of other authors has substantiated Shaffer's and Woodyatt's working theories.

The amount of acid formed is considerable and far more than physicians realize. Benedict's fasting subject did not excrete in the thirty-one days of the fast over 7 grams β-oxybutyric acid in any twenty-four hours, but the fat subject of Folin and Denis excreted 18.4 grams on the fourth fasting day, and Forsner[4] by forcing up the limits of fat in the diet obtained an excretion of 42.8 grams of acid bodies in one day. S. R. Benedict[5] obtained 32 grams when he depleted glycogen storage with phloridzin. It is in diabetes, however, that the excretion of ketone bodies reaches extremes. Thus, Case No. 4, male, onset at fifteen years of age, without diabetic heredity, three years and two months later, excreted during three successive days of coma, 437 grams β-oxybutyric acid as calculated from β-oxybutyric acid and diacetic acid extracted from the urine. This large quantity is nearly the maximum found in the literature. It is equivalent to the elimination of 3 grams β-oxybutyric acid per kilo body weight daily for three days for an individual weighing 50 kilograms, or if the acidity is expressed in terms of hydrochloric acid, approximately 1 gram of hydrochloric acid per kilo each twenty-four hours. It is, therefore, not strange that the kidneys which bear the brunt of excretion of this acid show "showers of casts." Naunyn estimates the quantity of β-oxybutyric acid in the tissues of a patient near coma at between 200 and 300 grams and Bock, Field and Adair[6] the total acid in the form of diacetic acid in one patient recovering from coma at 103 grams.

[1] Shaffer: Jour. Biol. Chem., Loc. cit., p. 305.
[2] Shaffer: Jour. Biol. Chem., 1922, **50**, xxvi; **54**, 399.
[3] Du Bois: Loc. cit., p. 264.
[4] Forsner: Skandin. Arch. f. Phys., 1910, **23**, 305.
[5] Benedict: Proc. Soc. Exp. Biol. and Med., 1914, **11**, 134.
[6] Bock, Field and Adair: Jour. Metab. Research, 1923, **4**, 27.

(*b*) **The Percentage Relation of Acid Bodies to One Another.**—The interrelation of acetone, diacetic acid, and β-oxybutyric acid to one another must be very intimate. Neubauer[1] considers that there is a reversible action between diacetic acid and β-oxybutyric acid, and that these readily change back and forth with one another. It is thought by some that there is a fixed proportion between these acids, varying with different patients but constant in the same patient. Folin[2] is inclined to doubt the existence of preformed acetone in the body, but explains its presence in the urine as a decomposition product of diacetic acid. At any rate, acetone seldom constitutes over a small percentage of the total acidosis, and acetone and diacetic acid combined not over 30 per cent.

(*c*) **Mode of Elimination of Acid Bodies.**—Practically all the acid bodies of the β-oxybutyric acid are eliminated by the kidneys. Only one of these—acetone—is excreted by the lungs, and the amount must be small. In experiments upon a healthy man following the feeding of oleic acid, I obtained an excretion of 0.847 gram acetone calculated for the twenty-four hours in the breath. The method of estimation of the acetone in the breath was not very satisfactory, and it would be advantageous to institute a series of experiments of this nature on a larger scale. The other two bodies are excreted as salts and even as free acid in the urine. Magnus-Levy[3] found that the concentration of these acids in the urine seldom rose above 1.5 per cent, and except in coma he never encountered values greater than 0.6 per cent. It is evident, therefore, that the elimination of the acid bodies is closely connected with the quantity of water excreted. β-oxybutyric acid circulates in the blood combined with alkali as a salt, but the acid is excreted in the urine to a large extent as free acid and the base retained in the body. It is only when much alkali is given that the large quantities of β-oxybutyric acid, such as were excreted by Case No. 4 during coma, are found.[4] I do not, however, remember data in the literature which show an increased elimination of acid bodies following the administration of alkalis to a normal individual with experimental acidosis. Such would be valuable.

It would be wrong to consider, however, that the only means the body has by which to free itself of acid is by the kidneys. The body has a most efficient pathway in the lungs through which carbonic acid is constantly removed from the body. In fact, so soon as this acid begins to increase in the tissues, being displaced

[1] Neubauer: Verhand. d. Kong. f. inn. Med., 1910, **27**, 566.
[2] Folin: Jour. Biol. Chem., 1907, **3**, 177.
[3] Magnus-Levy: Arch. f. exp. Path. u. Phar., 1899, **42**, 200.
[4] Joslin: Jour. Metab. Research, 1921, **1**, 306.

by the stronger β-oxybutyric acid, it also rises in the blood; this stimulates the respiratory center with resulting hyperpnea and the excess of carbonic acid is removed by the increased ventilation. The total quantity of carbon dioxide for the twenty-four hours is not increased save for the increase due to the increased metabolism which accompanies acidosis, and indeed the percentage of carbon dioxide in the alveolar air is actually diminished because it is diluted in consequence of the increased ventilation.

Carrasco[1] writes: "In truth, while acidosis is developing, or its intensity rising, the amount of CO_2 eliminated in unit time rises independently of any increase in metabolism, so that if this is not kept in mind, the data obtained from the study of the respiratory metabolisms *at that time* gives a false impression of the respiratory quotient. On the other hand, the decrease of CO_2 tension in the alveolar air does not depend exclusively on the greater dilution of this gas as a result of better ventilation, but also and primarily on the fact that the tension of CO_2 in arterial blood, with which that in alveolar air is in equilibrium, is low, because the carbonic acid has been partly dispossessed of its salts in the blood by the action of organic acids in the blood."

(*d*) **Safeguards of the Body Against Acidosis.**—The body is admirably protected against danger from acidosis. Proof of this exists in its storage of glycogen. If sufficient exists there will be no need to call upon excessive katabolism of fat for body needs. Since in diabetes there is little glycogen in storage and the carbohydrate which is eaten is often lost to the metabolism, one should never cease to attempt to build up a storage of glycogen by the diet, and insulin.

If the diet of the diabetic individual is unrestricted, he often eats so large a quantity of carbohydrate-forming material that enough of it is oxidized to prevent excessive metabolism of fat. Thus Case No. 295, male, onset at sixteen years, seven years later excreted 10,000 cc. of urine containing 680 grams of sugar, and yet failed to show a positive reaction for diacetic acid. When the carbohydrates in his diet were restricted to even 280 grams, acidosis appeared; when the diet was still further restricted, the acidosis became extreme. By devices such as this the diabetic may survive for a time, but the disease advances. In this way, Case No. 1887 and Case No. 1456 were kept alive, but I know of few others. The whole aim of diabetic treatment is to protect the patient by promoting by every means in our power the combustion of carbohydrate and preventing the excessive and defective katabolism of fat.

Other factors of safety are available to thwart acidosis, and these

[1] Carrasco Formiguera: Joslin: Tratamiento de la Diabetes Sacarina, Montaner y Simon, Barcelona, 1925, p. 315.

factors are of a more general type since they offset acidosis of any origin. They represent symptomatic rather than etiological therapy. For their proper understanding a discussion of the maintenance of the normal alkalinity of the body is desirable.

"Any modification of the normal equilibrium between acids and bases within the organism whereby the power to neutralize acid is diminished is to be regarded as a condition of *acidosis*."[1] The formation of acid never goes on to such a degree that the blood shows an acid reaction. Such a condition is incompatible with life. In fact, so constant is "the reaction of the blood that a change from the reaction of ordinary tap water, which is more alkaline than the blood, to that of distilled water, which is much more acid than blood, would be fatal." If the blood were acid, the carbonic acid would be displaced from its combination with an alkali by the stronger β-oxybutyric acid and set free in every cell of the body, and no alkali would be available to combine with it and take it back to the lungs for elimination. The normal blood and respiratory exchange is represented by the following formula: $2NaHCO_3 = Na_2CO_3 + CO_2 + H_2O$.

The above formula clearly shows how easy it is for β-oxybutyric acid, which is stronger than carbonic acid, to seize upon free alkali and thus hamper the removal of carbonic acid from the tissues.

"What is essential and common to all conditions of acidosis is a depletion of the alkali of the body. This involves at least a diminution of the bicarbonates of the blood, and in severe cases it probably involves the draining away of very large quantities of alkali from many sources.

"Nothing is simpler than the process by which this condition is established. If an acid is poured into an aqueous solution of carbonic acid in equilibrium with the air, to which a certain amount of a bicarbonate has previously been added, the acid will react, according to its concentration and avidity for base, to a greater or less degree with the bicarbonate, forming in due amounts its own salt and free carbonic acid, which must escape into the air, since the solution is already in equilibrium with the carbonic acid of the atmosphere. Thus, for instance, a solution of sodium bicarbonate to which half of the equivalent amount of hydrochloric acid has been added will in the course of time contain just as much free carbonic acid as it did before and just half as much bicarbonate. Now the laws governing the equilibria between acids and bases determine the fact that it is in like manner *chiefly bicarbonates which react with acids introduced into the blood*, and when the resulting carbonic acid has been liberated by the lung the result is very

[1] Henderson: Trans. Assn. Am. Phys., 1916.

similar to that of the simple chemical experiment. It is to be observed, however, that the respiratory process tends, under these circumstances, to eliminate more than the newly liberated carbonic acid; the tension of carbonic acid in the blood is thus diminished nearly in proportion to the diminution of bicarbonates, and since the hydrogen-ion concentration is proportional to the ratio of the free carbonic acid to the bicarbonates, the degree of alkalinity of the blood is unchanged by the introduction of acid—hence the theory that the hydrogen or hydroxyl ion is the hormone of respiration—*but the equilibrium is changed.*

"Carbonic acid is constantly being formed in the tissues and being removed from the tissues where its concentration is highest by the bicarbonates of the blood as shown by the above formula and is taken to the pulmonary alveoli where it is set free. If the CO_2 accumulates too rapidly in the tissues and blood, hyperpnea or increased pulmonary ventilation appears as a result of the stimulation of the respiratory center, which is extraordinarily sensitive to decreased alkalinity. Hyperpnea is the best clinical sign of acidosis. As a result of the hyperpnea the CO_2 may be reduced. By this process of removal of CO_2 by the lungs alkali is left available to neutralize the offending β-oxybutyric or other acid which can then be eliminated through the kidneys. $NaHCO_3 + CH_3.CHOH.CH_2.COOH = CH_3CHOH.CH_2COONa + H_2O + CO_2$. The β-oxybutyric can then be removed by the kidneys and the CO_2 by the lungs, but in the process considerable alkali is lost.

Howland[1] describes admirably another phase of the maintenance of normal blood alkalinity. "If the bicarbonates of the plasma were the only method of defense of the body the organism would succumb to acidosis as soon as the bicarbonate was depleted by the excretion of neutral salts through the kidneys; every molecule of an acid would rob the body of a molecule of bicarbonate." This involves another mechanism "by which acids may be removed, leaving behind part of the base with which they have been combined, this base being available for further neutralization. The elimination is by the way of the kidneys. These have the capacity to excrete an acid urine from a nearly neutral blood. They remove acid phosphate and save base with each molecule of acid phosphate that they excrete. Thus, although alkali is eliminated in the urine, it is much less than would be the case without this specialized kidney activity, and can readily be replaced under normal circumstances by the alkali of the food. For instance, with the introduction of a foreign acid $-Na_2HPO_4 + HCl = NaCl + NaH_2PO_4$ —the hydrochloric acid is neutralized, the sodium chloride and acid sodium phosphate

[1] Howland: Johns Hopkins Hospital Bull., 1916, **27**, 63.

are excreted by the kidneys or the following reaction may take place—$Na_2HPO_4 + H_2O + CO_2 = NaH_2PO_4 + NaHCO_3$. By his method the sodium bicarbonate reserve of the body is renewed.

"Henderson and Palmer showed the magnitude of alkali sparing very prettily by titrating with alkali the acid urine back to the normal reaction of the blood. The alkali spared was found in normal subjects to vary in terms of tenth-normal alkali, between 200 and 800 cc. This is equivalent to saying that the kidneys eliminate from 200 to 800 cc. of tenth-normal acid in twenty-four hours."

The large amount of alkali stored in the body is another safeguard against acidosis. Not only are sodium and potassium present in considerable quantities, but in emergency the organism can fall back upon the calcium and magnesium of the bones. Gerhardt and Schlesinger[1] originally pointed out that these alkalis met an attack of severe acidosis by changing their path of excretion from the bowels to the kidneys, in this manner removing β-oxybutyric acid. In a study of the urine of Case No. 4 during coma,[2] McCrudden found unusually large quantities of calcium and magnesium excreted in the urine. Whereas 40 per cent of the magnesium is normally excreted in the feces, in Case No. 4 during three days 0.55 gram was found in the urine, but only 0.15 in the feces. Similarly, 2.03 grams calcium appeared in the urine, but 0.75 gram were eliminated by the intestinal tract.

The elimination of nitrogen in the form of ammonia instead of urea, as in health, is still another important, and indeed a most remarkable means of defense of the body against acidosis. How efficiently Nature works is evident when it is realized that 1 gram of ammonia (NH_3 molecular weight 17) can neutralize five times as much β-oxybutyric acid as 1 gram sodium bicarbonate ($NaHCO_3$ molecular weight 84). The formation of ammonia has been shown by Bliss,[3] to be a generalized tissue phenomenon. Just as acid production goes on throughout the body so does ammonia formation accompany it.

Finally, the proteins constitute a means of protection. They have the power to unite with both acids and alkalis. Their part in the prevention of acidosis needs further investigation.

2. **Acidosis in Diabetes.**—(*a*) **Extent of Acidosis in Mild, Severe, and Extreme Cases.**—A moderate acidosis represented by the excretion of 5 to 10 grams β-oxybutyric acid, the elimination of 2 grams ammonia, or a fall of carbonic acid in the alveolar air to 4 per cent, or 29 mm. mercury may or may not be harmful to an

[1] Gerhardt and Schlesinger: Arch. f. Path. u. Phar., 1899, **42**, 106.
[2] Joslin: Jour. Med. Research, 1921, **1**, 306.
[3] Bliss: Jour. Biol. Chem., 1926, **67**, 109.

individual, but it is a sign of danger. When the quantity of acid present is double this amount, diabetic patients invariably show that they are burdened with disease, but it would be unfair to attribute this state to the acidosis alone, and not to the neglected disease itself. In former days, when the acidosis of patients was not controlled, over and over again I saw diabetic cases who carried an acidosis of 4 grams ammonia for years, with only gradually declining health. Even so extreme a case of diabetes as Case No. 344, eight years after onset showed 51.5, 52, and 54.8 grams β-oxybutyric acid respectively on four different days, and yet travelled safely for thousands of miles, dying of tuberculosis without coma four months later. But it may be considered that the acidosis is very severe whenever β-oxybutyric acid reaches an excretion of 30 grams in twenty-four hours, the ammonia 5 grams, or when the carbon dioxide tension of the alveolar air is 3 per cent the equivalent of a pressure of 22 mm. Hg. or the volume per cent of CO_2 in the blood under 30. When the volume per cent of CO_2 falls below 20, coma is present or imminent.

(*b*) **The Danger from Acidosis** varies according to the rapidity of onset, the age of the patient and the condition of the kidneys. It is my impression that fatal coma may result from an acidosis of only moderate degree which has come on suddenly, whereas in another individual the gradual development of an acidosis of equal severity has been borne with comparative ease. The cases of coma which are relieved by prompt treatment are generally cases in which a moderate acidosis has suddenly appeared as the result of some temporary cause, such as excess in food either endogenous or exogenous, often as a result of an infection which in turn has rendered insulin inert, perhaps as Lawrence and Buckley[1] think through stimulation of the thyroid and adrenal glands.

Children and adults under the age of forty years withstand acidosis better than older patients. Goodall and Joslin[2] found that the former group of patients tolerated an acidosis estimated in terms of ammonia of 4 or 5 grams far better than the latter group bore an acidosis represented by 2.5 to 4 grams ammonia. This was due, in our opinion, to the greater vulnerability of the kidneys of older people. The sound kidneys of young people readily excreted the acid, but the kidneys of the elderly or diseased kidneys in any individual excreted the acid with difficulty, and a trifling acidosis in such individuals might lead to serious results. Carrasco[3] emphasizes the good results which follow the appropriate

[1] Lawrence and Buckley: Brit. Jour. Exp. Path., 1927, **8**, 58.
[2] Goodall and Joslin: Boston Med. and Surg. Jour., 1908, **158**, 646.
[3] Carrasco Formiguera: Joslin: Tratamiento de la Diabetes Sacarina, Montaner y Simon, Barcelona, 1925, p. 319.

treatment of even a mild acidosis in the aged and arteriosclerotic. Tileston and Comfort have shown from investigations upon the non-protein nitrogen in the blood of children and the phenolphthalein test that the secreting capacity of the child's kidney was better than that of an adult.[1] Harmful acidosis occurred in Case No. 347, first seen in 1910, male, aged fifty-one years, with an onset sixteen months before. He was discharged from the hospital sugar-free with no acidosis, but the urine contained a little albumin, the blood-pressure was 175 mm. mercury, and the heart extended half-way to the anterior axillary line, the liver three fingerbreadths below the costal margin and the spleen palpable. The patient, as is often the case with diabetic adults on diet, upon his own initiative still further restricted the quantity of carbohydrate which he was allowed, thus forcing the katabolism of fat, an acidosis developed, and with it marked albuminuria; both rapidly increased. Cardiac weakness ensued and coma gradually developed from which he was unable to recover.

(*c*) **Culmination of Acidosis in Coma.**—The effects of extreme acidosis artificially induced in normal individuals are very suggestive of the beginning symptoms of coma in diabetic patients. Such experiments show the relation of acidosis to coma quite as effectually as the coma which Walter[2] originally produced in animals by the injection of hydrochloric acid. It is impossible to state how much β-oxybutyric acid and its allied bodies are necessary to produce coma. There are probably wide variations depending on the storage of carbohydrate, protein, alkalis and water, as well as upon the ability of the cardio-renal system to excrete the acid when formed. In some cases, like Case No. 4, large quantities of acid are excreted, but undoubtedly more often large quantities are retained.

Diabetic coma usually creeps on so insidiously that unless one is in the habit of treating diabetic patients it may be overlooked until all at once its spectacular features—anxiety and exaggerated respiration with the absence of cyanosis—stare one in the face. The onset can be traced to some change by which less carbohydrate, but more protein and especially more fat enters into katabolism by design or accident. In one instance, marked nervous excitement on the part of the patient appeared to play a great role, but I think the accompanying refusal of food and later vomiting made this case, also, one of sudden carbohydrate restriction and excess fat katabolism. Typical examples of the onset of coma are Cases Nos. 310, 252, 220, 836 and 729. Case No. 310, who had had diabetes twenty-one years, showed a moderate acidosis over a period of months, then

[1] Tileston and Comfort: Am. Jour. Dis. Child., 1915, **10**, 278.
[2] Walter: Arch. f. exp. Path. u. Pharm., 1877, **7**, 148.

sailed for Europe, became seasick, was unable to retain food, and in three days died of coma. Case No. 252, while upon a rather more restricted diet than usual, nine years after onset, underwent exceptional exertion and coma developed. Case No. 220, having lived comfortably for years despite a severe acidosis, had a gastro-intestinal attack, was much debilitated, the diet was disarranged, and coma followed. Case No. 836 after suffering with diabetes for only three months, travelled several thousand miles, and during the latter part of the journey acquired diphtheria; on my first visit (eight hours before death) this was discovered, and along with it diabetic coma. (Compare the recent work of Lawrence and Buckley[1] on the inactivation of insulin by diphtheria toxin.) Case No. 729, a severe diabetic, three months after her last visit to me, without my knowledge, was taken to a dentist's office, given ether[2] by her physician, and had all her teeth extracted. This was on Monday; she was taken home, became unconscious Wednesday, and died on Friday.

E. CAUSES OF DEATH.

1. **Preamble.**—The scenes are shifted and the actors changed. No longer is the setting Youth and the villain Coma, but the stage is arranged for an Old Age act and an old actor named Arteriosclerosis, renowned for the multiplicity of his roles. Coma was cunning and clever and oft secured his shining mark, but Knowledge and Education now thwart him where formerly Chance failed. Arteriosclerosis is almost always successful if he is given time, but he, too, is somewhat restrained by Knowledge and Education and has been persuaded now and then to consent that Old Age shall end the play. For what he was rather than for what he is, the first place in a discussion of causes of death in diabetes is still given to Coma, chiefly to point out that this villain should no longer be permitted to take any part, because Knowledge and Education have been joined by Insulin.

The above are not fantastic words. They truly portray the change which has taken place in the causes of death in diabetes. They may not apply to all diabetics, but they hold for diabetics in hospitals. So completely have the causes of death altered that in a consideration of the same one finds it necessary to be governed almost entirely by data assembled since the introduction of insulin. Coma and arteriosclerosis, however, are so important and so frequently preventable, the latter particularly when it takes the form

[1] Lawrence and Buckley: Brit. Jour. Exp. Path., 1927, **8**, 58.

[2] The blood sugar is increased during the administration of ether, according to Atkinson *et al.* Atkinson *et al.*: Jour. Biol. Chem., 1922, **52**, 5.

of gangrene, that they merit all the emphasis laid upon them in the past. A more detailed treatment of these complications will be found in later pages 659 and 692.

Seventeen hundred and fifty-six of my diabetic patients had died by July 1, 1926. Their causes of death are recorded in Table 161, and to allow a proper interpretation are grouped into three periods. These periods or eras are justified, because each represents a predominant type of treatment. First was that of Naunyn, which

TABLE 161.—CAUSES OF DEATH IN DIABETES

	Author							
	Von Noorden		Naunyn Era 1894–June 1914.		Allen Era June 1914–Aug. 1922.		Banting Era Aug. 1922–July 1926.	
	No.	%	No.	%	No.	%	No.	%
Total deaths	...		342		805		609	
A. Coma present	169	58	208	60.8	338	42.0	122	20.0
Coma incidental to other diseases	...		8	2.3	31	3.9	22	3.6
B. Coma absent	123	42	134	39.2	467	58.0	487	80.0
1. Cardiorenal, vascular, total	40	14	45	13.1	166	20.6	207	34.0
Cardiac	11		20		84		127	
Nephritis	9		12		29		32	
Apoplexy	19		9		37		36	
Arteriosclerosis	1		4		16		12	
2. Infections, total	18	6	29	8.5	145	18.0	163	26.8
Pneumonia	8		13		54		53	
Bronchitis	...		...		2			
Influenza	...		1		25		3	
Erysipelas	...		1		...		2	
Pertussis	...		...		1		2	
Meningitis	...		...		1		5	
Diphtheria	...		...		1			
Tonsillitis	...		...		...		1	
Acute abdominal	...		...		...		4	
Pancreatitis	...		...		...		1	
Gall stones	...		...		1		2	
Appendicitis	...		2		3		3	
Carbuncle	3		4		10		6	
Abscess: Mastoid	...		...		1			
Lung	...		...		1			
Liver	...		...		1			
Gall-bladder	...		...		1		2	
Paranephric	...		...		1			
Gangrene, sepsis	7		8		41		77	
Gas bacillus	...		...		...		1	
Multiple infections	...		...		1		1	
3. Tuberculosis, total	14	5	16	4.7	37	4.6	32	5.3
Pulmonary	...		16		36		32	
Miliary	...		...		1			
4. Cancer, total	12	4	9	2.6	27	3.4	30	4.9
Face	...		1		...		1	
Thyroid	...		...		...		1	
Tongue	...		...		...		1	
Larynx	...		...		...		1	
Esophagus	...		1		...		1	

TABLE 161.—CAUSES OF DEATH IN DIABETES.—(*Continued.*)

	Von Noorden		Author.					
			Naunyn Era 1894–June 1914.		Allen Era June 1914–Aug. 1922.		Banting Era Aug. 1922–July 1926.	
	No.	%	No.	%	No.	%	No.	%
Stomach	...		3		2		1	
Intestine	...		...		1		2	
Rectum	...		...		1			
Peritoneum	...		...		1			
Liver	...		2		8		3	
Pancreas	...		...		5		6	
Kidney	...		1		...		1	
Bladder	...		1		3		3	
Prostate	...		...		2		2	
Breast	...		...		3		3	
Uterus	...		...		1		1	
Lymphoblastoma	...		...		...		1	
Location?	12		...		...		2	
5. Inanition	...		1	0.3	18	2.2	2	0.3
6. Miscellaneous, total	39[1]	13	34	10.0	74	9.2	53	8.7
Pernicious anemia	1		2		...		1	
Ulcer: Gastric	1		...		...		2	
Duodenal	...		...		1		2	
Cirrhosis	3		...		3		6	
Enlarged prostate	...		...		1		3	
Hyperthyroidism	...		...		...		3	
Insanity	...		...		3		1	
Myelitis	...		...		...		1	
Suicide	...		1		2		5	
Accidental	...		...		5		11	
Insulin reaction	...		...		...		1	
Old age	...		2		...		1	
Unknown	...		18		6			
Diabetes	...		11		53		16	

extended from 1898, save for 2 earlier cases, until June, 1914; second that of Allen, with emphasis laid upon undernutrition, and this lasted until August, 1922; the third began with Banting and the use of insulin. For comparison I have inserted data from Von Noorden.

In the Naunyn Era coma was all important, and the habit was then established of the division of all diabetic deaths into those with coma present, meaning acidosis, and those with coma absent. The dividing line is not always easy. Attention is called to the greater reliability of tabulations in the Banting Era. The number of cases under such indefinite headings as *bronchitis*, *inanition*, *unknown*, and the bare title *diabetes* is reduced.

So protean in character have the causes of death in diabetes become that real danger exists that diabetes itself as a cause of death will disappear largely from the death certificate. The ten-

[1] Detailed diagnosis of 34 of von Noorden's non-coma cases in this group is omitted.

dency to this will be progressive because of arteriosclerosis. Angeline Hamblen of the Massachusetts State Board of Health tells me that an analysis of 340 death certificates for the first six months of 1927 reveals that by the recognized rules of the International Reports of Deaths 11 per cent of the diabetic deaths in Massachusetts, exclusive of Boston, go unrecorded. This does not occur in statistics privately compiled, and this adds to their importance. Private statistics disclose the causes of death of all diabetics and thus give the true and final picture of the disease.

(*a*) **Deaths With Coma.**—Twenty per cent of the 609 deaths in the Banting Era ending July, 1926, have been due to coma. Formerly the deaths of all the children, 87 per cent of the deaths during the first year of diabetes, and in the Naunyn Era as high a percentage as 61 per cent of the 342 deaths, were due to coma. This fell to 42 per cent of the 805 deaths in the Allen Era, June, 1914, to August, 1922. In the years ending July 1, 1926, and July 1, 1927, respectively 10 per cent and 0 per cent of the fatalities were due to coma. Ten per cent is the percentage which holds for the mortality among Jews since the introduction of insulin, August, 1922. Best of all, in the two years ending July 1, 1927, there have been but 7 deaths among 245 children, and, although 6 of these were due to coma, the total mortality for children is but 3 per cent in contrast to 1916 when there was a yearly mortality among young and old of 10 per cent. If as many cases had succumbed to coma in the Allen and Banting Eras as in the Naunyn Epoch, the deaths from coma would have been 863 instead of 460. Insulin and the newer knowledge of diabetes which has come in its train have saved the lives of 403 of my patients from a coma death.

Coma is still needless and today is universally so regarded, although in June, 1922, when this statement was made in public[1] it was received here with incredulity and in Germany with criticism.[2] In 1926 coma and cancer killed the same number of patients, 6 each from among the 1138 cases treated. None of these patients died in a hospital. If deaths from coma can be abolished in the hospital, they should be abolished in the home. When one sees the word coma on a death certificate, there is reason for hope, because coma is curable whereas many complications of diabetes are not.

No death from coma took place among the 1241 cases traced of the 1329 treated July 1, 1926 to July 1, 1927.

(*b*) **Deaths Without Coma.**—1. *Cardio-renal and Vascular.*—When patients ceased to die of coma, they lived to die of arteriosclerosis. In the Naunyn Era the average age at death was 44.8 years; in the

[1] Joslin: Shattuck Lecture, Boston Med. and Surg. Jour., 1922, **186**, 833.
[2] Von Noorden: Loc. cit., p. 325.

Banting Era it is 54.2 years. It is not surprising that arteriosclerosis has advanced to first place as a cause of death, because the average diabetic is growing old. If one includes all the cases classified as cardio-renal-vascular and gangrene under this heading, it is responsible for 47 per cent of the total deaths now in contrast to 16 per cent in the Naunyn Era. It would be a shame if this distressing complication must continue to increase. Fortunately in diabetes there is more chance of its prevention than has been usually supposed. The subject is treated in detail on page 675. Irrespective of the possibility of the prevention of arteriosclerosis as a whole there is a certainty that it can be prevented to large degree in the form in which it has been so fatal to diabetics in the past, namely, gangrene. Can one not also derive hope from the fact that 87 per cent of the diabetics at autopsy who have gall-stones show arteriosclerosis, too? It is time to talk more of the prevention of gall stones than of operations for their removal, but one should prevent the deposit of cholesterol in the arteries as well as in the gall-bladder.

The most usual form for the arteriosclerosis to take is that which affects the heart. More than one-fourth (127) of all the non-coma deaths since August, 1922, were due to heart disease. Coronary thrombosis is the common type and symptoms of angina pectoris are those most frequent. Disease of the heart in diabetes is practically confined to some form of arteriosclerosis. Next to the heart stand the legs as a site of arteriosclerosis. If to the 12 cases under the heading arteriosclerosis, Table 161, we add the 77 cases of gangrene, a total of 89 deaths is reached. Nephritis caused 32 and apoplexy 36 deaths. Thus combined they are less than the number of gangrene cases. Possible reasons for the much more rapid increase of arteriosclerosis of the heart and extremities, in contradistinction to that of the head, apoplexy, is elsewhere discussed. See pp, 402, 689.

2. *Infections*—The advent of an infection lowers the tolerance of a diabetic for carbohydrate and thus increases the severity of the disease. This is an old clinical fact which Lawrence and Buckley confirmed in animals with diphtheria toxin.[1] In the Banting Era meningitis claimed 5, acute abdominal disease 4, influenza 3, erysipelas and whooping cough 2 each, and tonsillitis 1. It is astonishing how well diabetic patients do following operations upon the tonsils or mastoid. Both D. Crosby Greene and Lyman Richards have told me that the diabetic patients get along more satisfactorily than non-diabetics. Gall stones and disease of the gall-bladder each caused the death of 2 cases, an extraordinarily small number, appendicitis 3 cases, carbuncle 6 cases, and a gas bacillus infection, pancreatitis, and multiple infections were responsible

[1] Lawrence and Buckley: Brit. Jour. Exp. Path., 1927, 8, 58.

for 3 more cases. Doubtless there were other instances of infection, but their diagnoses were merged with deaths from coma. Some years ago Professor John P. Peters of Yale drew attention to the omnipresence of an infection in nearly every coma case. Sixty units of insulin would not keep Case No. 5872 sugar-free when his carbuncle was unopened and the carbohydrate in his diet 134 grams, but when it was healed he left the hospital sugar-free, taking no insulin, and on a diet containing 156 grams carbohydrate. Often diabetic patients with an infection later do so well that their diabetes may remain concealed save from the alert observer.

3. *Tuberculosis.*—Since August, 1922, pulmonary tuberculosis has been responsible for the death of 32 cases, 5 per cent. This is less than heretofore and corresponds to what has taken place in the community. The medical profession has too pessimistic a view about this complication. When the treatment of the diabetes is faithfully carried out, these patients do quite well. The trouble in the past has been that consumption was usually advanced when diagnosed. In a diabetic the temperature, pulse, and respiration may give no clue to the diagnosis, and the loss of weight is attributed to the diabetes. The number of patients dying with tuberculosis is small, but probably nearly accurate. This appears true from evidence at autopsy at the Deaconess Hospital. At the Peter Bent Brigham Hospital among 37 fatal cases upon which a postmortem was performed 7 had active tuberculosis.[1] Diabetic patients, of course, have healed foci of tuberculosis just as the ordinary individual in the community, but in my group of cases it has not been a notable factor as the cause of death. The majority of my patients are able to pay their hospital board. Patients entirely dependent upon charity, as those in the wards of the large city hospitals, could be expected to show more tuberculosis.

4. *Cancer.*—Thirty of the patients, in the Banting Era, died of cancer. This is almost double that of earlier epochs and proves the diabetic is living long enough to acquire diseases common to the community as a whole. The primary foci were in widely diversified areas: thyroid, face, tongue, breast, esophagus, larynx, stomach, intestine, rectum, liver, pancreas, kidney, bladder, prostate, cervix, uterus, spine, peritoneum. There was also one case of lymphoblastoma.

5. *Inanition.*—Inanition first appeared as a cause of death in my mortality tables in 1916, but to it should be ascribed other deaths. One should not be oblivious to the effects of undernutrition which underlie and are responsible in large degree for the nonresistance of diabetic patients to infections. Few individuals ever die from pure starvation. They succumb before the end stage is

[1] Fitz and Murphy: Am. Jour. Med. Sci., 1924, **168**, 313.

reached, because their general nutrition is lowered. In the Allen Era the number of deaths from this cause numbered 18, but the number of lives saved by undernutrition was far greater than those lost. One must never cease to be grateful to Dr. Allen for adoption of undernutrition as a method of treatment. In the Naunyn Era the diabetics died of coma too soon for inanition to develop and in the Banting Era the patients are not exposed to it. Probably closer observation of the symptoms at the time of death of these cases of inanition would have shown hypoglycemia to be very common. See Case No. 1085, page 215. Since insulin has been introduced there have been but 2 deaths from inanition.

6. *Miscellaneous.*—Deaths from cirrhosis[1] of the liver have increased to 6 and the suicides to 5, but the accidental deaths have risen most of all. Longer durations of life of the patients and better ability to move out of the house expose them more to accidents. Gastric and duodenal ulcer now appear in the lists, but for years I never saw a case. Thyroid disease figures as well, but the fatalities are small in comparison with the many cases seen with Dr. F. H. Lahey of the Deaconess Staff.

7. *Imperfect Supervision.*—It is not customary in the tabulation of causes of death to include what is quite as important: namely, imperfect medical supervision, but I believe more deaths to be chargeable to this deficiency than to any other single factor. This is a reproach and an encouragement at the same time. It has radically affected my own treatment of diabetic patients; it shows the necessity first for better education of the patient, so that when not doing well the advice of a physician shall be sought; it shows also the need for closer coöperation between the family physician and the physician who sees the patient in consultation or at the hospital. Closer supervision of the cases demands an enormous amount of time, but time so spent will be repaid by lives saved. Patients must understand the facts and be made to realize that lack of supervision often means needless death. Each physician has in his own hands the protection of the lives of his diabetic patients.

8. *Needless Diabetic Deaths.*[2]—The needless mortality in diabetes is unfortunately greater than we realize. Patients who have pneumonia, tuberculosis, and cancer usually die of pneumonia, tuberculosis, and cancer, but diabetics seldom die of their disease *per se*, but of complications which are largely preventable, coma, gangrene, infections. Coma still is the chief preventable complication. Outside of the hospital it still occurs, but it rarely develops in a hospital, and patients who enter with it usually recover. More than 66% of all my patients have died of coma.

[1] The records of these cases and that of one living patient I am placing in the hands of Dr. James Bordley who was kind enough to show me another case in the wards of Dr. Longscope and Dr. Harrop at the Johns Hopkins Hospital.

[2] Joslin: Boston Med. and Surg. Jour., 1922, **186**, 833.

Anyone who sees or has reported to him many deaths from diabetic coma becomes appalled at their needlessness. A boy, Case No. 2090, is told to eat everything and in two days is in coma. A diabetic, Case No. 44, goes on a drunk, and as he emerges from alcoholic coma he lapses into diabetic coma. Deaths like these are not far removed from manslaughter and suicide. Another diabetic boy, Case No. 1870, amenable to treatment, drops out of medical supervision, coma appears, and he dies in the tenth month of the disease, though from other cases it is reasonable to conclude he could have lived years. Two young adults, Cases Nos. 2389 and 2401, refuse to submit to dietetic treatment and die respectively in seven and six months after the onset of the disease. Deaths like those just recounted and others resulting from the omission of insulin can be traced to the advice of the laity or irregular practitioners and often to the patients themselves. For all such deaths one feels regret, but not the keen concern excited by deaths under supervision, trained yet not quite free from errors of judgment. All these deaths most commonly occur when the diet of a patient is suddenly changed. When the carbohydrate is restricted and protein and fat simultaneously increased, death from coma may take place the same week unless resort is had to insulin. How many such cases! Nearly all of us have one or more such sorrowful deaths to our discredit. It is, therefore, well to hold to the rule in severe, long-standing, complicated, obese and elderly cases, as well as in all cases with acidosis, to make changes in the diet gradually, not suddenly or radically.

Infections precipitate coma. As said above, they make the diabetes worse and unless one is cautious there will be added to the harmfulness of the infection that of a high protein-fat diet as well. Petrén has shown, and so have Newburgh and Marsh, that a diabetic will tolerate much fat if the nitrogenous metabolism is low, but in the presence of an infection or in hyperthyroidism the endogenous protein metabolism is high and even more dangerous than the exogenous. The diabetic is running in crowded traffic when in the midst of an infection.

It not infrequently happens that the infection is not recognized. Better statistics upon this point and in general about the circumstances attending coma should be accumulated. Thus, Case No. 836, seen in consultation one evening, was found to be in partial coma, but I was able to demonstrate to the physician a membrane in the throat, and three hours after the patient's death the following morning, the Board of Health reported a positive culture for diphtheria. This was in 1914. At that date there was no thought of saving the patient, but today one would be quite chagrined to lose him. Examples of latent infections are described in the section on surgery. Appendicitis is one of the most important.

All cases of coma can be traced to increased metabolism, endogenous or exogenous, and in that metabolism fat and protein take an excessive share, because insulin is not available to lay its restraining hand on their katabolism. Sometimes the fat is taken in obvious excess, as happened when a diabetic, Case No. 1511, of long duration, living with little dietetic restriction, went to a fashionable hotel, suddenly decreased carbohydrate and made up by indulging to the limit in *larded* mushrooms. The same result occurred when a fairly well-nourished but severe diabetic, Case No. 310, who had frequently shown acidosis, was taken seasick on a steamer, retained no food, lived on her own fat and protein. Remember that a little carbohydrate as such goes a long way toward preventing coma in a mild or moderately severe case of diabetes. The diabetic dog, whether fat or fat fed, is prone to coma. Beware before you expose a diabetic to a high-fat diet, whether endogenous or exogenous.

Then there were the cases of coma in the old days resulting from operations with ether as an anesthetic. If ether is used, it is a good plan to be as rapid and as skilled as the Mayos and to use as little ether as their anesthetists. It is safe to employ it if you know how to protect the patient with a store of glycogen in liver and muscles through the aid of insulin. Ether lowers the tolerance and makes the diabetes temporarily worse. However, this does not mean that diabetics should not be operated upon or not take ether, but it demonstrates that ether anesthesia is a burden which a light case of diabetes may easily bear, which may change a moderate to a severe case, and which to a severe case may be fatal.

Diabetic patients will live untreated for many years without the appearance of coma. They suffer from complication after complication. They are tormented with sepsis, neuritic pains, and pruritus; yet they still live. Their diet is atrocious. Along comes an enthusiastic young doctor and immediately fat and protein are increased, carbohydrate diminished, and the patient goes into coma because such a diet requires extra insulin which may not be available. Out of carbohydrates it is impossible to form the acid bodies. When, therefore, carbohydrate is suddenly replaced with fat, we deliberately furnish our diabetic patients with material which, though it acts partly as a food, acts far more as a poison. Diabetic patients need fat; it forms the chief constituent of their diet; but they must not be poisoned with it, they must be allowed only an amount they can assimilate.

Omission of insulin is a most frequent cause of coma, but fortunately the patient usually escapes death. Not so with Case No. 4665, who took up Christian Science. Contrary to the Christian Science healer's advice she gave up insulin and coma with death promptly ensued. A boy, Case No. 6033, omitted insulin and upon

a layman's advice took herbs; the next he remembers was the attention of a doctor at the Deaconess Hospital.

Deaths recorded under the title "coma" are by no means purely coma. Since this list was compiled an instance, Case No. 5176, has occurred at the Deaconess Hospital in which coma was the precipitating cause and hypoglycemia a factor, but quite possibly of greater import was the evidence of pulmonary emboli which the autopsy disclosed. It is possible that this was related to the numerous venepunctures. One does not like to think so, but it may be the truth. Patients almost moribund are in a state to develop thrombosis very readily. From another hospital another case has come to my attention. For this reason during coma more frequent recourse is made to micro tests for examination of the blood, because such tests can be made from a few drops removed from the ear or finger.

Autopsies are necessary if a doctor wishes to have his case reports rated valid. It is altogether too easy to credit deaths to coma.

9. *Gangrene.*—Gangrene stands next to coma as a preventable cause of death. This is the reason for our Beauty Parlor for Diabetics' Feet at the Deaconess Hospital. In the first place, injuries to the feet should not occur. A diabetic should keep his feet as clean as his face and protect them with equal care. Never allow one of your diabetic patients to develop gangrene ignorantly. Warning and admonition should penetrate so deeply the minds of your cases that if such a catastrophe should ever occur the unhappy patient will feel compelled to say: "Doctor, you warned me about injury to my feet, about the dangers in cutting corns, toe nails, about blisters from new shoes or old shoes with poor linings, about nails in my shoes, flat-foot plates, and hot-water bags. You are not to blame for my present condition." The time spent upon such homely advice yields fabulous returns in gratitude from patients and in peace of mind when patients coming for treatment of gangrene are found not to have been those formerly under one's own care.

Pneumonia, tuberculosis, cancer, heart disease, nephritis, and old age, all occur with diabetics as with any group of patients, but such causes of death should not distract our attention from the main causes—coma and gangrene.

But what I consider of far more importance is the number of procrastinating cases of mild infections in mild diabetics, chiefly in their lower extremities, which frequently prove fatal. There have been but 8 cases of gangrene of the legs in diabetics under fifty years of age in my personal experience. In other words, these conditions develop at a time of life when diabetes is mild. Why should they so frequently be fatal? Consider with what these mild cases of diabetes have to contend. Handicapped by a lingering infection, which only too often is allowed to continue

for months, with kidneys less efficient for throwing off the attack of acidosis, deprived of exercise—that proved stimulus to sugar consumption—for whoever heard of a poor old gangrenous diabetic taking exercise in the old days—these pitiful patients used to meet a fourth enemy in ether anesthesia, unprotected by insulin. Is it any wonder that a formerly innocent disease became virulent and that the victim died of coma?

Coma killed 94 per cent of 50 cases of diabetes treated by von Noorden[1] in the first three decades of life, but only 25 per cent of 112 cases after the age of fifty years. Coma was responsible for 86 per cent of 139 deaths in my own series prior to June, 1923, for the age period birth to fifteen years; for 72 per cent of 159 deaths between sixteen and thirty years; for 52 per cent of 267 deaths between thirty-one and fifty years, and 25 per cent of 322 deaths between fifty-one and eighty-three years. Of 49 fatal cases reported by Murayama and Yamaguchi death was due to coma in only 10 per cent.

TABLE 162.—CAUSES OF DEATH IN DIABETES ARRANGED ACCORDING TO DECADE OF ONSET (VON NOORDEN).[2]

Decade.	Cases.	Coma.	Cardiorenal.	Apoplexy.	Arteriosclerosis.	Pneumonia.	Tuberculosis.	Carbuncle.	Gangrene.	Cancer.	Pernicious anemia.	Gastric ulcer.	Cirrhosis of liver.	Misc., not coma.
0–10	10	9	..	..	..	1								
11–20	14	14												
21–30	26	24	..	..	..	..	2							
31–40	64	52	..	..	1	..	3	..	..	..	..	..	..	8
41–50	66	37	8	1	..	2	4	..	..	..	1	1	..	12
51–60	61	19	7	8	..	1	5	3	1	7	..	..	3	7
61–70	49	14	5	8	..	4	..	..	6	5	..	..	..	7
71–80	2	..	..	2										
Total cases	292	169	20	19	1	8	14	3	7	12	1	1	3	34
Per cent	..	58	7	7	0.3	3	5	1	2	4	0.3	0.3	1	12

TABLE 163.—PERCENTAGE OF DEATHS DUE TO COMA AT DIFFERENT AGE PERIODS. JOSLIN. PRIOR TO JUNE, 1923.

Age period	Total deaths.	Coma. No.	Per cent.
0–15	139	119	86
16–30	159	114	72
31–50	267	140	52
51–83	322	81	25

[1] Von Noorden: Die Zuckerkrankheit, Berlin, 7th edition, 1917, p. 342.
[2] von Noorden: Ibid.

F. PATHOLOGY.

The present generation has seen the transfer of diabetes from a symptom associated with multitudinous clinical states to a disease with a definite pathological basis in the pancreas and notably in the islands of Langerhans. Beginning with Cawley in 1788, the connection between gross lesions of the pancreas and diabetes was noted and similar observations were repeated with increasing frequency as time went on. The removal of the pancreas of dogs by von Mering and Minkowski in 1889 with resulting diabetes established the relation between the gland and the disease and opened a field for experimental study. It was not, however, until 1900 and 1901, that Opie localized the essential morbid process in the islands of Langerhans, and Weichselbaum and Stangl described the hydropic degeneration and vacuolation of the island cells, that the pathologist hoped to diagnose the disease without the help of the clinical records.

The pancreas is man's protection against diabetes. Destroy it by disease or remove it by experiment, and diabetes results. The annihilation of the gland is the essential feature; the means by which this is produced is immaterial. Pathologists, however, would not have been baffled so many years did not another factor enter into consideration.

A small remnant of healthy pancreas will suffice to prevent diabetes. This explains why fairly extensive destruction of the gland by necrosis, infection, or the inroads of malignant disease frequently is unaccompanied by diabetes. Minkowski's extirpation experiments proved this point when he showed the disease was averted if the remnant amounted to one-tenth of the gland. This would be equivalent to 5 or 10 grams. These pathological and experimental observations, however, almost added to the difficulty of explaining diabetes in the presence of an apparently normal pancreas until Opie's discovery.

The weight and estimated size of the pancreas are misleading criteria of its state, whether normal or abnormal, because of the great variation in connective tissue and fat, chiefly interlobular, which are present in the organ. Thus of two pancreases, both of which contained but little pancreatic tissue, the one weighed 30 grams and the other 240 grams. This variation is not altogether dependent on the weight of the individual from which the organ came, as both women weighed over 200 pounds.

The islands of Langerhans[1] (Fig. 22), embedded in the pancreas, and constituting about 3 per cent of its weight, Opie showed to be the

[1] See page 33 for literature.

seat of its protective agency against diabetes. They are particularly well supplied with bloodvessels. Clark[1] has shown the number of islands in a healthy human pancreas may vary from 250,000 to 1,750,000 but any estimation is unreliable. They vary in number in various animals, but are far more numerous in young animals and twice as frequent in the tail (Warfield) as in the head of the

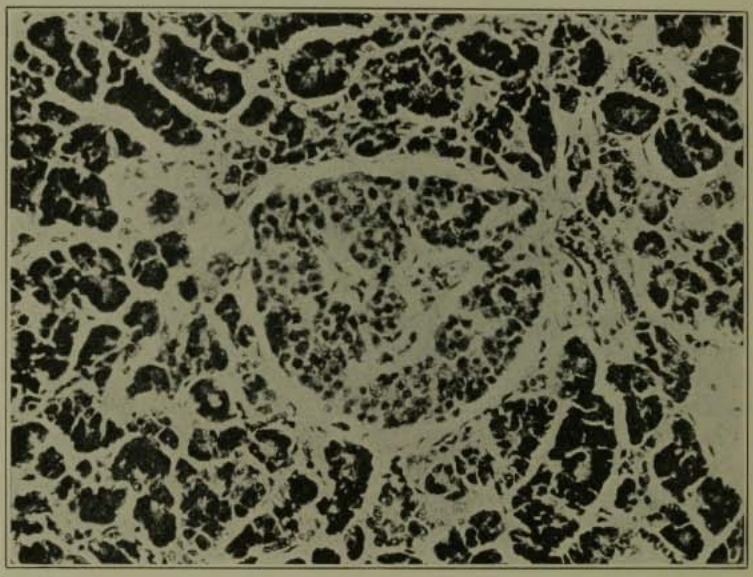


FIG. 22.—Normal island of Langerhans whose cells produce the insulin required by the body. × 250. (Mallory.)

organ, which may account for the mildness of diabetes associated with gall stones. In serial sections of the pancreas in 12 cases of diabetes Conroy[2] found the average number of islands per cross-section to be 74 as compared with 184 in 12 normal controls. In the pancreas of a child born of a diabetic mother Gray and Feemster[3] found approximately twenty-four times as much insular tissue as in the normal pancreas.

The origin of the islands is considered by one group of pathologists to be in the epithelium of the ducts and the islands themselves as wholly independent of the acinous tissue. They would be to the pancreas what the parathyroids are to the thyroid and the pars anterior and pars posterior of the pituitary are to each other. The other school is absolutely positive that the islands have no surrounding

[1] Clark: Anat. Anzeiger, 1913, **43**, 81.
[2] Conroy: Jour. Metab. Research, 1922, **2**, 367.
[3] Gray and Feemster: Arch. Path. and Lab. Med, 1926, **1**, 348.

membrane and that their cells can develop from the cells of the acinous tissue and they claim that cells in transition between the two types of tissue are plainly in evidence. Even the alpha and beta granules are denied by the latter school as proof of independence in character although with alteration of the latter[1] diabetes has been considered to be associated.

These diametrically opposite views have most recently been vigorously stated by Ukai[2] and Otani[3].

As congenital anomalies, aberrant pancreatic tissue[4] is found in the liver and in the mucosa of the small intestine and this aberrant tissue is capable of secretion.

That the pathological signs in the diabetic pancreas are by no means confined to the islands of Langerhans all are agreed, although this does not prove that any part of the pancreas save the islands is involved in the disease. The acinous tissue shows definite changes and perhaps the outstanding feature in the diabetic pathology of the pancreas in the last few years is the demonstration, largely suggested by the work of physiologists and clinicians, that in diabetes the external as well as the internal secretory activity of the pancreas is impaired.[5]

The independence of the islands of Langerhans is of great importance from the point of view of their regeneration. Obviously the greater the supply of tissue which can lead to the development of new islands the better.

The arguments in favor of the integrity of the islands and their association with the conventional symptoms of diabetes which appear to me as most convincing are (1) the demonstration of the principal islet in certain species of fish, to be later described, from which insulin can be prepared whereas it is not obtainable from the rest of the organ; (2) the improbability that acinous cells, which do not secrete insulin, could later acquire so specific a function as to produce that complicated hormone and (3) Wilder's[6] patient from the Mayo Clinic without diabetes but with hypoglycemia so intense that to prevent collapse he was compelled for weeks to take food every two hours and for a time every half hour, and as much as 1000 grams cane sugar daily, all because, as proved by autopsy a cancer of the islands had metastasized in the liver. An extract of the metastatic nodules in the liver lowered the blood sugar of rabbits, while that of the surrounding tissue did not. Even at two hours after death the liver contained 8.25 per cent glycogen.

[1] Homans: Cited by Macleod: Loc. cit., p. 6.
[2] Ukai: Mitt. a. d. allg. Path. u. path. Anat., 1926, **3**, 173.
[3] Otani: Am. Jour. Path., 1927, **3**, 1; **3**, 123.
[4] Seyfarth: Klin. Wchnschr., 1924, **3**, 1085.
[5] Dubnova and Izigson: Klinidus. Medits., 1927, **5**, 531. See also p. 565.
[6] Wilder, Allan, Power, and Robertson: Jour. Am. Med. Assn., 1927, **89**, 348.

Twenty instances of adenomas of the islands of Langerhans have been collected by Warren.[1] These tumors are characterized by resemblance to the islands in arrangement of their cells and in appearance of the individual cell, by absence of mitotic figures, by the presence of a definite capsule and by compression of the adjacent tissue. Warren believes them not to be so rare as the small number of reported cases would imply.

A case reported by Goldblatt[2] of an atypical adenoma of the pancreas originating in the islet tissue is also in point. "That this tumor is of benign nature is deduced from the following facts: it is definitely and completely encapsulated. Neither the capsule nor the neighboring pancreatic tissue shows any signs of direct invasion by the new growth. There is no metastasis. There are no mitotic figures. The general arrangement of the tumor is unlike that of some cellular adenomata found in other organs of the body. The epithelial cells of the tumor and their arrangement with relation to the vascularized trabeculæ show unmistakable signs of differentiation, since there is such a striking resemblance to the islets of Langerhans. In size, shape, staining characteristics, and the minute structure of the cytoplasm and nucleus the cells resemble very closely those of the islands. The tumor here described is in all respects like those reported by Nichols, Helmholz, Morse, and others. The only differences are that this growth is much larger than any hitherto reported, and that by reason of its size and location it had exerted pressure upon the pancreatic ducts and had caused clinical signs and symptoms suggestive of pancreatic insufficiency. In this respect it differed from most adenomata hitherto described. Glycosuria was never found."

Fairly extensive removal or destruction of the pancreas does not produce diabetes provided the islands of Langerhans or a sufficient number of them are left intact. This is shown by the absence of diabetes following experimental removal of less than a certain minimum amount of tissue and by partial destruction of the gland, but not of the islands, in infections and other lesions and by ligation of the ducts which results in atrophy of the acini, but not of the islands, a procedure utilized by Banting in his preparation of insulin. Fortunately Banting did not know that only partial atrophy of the acini took place as a result of the ligation of the duct. In a positive way it is proved by Macleod's[3] experiments with the angler fish and the sculpin. In these fish the islands are collected in a principal islet distinct from the balance of the pancreas. Extracts of the principal islet act powerfully in lowering the percentage of sugar

[1] Warren: Am. Jour. Path., 1926, **2**, 335.
[2] Goldblatt: Jour. Cancer Research, 1921, **6**, 277.
[3] Macleod: Loc. cit., page 26.

in the blood in contrast to extracts of the remaining zymogenous tissue which are inert.

When one-fourth of the pancreas is left Allen found a lessened tolerance for sugar, which is more marked if the remnant is but one-fifth although diabetes does not then develop even if the animal is placed on a carbohydrate diet. Leave but one-sixth of the pancreas and a carbohydrate diet produces a mild diabetes which is transitory and does not even develop if the diet has been of protein. One-tenth of the pancreas may, but usually does not, suffice to prevent diabetes. Whatever the process or processes may be which cause diabetes it is justifiable to infer from these experiments of Allen that at least 90 per cent of the gland's efficiency must be impaired. So extensive an insult to the pancreas should leave its mark and because it is not found at autopsy is proof that the door to methods, which will disclose it, has not yet been unlocked, and indeed will not be opened save as the result of fundamental research which will throw light upon the method of measuring cell activity.

No single distinctive lesion of the islands was encountered in 26 of my cases reported in the Warren and Root[1] series, or in 10 cases of diabetes in children studied by Warren.[2] This was to be expected in light of the work of Allen,[3] Opie[4] and Cecil.[5] This was true even of the young uncomplicated cases of diabetes among whom, if among any group, one might expect uniformity of pathological appearance if there were one definite causal agent giving rise to the disease. The number of islands was reduced in 7 of the 35 cases. Warren believes the reduction of insular tissue in certain cases of diabetes in children is congenital, rather than the result of disease. Uniformity in reduction however, is so lacking that it could hardly represent the *anlage* of Naunyn. Thirteen of the pancreases showed varying degrees of hyalinization of the islands. (Fig. 23 and 26.) Only 1 of the 13 patients whose islands showed hyaline change was under forty-five years of age. Five showed more or less sclerosis of the islands. In 4 there was some lymphocytic infiltration about scattered islands, and there was no demonstrable pathology in the islands of 13. The islands of 3 showed the type of enlargement described by Cecil as adenomatous. In the few instances in which were found changes in the islands suggesting hydropic degeneration, postmortem change could not be ruled out. The most likely case, No. 1870, only fifteen years of age, died in coma after diabetes of short duration and was autopsied within an hour.

[1] Warren and Root: Boston Med. and Surg. Jour., 1926, **194**, 45.
[2] Warren: Jour. Am. Med. Assn., 1927, **88**, 99.
[3] Allen, F. M.: Glycosuria and Diabetes, Boston, 1913.
[4] Opie, E. L.: Disease of the Pancreas, Philadelphia, 1910.
[5] Cecil, R. L.: Jour. Exp. Med., 1909, **11**, 266.

No hydropic degeneration was apparent, but it was found in a slide of a pancreas sent to Dr. F. B. Mallory by Dr. Willard S. Hastings from a case of fulminating diabetes. In this section every island showed extreme hydropic degeneration.

The pancreas in a case of Dr. Starrow and Dr. Stansfield of Worcester, a child of six years who had had diabetes for six weeks, presented, upon examination by Warren, evidence of relatively acute injury. "The swollen, red condition of the pancreas, the

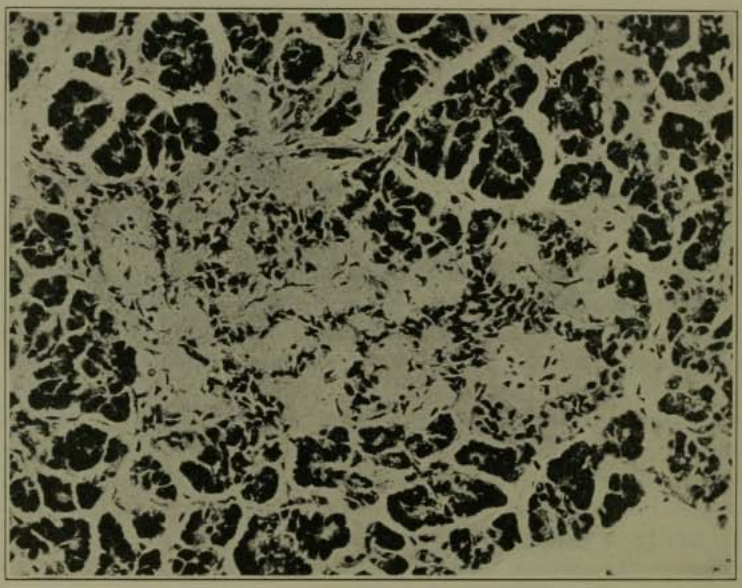


FIG. 23.—Island of Langerhans showing moderate hyaline thickening of stroma with atrophy and disappearance of the insulin-producing cells. × 250. (Mallory.)

moderate infiltration with lymphocytes and polymorphonuclear leukocytes, the hyperplastic lymph node adjacent to the pancreas, and the rapid course of the disease following a sudden gastro-intestinal upset all suggest a toxic origin for the disease. Owing to the difficulty of distinguishing naked nuclei from lymphocytes in the tissue at hand, lymphocytic infiltration of the islands cannot be definitely stated to have been present, although I believe it was in this case. I feel quite certain that the change in the island cells is due to hydropic degeneration."

Conroy found hydropic degeneration in only 1 of his 12 cases of diabetes.

Wide variation in the condition of the islands in the same pancreases, and even in the same section, was the outstanding feature

of the various pathological changes. In one case of fourteen years' duration, Case No. 263, every stage was present from apparently normal islands to masses of hyaline imbedded in the stroma. We have found no pancreas in this series, no matter how severe the disease process or how marked the changes in the islands, in which a greater or less number of apparently normal islands could not be found. Moreover, a large number of pancreases from cases of diabetes other than those included in this series each showed at least a few apparently normal islands. "Lymphocytic infiltration of the islands, found among children, is a lesion not encountered in older diabetic patients and hyalinization of the islands is not found in the young.

"In children there is little pathological change in either islands or acinous tissue, though commonly reported in the old, and that present does not appear sufficient to account for the marked disturbance in function. Consideration of the anatomical pathology of diabetes in children leads to the hope that, through treatment which allows the element of time to act, irreversible changes in the pancreas may be avoided."

The acinar tissue of the pancreas presented varying degrees of sclerosis in some cases independent of pathology in the islands. The acinar sclerosis was not apparent in any case much under two years' duration even though the islands showed considerable change. In Case No. 3592, who showed slight acinar sclerosis, the duration as given was six months, but an accurate history could not be obtained and the disease probably had lasted for a much longer time. Warren points out that fibrosis may at times be due to chronic passive congestion. There is enough reason for such congestion and often evidence of it in other organs.

Allen[1] believes that the changes in the islands and acinous tissue as well represent the result of an acute, subacute, or chronic pancreatitis. "I think that acute blood-borne infection is the most common cause, especially in the young and that diabetic symptoms follow them immediately or, more often, after months or years of functional wear and tear."

1. **Acute Pancreatitis Preceding Diabetes.**—Warfield[2] has found 7 cases in the literature and added 4 of his own in which diabetes developed after acute pancreatitis. Two of his own cases followed influenza and 2 an apparently acute pancreatitis. The diabetes began during or soon after the attack in 6 cases, but an interval of 6 years intervened in another. Warfield explains the absence of diabetes in hemorrhagic pancreatitis on the ground that the patients live for too short a period for it to develop. The diabetes was

[1] Allen: Jour. Am. Med. Assn., 1927, **89**, 661.
[2] Warfield: Jour. Am. Med. Assn., 1927, **89**, 654.

permanent in the 5 cases in which the subsequent history was known, although its later mildness in one of the cases which survived the acute pancreatitis suggested a recovery from the diabetes. Quite rightly Warfield emphasizes the importance of the explanation of pain in the epigastrium in the beginning of diabetic coma. He considers that in some instances it may be related to an acute pancreatitis. That coma is occasionally associated with appendicitis is well-known and it is useful that Dr. Warfield has called attention to a possible pancreatitis, so that all can be alert to diagnose such an instance.

Warfield makes the statement that to his knowledge "no case of disease of the head of the pancreas has ever been followed by diabetes." Already attention has been drawn to the mildness of diabetes when the lesions of the pancreas are due to an extension of the pathological process from the biliary tract.

Rodriguez[1] also reports a case of acute pancreatitis preceding the onset of diabetes and Dunn, Vatcher, and Woodwork[2] two others. A woman, aged fifty-nine years, was admitted to the hospital in a semicomatose state with a history of possibly five years of dyspepsia with a few colicky pains in the right hypochondrium. Six weeks previous she had developed a superficial infection of the leg but the urine was free from sugar. Three days before admission she had required morphine because of sudden severe epigastric pain accompanied by vomiting, which had persisted for thirty-six hours. A diagnosis of acute pancreatitis was made, but operation was postponed because of sugar and diacetic acid. The blood sugar even after 20 units of insulin was above 0.60 per cent, but by the sixth day had fallen to 0.106 per cent. It rose on the twelfth day to 0.28 per cent. On the thirteenth day while the nurse was giving an enema the patient suddenly became pulseless, unconscious and died in half an hour. The autopsy revealed areas of fat necrosis in the omentum and blood-stained fluid filled the abdomen. The gallbladder was small and shrunken and contained two large and several small stones. The pancreas was soft, mushy and edematous, and was easily torn by the dissecting finger. Similar areas of fat necrosis were found on the surface of the pancreas, only more abundant and coalescent. Pus could be expressed from these necrotic areas in the pancreas.

Gangrenous pancreatitis in the course of diabetes may occur. Case No. 3267 developed diabetes in December, 1922, when she was forty years of age, without diabetic history, and was first seen in August, 1923, with 6.6 per cent sugar and blood sugar 0.27 per cent.

[1] Rodriguez: Jour. Am. Med. Assn., 1924, **82**, 203.
[2] Dunn, Vatcher, and Woodwork: Lancet, 1926, i, 595.

With 15 units of insulin she became sugar-free with a tolerance for 78 grams of carbohydrate. During the summer of 1925 diet was broken and on September 22, 1925, she developed nausea, vomiting, pain in the abdomen, and labored breathing, but under the treatment of her physician, Dr. Coulson of Lawrence, came out of coma. On account of unusual symptoms she was referred to the Deaconess Hospital on September 25, three days later, when the blood sugar was 0.44 per cent, the non-protein nitrogen 98 mg. per 100 cc., the plasma CO_2 8 volumes per cent, and the alveolar air CO_2 (registered as milligrams mercury by the Fridericia apparatus) 13. With insulin the patient at first improved, but she gradually failed and the next day was unresponsive. The autopsy revealed atheroma of the coronary arteries, and calcified plaques in the abdominal aorta; numerous small stones in the gall-bladder; an infectious pancreatitis with areas of fat necrosis in the peritoneum.

Gangrenous pancreatitis may precede diabetes. Case No. 670 was operated upon for acute gangrenous pancreatitis in December, 1907, at thirty-nine years of age. There was a history of severe epigastric pain for nine years previously. March 12, 1908, he was discharged from the hospital free from sugar. Symptoms of diabetes with glycosuria appeared in the summer of 1909 and persisted without the urine being sugar-free until a few days before death in coma in November, 1913 when I saw the patient. The case is reported in detail by Jurist.[1]

Pancreatic calculi preceding diabetes are rare. My attention was first directed to this condition by Hackney of Uniontown, Pennsylvania. At operation in March, 1923, by Dr. C. M. Luman cholelithiasis and chronic appendicitis were found, but the urine was sugar-free. In September of the same year the patient reëntered the hospital with marked diabetes, blood sugar 0.40 per cent, total sugar excreted 185 grams. Four years later following many lapses of diet and irregularities in the use of insulin the patient succumbed to hypoglycemia, 0.013 per cent, despite the intravenous injection of 90 grams of dextrose. At the autopsy the pancreas weighed 190 grams; it was ovoid, constricted near the middle, the greatest diameter 12 cm., the lesser diameter being 4.5 cm. and the diameter of the constricted portion 2.5 cm. The part of the organ corresponding to the head of the pancreas had a smooth rounded surface and on incision was found to consist of a fibrous wall having an average thickness of about 5 mm. containing approximately 15 cc. of cloudy, white liquid, in which about 100 irregular-shaped calculi less than 5 mm. in diameter were found. The other half of the

[1] Jurist: Am. Jour. Med. Sci., 1909, **138**, 180.

organ had an irregular, nodular surface, and on dissection was found to consist of solid white tissue in which ducts having diameters up to 3 mm. and encrusted with concretions were seen. (Figs. 24 and 25.)

FIG. 24

FIG. 25.—Calculi in pancreas. (Courtesy of J. S. Hackney of Uniontown, Pa.)

Later Dillon's[1] reprint, hitherto having escaped my attention, disclosed that in 2800 necropsies at the Pennsylvania Hospital there

[1] Dillon: Ayer Clin. Lab., Penna. Hosp., 1924, Bull. No. 8, p. 35.

were but 2 cases of pancreatic calculi and in but 1 of these was glycosuria observed. The patient, aged fifty-five years, was without preceding gastro-intestinal symptoms, eventually developed pulmonary tuberculosis and died after three and a half years of diabetes. The total pancreas weighed 5 grams and judging from the sections fully 90 per cent was composed of fibrous tissue.

A third case of pancreatic calculi is my own Case No. 6359, and was discovered by Dr. Bogan in a routine Roentgen-ray taken of the chest. The patient's diabetes developed five years before at the age of eighteen years, had evidently grown increasingly intractable and when she came under my supervision in September, 1927, she required 45 units of insulin to metabolize carbohydrate 74 grams, protein 54 grams, fat 88 grams, and even then frequently showed traces of sugar. Despite the relatively high calories per kilogram body weight she lost 3½ kilograms in twenty days. Duodenal contents were not obtained. On account of severe pains in the legs they were also examined by Roentgen-ray and sclerotic arteries demonstrated. In reporting the case and showing the Roentgen-ray films of the pancreas at the Staff Meeting of the Deaconess Hospital, Roger Lee commented upon the marked clearness of the calculi as contrasted with biliary calculi, thus suggesting the marked predominance of calcium.

The case is also of interest because it was diagnosed in the life time of the patient, who still lives.

Hemochromatosis was observed in but 1 patient, Case No. 2693.

A diagnosis of diabetes from an examination of the pancreas alone, even though obtained soon after death, is not possible in any large percentage of the cases according to most pathologists. As a matter of fact, diabetic patients seldom die of diabetes today. Uncomplicated diabetes was responsible for deaths in only 12 per cent of Wilder's[1] 81 cases upon whom a postmortem was performed. I believe that clinicians and pathologists must correlate their findings much more than they have heretofore. Both should study the case during life.

2. **Hydropic Degeneration.**—Hydropic degeneration according to Allen characterizes the pancreas in diabetes. In the emphasis he lays upon it, it is clear that he has been influenced by his observations upon experimental diabetes in dogs. In the Deaconess series Warren and Root could not confirm his findings. Allen says that hydropic degeneration can be shown experimentally when dogs have been rendered diabetic by the removal of the larger portion of the gland. In sequence the changes are: disappearance of the granules

[1] Wilder: Southern Med. Jour., 1926, **19**, 241.

in the cells of the islands, swelling of the cells with fluid, and eventually disappearance of the islands. These changes are the result, not the cause, of the diabetes. These susceptible animals, according to Allen, develop diabetes if overfed. This takes place irrespective of the quality of the food, carbohydrate, protein, or fat, only the time required for the effects of fat feeding is longer. The dogs are potentially diabetic, but free from symptoms on limited diets. Overfeeding causes active diabetes, which in turn causes the hydropic changes. Allen concludes that hydropic degeneration of the islands in partially depancreatized dogs is a specific diabetic phenomenon

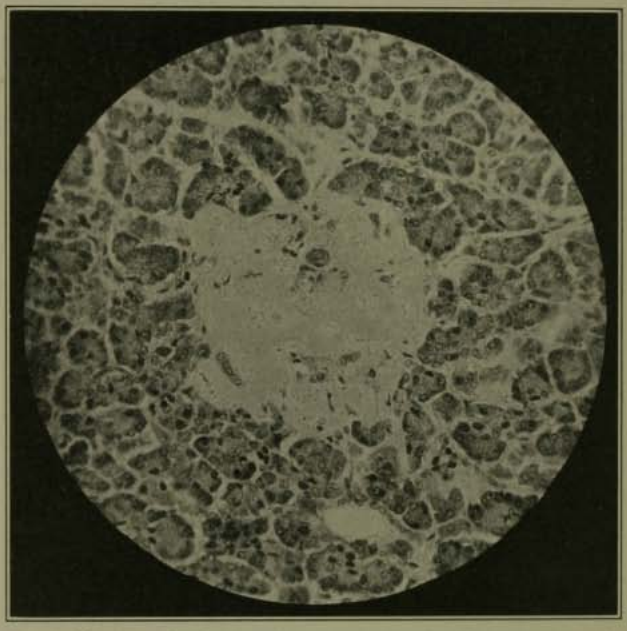


FIG. 26.—Marked hyaline thickening of stroma in island of Langerhans with complete disappearance of the functioning cells. × 300 (Warren).

produced solely by overstrain of the function of the cells by diets in excess of weakened assimilative power, that the condition begins within four to seven days, and attains a maximum in a month, and that by six to eight weeks all *beta* cells are gone. With restriction of diet the hydropic change is probably reversible within certain limits and recovery may take place.

The demonstration of hydropic change in every pancreas would be important because it would render possible the microscopical diagnosis of active diabetes, furnish proof that the internal secretion resides in the islands, afford additional evidence of the identity of

experimental and clinical diabetes, explain the lowering of assimilation in diabetics when upon excessive diets, and constitute a proved example of an anatomical lesion resulting from overstrain of cells producing an internal secretion.

According to Allen, in partially depancreatized dogs the islands of Langerhans undergo various changes: (1) The stage of swelling of the *beta* cells caused by thinning out of the granular contents; (2) the stage of vacuolation of the *beta* cells as the granules disappear; (3) the stage of degeneration marked by the shrinkage of the

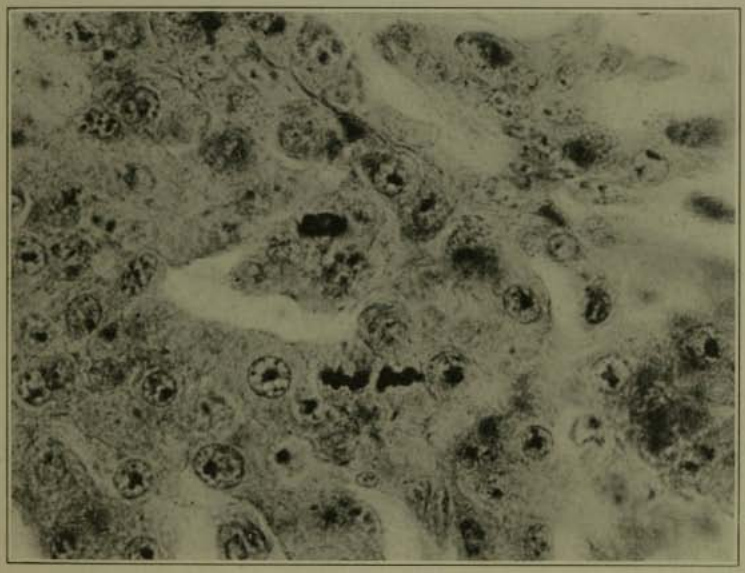


FIG. 27.—Three mitotic figures in an island of Langerhans in one microscopic field; four others were present in other parts of the same section through the island. (From a case of lobar pneumonia.) The section illustrates the great regeneration of island cells which may occur and suggests that in diabetes, if the island cells are rested by the use of insulin, regeneration may to some extent at least take place. × 1000. (Mallory.)

nuclei in conjunction with the breakdown of the cell-body, and (4) the stage in which the *beta* cells have disappeared, leaving the islands composed only of *alpha* cells. This last stage is found only in animals; it has not been found in human diabetes. Hydropic degeneration is not due to hyperglycemia, *per se*.

3. **Effect of Insulin Upon the Pancreas.**—Insulin exerted no influence upon the pancreas so far as Warren and Root could determine. They found "no difference between the pancreases of those cases given insulin and those under dietary treatment alone, although we have the impression that in Case No. 263, treated with insulin

for thirteen months, there are more apparently normal islands than would ordinarily be the case."

4. **The Involvement of Pituitary, Thyroid, Adrenals, and Ovaries.**—The association of other endocrine glands with diabetes was shown by Case No. 4289 who entered the hospital with acute thyroid "storm" and diabetic coma. With Lugol's solution and insulin the patient recovered from both these complications to succumb in two weeks to septicemia arising from a furuncle. Her diabetes was of recent onset and was preceded by goiter and symptoms of hyperthyroidism. At autopsy a hyperplastic thyroid gland containing 0.9 mg. iodine per 100 grams gland was found by R. B. Cattell. The adrenals were enlarged, weighing 19.5 grams, and small ovarian cysts were present. The liver contained 5.5 per cent fat, or a total of 99 grams, and no glycogen by either chemical or pathological tests. The insulin content of various tissues per 100 grams of tissue was as follows: pancreas, 25 units; liver, 3 units; kidneys, 10; heart, 3; thyroid, 9. The pancreas weighed 30 grams. The islands were larger than normal, but the usual number were present. Several islands showed a slight degenerative change, with nuclear pyknosis and rounding of the cytoplasm.

Case No. 5176, cited on page 885, showed several small foci of fibrosis involving both islands and parenchyma, with infiltration by lymphocytes and plasma cells. The islands were numerous and except where involved in the foci of fibrosis were negative.

The pancreatic changes in diabetes associated with hyperthyroidism are indefinite. Holst[1] on the basis of 9 cases showing anatomical changes in the pancreas states that usually the pancreas is atrophic, the islands are reduced in number, and those islands present may be necrotic or fibrosed. Not enough work has yet been done to establish any constant pathology in this condition.

The pituitary gland, according to Kraus[2] presents certain changes in its anterior lobe in diabetes which are nearly constant in young people. He noted a decrease in the number and size of the eosinophilic cells as well as their degeneration, and the weight of the gland was below normal. Thus in a series of young diabetics the weight was 0.54 grams and of older diabetics 0.63 grams. He considers the change in the pituitary to be secondary to the diabetes, not invariably constant as shown especially by the cases who have been treated by insulin.

5. **Effect of Coma Upon the Pancreas.**—Coma causes no distinctive pathology of diabetes in the pancreas. Warren and Root make this statement based upon autopsies on 6 patients who either died in

[1] Holst: Acta Med. Scand., 1921, **55**, 302; Schweiz. med. Wchnschr., 1923, **53**, 725.
[2] Kraus: Centralbl. f. allg. Path. u. path. Anat., 1923–1924, **34**, 113; 1925, **36**, 305; Virchow's Arch., 1923–1924, **247**, 1.

coma or within one month of recovery from it. In 4 of these cases the diabetes had lasted less than one year and seven months.

A case of coma, reported by Allen[1] was treated with 270 units of insulin. In the pancreas of this patient hydropic changes in the pancreatic islands were so slight that they were discovered only by long search. "The relative absence of such changes under insulin treatment is suggestive, but requires confirmation before any theoretical application is made. If infection be assumed as the chief

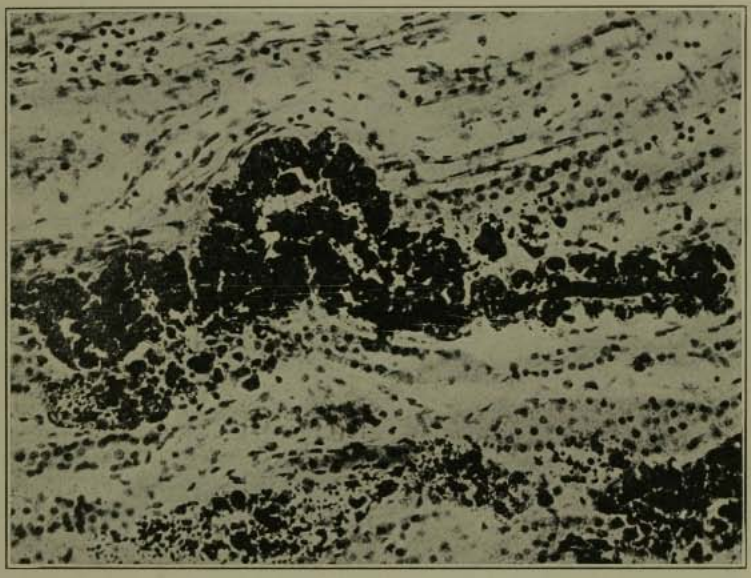


FIG. 28.—Kidney: The dark droplets and masses are glycogen (stained red by Best's carmine solution) in Henle's tubules where they make their appearance characteristically in diabetes. × 250. (Mallory.)

cause of death, there is a previous observation of almost as slight vacuolation of island cells in a case of diabetes with carbuncle, apparently explainable by the fact that the terminal severe stage of the previously mild diabetes was too short for the production of advanced hydropic degeneration, which requires at least several days."

6. **Regeneration of Islands.**—Bliss[2], working at the Physiatric Institute in 1922, noted that the pancreatic remnant in a partially depancreatized dog had doubled in size by the end of a year. "Copp and Barclay[3] at the Physiatric Institute . . . . have shown

[1] Allen: Jour. Metab. Research, 1922, **2**, 803.
[2] Bliss: Jour. Metab. Res., 1922, **2**, 385.
[3] Copp and Barclay: Jour. Metab. Res., 1923, **4**, 445.

that in dogs in which a diabetic status was induced by the ablation of a large portion of the pancreas, and by overfeeding, if the damage to the islands of Langerhans had not progressed beyond the stage of hydropic degeneration of the beta cells, the process could be reversed by a proper dietetic treatment or with insulin if necessary." Graner,[1] working in Bensley's laboratory, tied or otherwise obstructed the duct of the pancreas and after sufficient time had ensued to allow for the destruction of the acinous and some of the islet tissue, restored the connection of the pancreas to the bowel. In 4 cases the second operation was successful and regeneration of the pancreas took place, and in 2 of these the regeneration was complete. Regeneration evidently begins first in the islets, but when the occlusion of the duct has been removed takes place in the acini.

Warren and Root found evidences of the power of the pancreas, and of the islands tissue in particular, to regenerate after acute injury. "Thus in a pancreas from a non-diabetic patient dying of lobar pneumonia (A15–16) we found numerous mitotic figures in the island cells, as high as seven mitoses in a single island. Mitotic figures can occasionally be found in the island cells of cases dying of diphtheria and of lobar pneumonia. At times necrotic cells are found. This injury and subsequent repair not only indicate the regenerative power of the pancreas, but perhaps explain the transient glycosuria occasionally encountered in acute infections."

The same transient injury to the islands may explain the severe drop in sugar tolerance noted in diabetic patients during acute infections. The rapid reëstablishment of the former level of sugar tolerance following recovery from the acute process may well represent the result of the rapid regeneration of the island cells.

In one of our cases, Case No. 896, whose diabetes had lasted for fourteen years and who had been under insulin treatment for five months, receiving 15 to 100 units daily with a gradual decrease of the insulin requirement, there was evidence of regeneration of the islands. No functioning acinar tissue was present. The bulk of the pancreas was occupied by a carcinoma from which the patient died, but the tail was not invaded by the tumor. Here the islands were closely packed. Some showed a moderate degree of hyalinization, but most were entirely free from hyaline or other degenerative changes. Columns of cells extended out from the islands into the surrounding stroma, and in places entire low-power fields were made up of island tissue. There were more islands than could be accounted for by their concentration due to contraction of the stroma of the pancreas following destruction of the acinar tissue.

Boyd and Robinson[2] reported what they consider an instance of

[1] Graner: Proc. Inst. Med. of Chicago., 1926, **6**, 80.
[2] Boyd and Robinson: Am. Jour. Path., 1925, **1**, 135.

regeneration taking place in the islands of the pancreas in a child dying by accident who had been treated for diabetes both without and with insulin during a period of seven years. During a year his tolerance for carbohydrate rose from 15 to 45 grams as proved by the omission of insulin and as also shown by the reduction of insulin from 90 to 30 units. The postmortem was immediate. The gross specimen was not abnormal. Microscopically there was no hydropic degeneration, fibrosis, or atrophy of the islets which were of normal number and size. There were occasional pyknotic nuclei in some of the cells. There were evidences of regeneration of the acinar, centro-acinar, and islet cells. The most striking feature in certain of the islets was the almost complete absence of A cells, the islets were not large as the other islets, had only about six or eight cells which were B cells and of large size, closely associated with the duct radicles, but with a lack of orderly arrangement of cells. Bensley[1] was impressed in this case by groups of small bulbous islands which resembled regenerative islands in experimental animals. He recognized regeneration of acinous and islet tissue after ligation of duct, the former having succumbed because of no outlet. "On the basis of these experiments and observations it is my opinion that, given appropriate conditions, the capacity of the pancreas for regeneration is 100 per cent. I believe that we shall ultimately learn how to control it . . . the regenerative emphasis seems to be on the island tissue as long as the duct remains closed." Boyd also refers to another similar case in a later report.[2]

7. **Cardio-vascular System.**—With arteriosclerosis in its various forms responsible for 47 per cent of the deaths in diabetes today, and with its demonstration in life by Roentgen-ray in approximately 90 per cent of the cases of five or more years' duration, it is not surprising that it should have been found in all diabetics of five years' duration who have been autopsied at the Deaconess Hospital. The extensive data at present accumulated, both from the autopsy room and the operating room, are not in available form, but should appear in print within a year.

The ages at death of diabetic patients imply the existence of arteriosclerosis. To justify its recognition as a sequel of diabetes, therefore, the pathologist must demonstrate its appearance in youthful diabetics and must show that it is peculiar in type. These questions have been discussed clinically in later pages. (See pp. 678, 688 and 689.)

The heart presented evidence of arteriosclerosis in 12 of the 17 cases over forty years of age who were examined by Warren and Root. Three showed extensive healed infarcts in the wall of the

[1] Bensley: Cited by Boyd and Robinson, Am. Jour. Path., 1925, **1**, 135.
[2] Boyd: Canad. Med. Assn. Jour., 1927, **17**, 1167.

left ventricle, 1 had an aneurysm of the wall of the left ventricle, 5 showed extreme sclerosis of myocardium (including 2 of the cases of infarct mentioned above), 3 showed moderate sclerosis (including the other case of infarct), 4 showed slight sclerosis, and 5 showed none. The coronary arteries were correspondingly affected in these patients. In 2 cases there was occlusion of a main branch of the coronary artery, in 1 the left branch of the coronary artery was practically occluded, in 7 there was marked coronary sclerosis, moderate sclerosis in 2, slight in 2, and no evidence of coronary disease in 6. In 2 of the negative cases a single slide of the heart wall was the only tissue available.

Arteriosclerosis of the aorta generally ran fairly parallel with that of the coronary arteries, though in a few cases the aortic changes were either more or less marked than those in the coronaries.

The frequency of severe myocardial damage and of sclerosis of the coronary arteries and the aorta is much greater than would be expected for similar age groups of non-diabetics. Of course our series is too small from which to draw any definite conclusions, but it does indicate an abnormal prevalence of vascular disease among diabetic patients. This may well be related to the abnormal fat metabolism and the striking tendency toward obesity.

In one sixteen-year-old boy (Case No. 1305) there were found at autopsy atheromatous plaques on the aorta. He had a high blood fat, and it seems quite possible that this is related to the arteriosclerosis. In addition large numbers of lipid-filled cells were present in the spleen. A similar case, a man, aged twenty-two years, reported by Smith[1] showed slight atheromatous plaques in the aorta.

The peripheral vessels, especially those of the legs, showed arteriosclerosis as would be anticipated, because 7 of the cases had had gangrene. Of such cases Wilder writes: "In all cases with gangrene there is serious sclerosis of the coronary arteries and very great coronary sclerosis and myocardial damage are present in 3 out of every 4 of them." I agree that arteriosclerosis in the legs implies its existence in the heart. Case No. 3210 died two hours before operation for gangrene and Case No. 4108 died at the very beginning of operation for gangrene. If the surgeons only realized how the hearts of these patients looked they would hardly be persuaded to operate at all. All types of arteriosclerosis are found in the legs, but I gather from conversations with Dr. Lawrence Smith and Dr. Shields Warren and from the surgeons that diabetics show rather more of the atheromatous type than of the senile type.

The frequency of chronic vascular nephritis in our series is also

[1] Smith, M. G.: Bull. Johns Hopkins Hosp., 1925, **36**, 203.

somewhat higher than is encountered in non-diabetic patients, reënforcing the other evidences of vascular disease. It was present in three-fourths of the cases over forty-five years of age.

The most remarkable example of arteriosclerosis in a diabetic in association with deposits of fat and cholesterol which I have seen is that reported by Gordon, Connor and Rabinowitch.[1] The patient was a mild diabetic, a familial diabetic, a gall-stone diabetic, the types of diabetes which in my experience are most benign. For thirteen years this mild diabetic, with the onset at the age of forty-five years, was conscientiously treated and studied, but throughout most of the period lived on a diet low in carbohydrate with an excess of fat and his weight rose in the five years before his death from 97½ pounds to 174 pounds. I abstract the following from the protocol of the autopsy:

"Equally interesting as the findings in the pancreas were those in the bloodvessels, particularly those of the base of the brain. The vertebral arteries contained large golden nodules. The arteries of the circle of Willis were beaded and resembled the usual severe arteriosclerosis except for the bright yellow color.

"Sections from the vertebral, basilar and internal carotid arteries showed marked fatty infiltration. The lumina of some of the vessels were narrowed by the thickened intima, and the large fatty cells beneath it. The media of some of the vessels were almost completely replaced by calcium and fat. The aorta showed marked fatty changes beneath the intima, had irregular thickening, by fibrosis, of the intima. In places the media was encroached upon by fat-laden cells, and small amounts of calcium were present between intima and media.

"In a section of the femoral artery the arteriosclerosis corresponded to the peripheral arteriosclerosis known as Monckeberg type. Chemical analyses of the bright yellow portions of the vessels suggested the presence of vegetable lipochromes in that they had high cholesterol contents.

"The heart weighed 420 gm. There was thickening and fatty degeneration of the aortic leaflets of the mitral valve and sinuses of Valsalva. There were some atheromatous plaques in the pulmonary artery and an increase in epicardial fat. The coronary orifices were patent, but the arteries were markedly sclerosed.

"A section of the coronary artery showed moderate intimal thickening and marked fatty infiltration beneath the intima. Many large fat-laden cells were present, partly encroaching upon the media of the vessel."

This patient did not live in vain. He became one of Woodyatt's

[1] Gordon, Connor and Rabinowitch: Am. Jour. Med. Sci., 1928, **175**, 22.

so-called pedigreed diabetic and as celebrated as his own cases and "Cyril K." and "Bessie B." With this portrayal before us I doubt if ever again any one will expose a diabetic to a low carbohydrate-high fat diet for so long a period. Without such treatment as this patient received in the decade before the discovery of insulin undoubtedly he would have died, but who of us believe with the evidence now available that if in the earlier years when the diet was restricted in carbohydrate, moderate undernutrition had been continued and obesity avoided, such excessive arteriosclerosis would have developed.

Carrasco[1] also shares my belief that the fat-protein diet may be responsible for some of the complications of the vascular system seen in diabetes who have followed this regimen for years.

Arteriosclerosis has been suggested by some as a cause of diabetes. If that is true why is it that as the diabetes progresses in duration and the arteriosclerosis increases the diabetes becomes less severe? Arteriosclerosis is a sequel rather than an antecedent of diabetes in my opinion.

8. **Glycogen.**—Glycogen was demonstrated in the nuclei of the liver cells in 15 of the 26 cases of Warren and Root. In the loops of Henle in the kidney no glycogen was found in 6 cases. Forty per cent of the insulin-treated cases showed no glycogen, while it was absent in only 11 per cent of the cases under dietary treatment. This last percentage was rendered unduly high by the small number in the series; it was quite remarkable to find no trace of glycogen in Henle's loops in diabetics who have not had insulin treatment. Warren and Root make no mention of the amount of glycogen in the muscles of the heart or muscles generally.

9. **Abnormal Deposits of Fat in the Diabetic.**—(*a*) **Obesity** preceded the onset of diabetes in 25 out of 26 of my patients reported by Root and Warren, and that 1 patient entered the hospital so ill that no adequate history of his previous weight was obtainable. The average maximum weights of those over forty years of age was 41 per cent above standard.

(*b*) **Gall-stones.**—The frequency of gall-stones in diabetes will be discussed on page 539. They were present in 6 of the 21 patients over twenty-five years of age at death and the seventh patient had a chronic cholecystitis with adhesions with obliteration of the gall bladder. In 4 of the cases large single stones occurred. Case No. 3592 had two large stones in the gall bladder consisting of radial cholesterol centers with superimposed layers of calcium-pigment-cholesterol which suggested a primary cholesterol stone deposited as a metabolic process due to increased cholesterol content of the plasma and bile. Aschoff has pointed out how such stones encour-

[1] Carrasco: Tratamiento de la Diabetes Sacarina, Montaner y Simon, Barcelona, 1925, p. 615.

age secondary infection of the gall bladder and this by extending to the pancreas may play some part in the etiology of diabetes. Hazel Hunt's preliminary analyses of these stones are suggestive of their being of a predominating cholesterol type.

The association of disease of the gall bladder and the coronary arteries is striking in our cases and deserves comment. Two of these patients died of angina pectoris, 1 with coronary thrombosis, 1 had

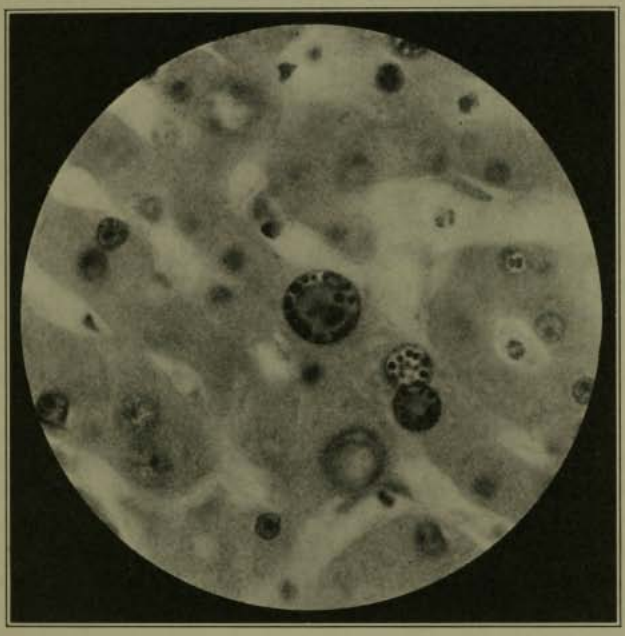


FIG. 29.—Liver. Glycogen in nuclei of liver cells in diabetes. Cytoplasm free from glycogen. ×1000 (Warren).

an old healed infarction of the left ventricle, and 2 had advanced coronary sclerosis and myocarditis. In 8 cases of gangrene at autopsy Wilder found gall stones in 5 and atherosclerosis in all.

Examination of the bloodvessels of our cases for cholesterol has been begun by Miss Hunt. A brief statement will be found on p. 687.

The trail of the harmfulness of an excess of fat in the diabetic can be seen (1) in his obesity, (2) in the deposits of fat in his arteries, whether large or small, (3) in the formation of gall stones, (4) in the fat in the liver which in animals experimentally may reach 25.3 per cent and, in addition, (5) in the spleen. These latter cases have escaped notice and this is my reason for recording the data of Warren and Root[1] in some detail.

[1] Warren and Root: Am. Jour. Path., 1926, **2**, 69.

10. **Lipid-containing Cells in the Spleen.**—The significance of large numbers of lipid-holding cells in the spleen is not clear, but their presence in the diabetic in conjunction with other abnormal deposits of fat deserves mention. In the average spleen removed at necropsy there is little evidence, either grossly or microscopically, of lipid content. Aside from this fairly common finding of lipid-containing cells in the spleen, there are a few cases recorded in which very marked hyperplasia of these cells occurs, and the lipid present does not as a rule give the staining reactions usually encountered. These cases are commonly associated with diabetes with lipemia. The first instance of this striking change in the spleen was mentioned by Coats.[1] The patient suffering from diabetes with lipemia had died in coma. Large lipid-containing cells made up most of the splenic tissue. Nine other cases have since been reported. To these Warren and Root add 3 more instances.

So far as can be judged from the staining reactions, the lipid is present in various forms and sometimes even varies in the same case, though cholesterol esters or related substances predominate. Thus in Case No. 1305, the larger droplets are presumably soaps or fatty acids among which, according to the reaction with osmic acid, are unsaturated fatty acids. The smaller droplets contain cholesterol esters.

In their first 2 cases, the long duration of the diabetes apparently has some relation to the condition. Two other cases of diabetes, about the same age as Case No. 1305, also died in coma. Their disease was of comparatively short duration, and the lipid-containing cells were not found in the spleen, nor was there any evidence of lipemia, though complete necropsies were done. In Case No. 1794, the blood fat was abnormally high five years before death. The gain in weight from 71 to 135 pounds under insulin treatment and the amount of body fat found at necropsy suggest that more frequent analyses of the blood would have revealed a more marked lipemia.

The spleen is not the only organ involved in this condition, though there the changes are more striking than elsewhere as a rule. Thus in Case No. 1305, lipid was present in the spleen, the endothelial cells of the liver sinusoids and the intima of the aorta. In Case No. 1794, lipid-containing endothelial cells occurred in the spleen, liver, coronary arteries and aorta. The lymph nodes and bone-marrow were not examined in either case. The fat was widely distributed in Case No. III, of Warren and Root being present in the heart muscle, the parenchymal cells of the pancreas and liver and the renal epithelium, while the entire reticulo-endothelial system of the spleen, lymph nodes, and liver contained lipid material.

[1] Coats: Glasgow Med. Jour., 1889, **32**, 95.

Oppenheimer and Fishberg[1] have stressed this involvement of the reticulo-endothelial system in lipemia and regard this group of cells as very important in relation to lipid metabolism. Very similar changes to those in the human cases were produced in rabbits by Anitschkow[2] through feeding cholesterol dissolved in sunflower oil.

In the discussion of their cases Warren and Root point out that there is another element of interest. Vascular lesions are very common. Whether these are merely xanthomas occurring in the intima of the vessels instead of the skin or definite atheromatous plaques is not easily decided. The case reported by Oppenheimer and Fishberg was a girl, aged six years, in whom yellowish patches occurred in the intima of the aorta and in the endocardium. Both patients reported by Lutz,[3] aged fifty-three and thirty-six years respectively, showed atheromatous patches in the aorta. The aorta in Smith's[4] case, a man aged twenty-two years, contained atheromata. In the other reported instances the condition of the vessels was not noted. Atheromata were found in the aorta of our Case No. 1305, aged sixteen years. Our Case No. 1794 died of a cardiac infarct resulting from coronary sclerosis at the age of thirty-three years. The aorta also was markedly sclerosed. The lipid present in the endothelial cells in the vascular lesions gave the same staining reactions as that in the cells in the spleen. Case No. III of Root and Warren, aged twenty-one years, showed numerous yellowish, raised patches in the intima of the aorta.

Here then are 5 persons from six to thirty-three years of age, with lipids in the blood that are taken up extensively by the cells of the reticulo-endothelial system, and all 5 show vascular changes.

The reticulo-endothelial system is probably involved in lipid metabolism, and may perhaps selectively absorb cholesterol compounds or phosphatides. Lipemia, produced by a high caloric diet, by a poorly-balanced diet or by the general cachectic state of the tissues in severe diabetes, may predispose to atheromatous degeneration in the arteries.

11. **The Duration of the Disease and the Effects Upon Its Pathology.**—Eight cases were under observation for remarkably long periods. The duration of the disease in 7 is known to have extended over fourteen to twenty-five years and 1 other, Case No. 1924, had been refused life insurance repeatedly because of sugar in his urine thirty years before death. These clinically were relatively mild cases. In 6 of the 8 cases the age at onset of the disease was under forty years, and the average age at onset of all 8 was thirty-six years. Of these 8 cases, 6 showed a considerable degree of hyaliniza-

[1] Oppenheimer and Fishberg: Arch. Int. Med., 1925, **36**, 667.
[2] Anitschkow: Beitr. z. path. Anat. u. z. allg. Path., 1914, **59**, 306.
[3] Lutz: Beitr. z. path. Anat. u. z. allg. Path., 1914, **58**, 273.
[4] Smith: Bull. Johns Hopkins Hosp., 1925, **36**, 203.

tion of the islands of the pancreas, 1 showed marked sclerosis of the islands and extreme hyaline change of the arterioles of the pancreas, and the islands in another appeared normal, though seemingly decreased in number. In all the cases there was a greater or lesser degree of sclerosis of the acinar tissue. The outstanding feature in all these cases is the presence of a few islands which show no demonstrable pathology, even though the majority may be seriously damaged.

12. **Pathological Evidence Upon the Question of Etiology of Diabetes.**—The variation and inconstancy of the pancreatic lesions are against an infectious origin for the disease, and the character of such lesions as may be present does not suggest the result of invasion by organisms. Indeed, one is tempted to wonder whether the changes in the islands may not be the result rather than the cause of diabetes. While it is true that in a few relatively early cases of diabetes we[1] found lymphocytes about the islands, this can hardly be considered as evidence for an infectious origin of the lesion.

Whatever the cause may be, it seemingly acts over a long period of time, perhaps throughout the duration of the disease. The pathology which we find in the pancreas at autopsy rarely represents the initial damage to the organ, but rather the result of a long struggle between the regenerative activity of the pancreas and the degenerative changes caused by the diabetogenic factor. The pancreas is not a static organ like the brain or myocardium, unable to repair itself after injury.

For some reason this static conception of the pancreas has become firmly established in spite of clinical and anatomical evidence to the contrary, probably because the diabetic patient cannot be cured and frequently goes steadily down hill in spite of treatment. We believe that this unfavorable course of the disease is not due to failure of the pancreas to regenerate, but to continued injurious action on the organ by the causal agent, eventually overcoming the regenerative efforts.

In any disease as insidious in onset and as chronic as diabetes, with pathological changes largely restricted to one portion of a single organ, one cannot expect any striking evidences of either destruction or regeneration. It is not unnatural that the conception of the diabetic pancreas as an inert organ, passively submitting to gradual destruction, has been firmly established.

We may assume that the lesions in diabetes are not infectious but toxic in origin. Their course is extremely chronic, and consequently the attempts at regeneration are slow. Mitotic figures would hardly be expected under the circumstances.

Practically all toxic lesions of the same age in the same organ resemble one another, as in toxic myocarditis or central necrosis of

[1] Warren and Root.

the liver. But in the islands of the pancreas showing either hyalinization or sclerosis, practically every stage from masses of hyaline or dense connective tissue imbedded in the stroma to apparently normal islands can be found. It is difficult to conceive a toxic substance of very chronic action or a long-continued functional strain totally destroying one island and completely sparing the next. Much more logical is the assumption that we are dealing with a gradual destruction of islands, a formation of new islands to replace them, exposure of these to the toxic substance with consequent pathological change and still more islands formed to take their places. The apparently normal cells found represent those most recently formed. Eventually the destructive process wears down the regenerative powers of the organ and the end comes.

13. **Hemochromatosis.**[1]—Hemochromatosis, as stated by Warren and Root, often known as bronzed diabetes, gives us an excellent opportunity to test this assumption. In this disease we are dealing with a known injurious agent, hemofuscin. This is a break-down product derived from hemoglobin and is deposited in various cells of the body, where it very slowly changes to hemosiderin. Eventually the accumulated pigment causes necrosis of the cell containing it. The liver is the first site of deposit, but as its cells become filled, the pigment overflows, one might say, to other organs. The pancreas is one of these.

In those cases of hemochromatosis where the pancreas has become seriously involved before death, diabetes occurs. If the pathology referable to the pigment cirrhosis of other organs be disregarded, this diabetes differs in no whit from diabetes mellitus, except that the course is more rapid.

Here then we have an ideal means of studying diabetes, with a known etiology and a fairly rapid course.

They had the opportunity of studying several cases of bronzed diabetes in this laboratory. They found the same variation in involvement of the islands as have been mentioned in cases of diabetes mellitus, ranging from the remains of islands represented by clusters of pigment-loaded endothelial leukocytes and fibroblasts in the stroma to islands without pigment and apparently normal. The conclusion is inevitable that new islands are being formed to take the place of those destroyed by the pigment deposits. In further substantiation of this evidence, occasional mitotic figures (in Case A 17–8) can be found in the cells of the younger, pigment-free islands (Fig. 30).

The pigment is not restricted to the island cells, but affects the acinar tissue as well. The same evidence of regeneration is offered by the acinar cells as by those of the islands.

[1] Mallory: Cited by Goodpasture: Am. Jour. Path., 1925, **1**, 1.

The well-established evidence of destruction and regeneration of parenchymal cells in the liver offers a striking parallel to the changes in the pancreas in hemochromatosis. Just as in the liver the parenchymal cells show every stage from newly-formed pigment-free cells through those containing hemofuscin and those containing hemosiderin to necrotic cells, the same steps can be traced in the acinar and island cells of the pancreas. If we substitute diabetes mellitus for hemochromatosis, hyaline formation in the islands for pigment deposit in the island cells, the analogy is complete.

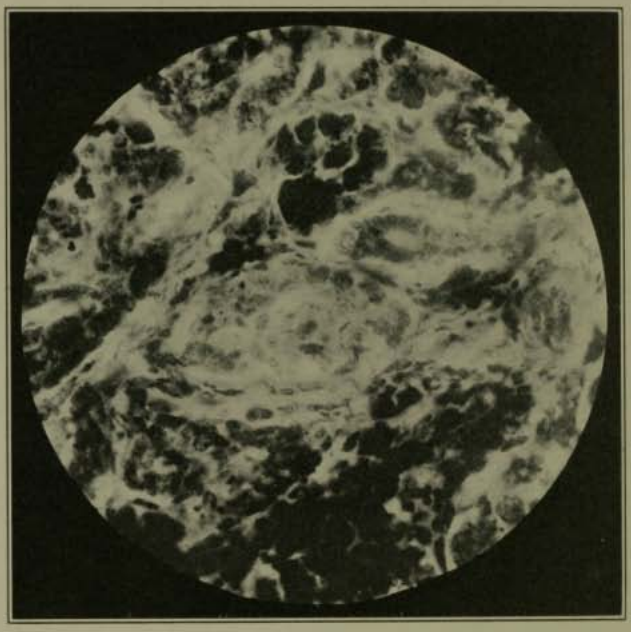


FIG. 30.—Hemochromatosis. Section of pancreas showing one island heavily loaded with pigment and another nearly pigment free, suggesting new formation. × 500 (Warren).

There is no reason to doubt that the increased fibrous tissue noted in the pancreas in some cases of diabetes mellitus accumulates in the same way as the fibrous tissue in cirrhosis of the liver. The parenchymal cells, sometimes of the islands, sometimes of the acinar tissue, or of both, are killed and disappear. Their stroma remains behind. The parenchymal cells regenerate and new stroma forms to support them. In this way the fibrous tissue gradually increases in amount. The increased fibrous tissue noted in the pancreas in some cases of diabetes is therefore not due to a simple proliferation of the interacinar and interlobular connective

tissue. Probably in most cases there has been damage to and regeneration of the acinar tissue as well as the islands. The inability of depancreatized dogs to live more than eight months without trypsin, as shown in Toronto[1] and Montpellier,[2] and the clinical evidence of disturbed external secretion of the pancreas in diabetic patients, as shown by Jones[3] and confirmed by Labbé[4] proves the entire gland to be involved.

In our series fibrosis of the pancreas is not found in those cases whose diabetes had existed less than two years. However, some of the cases of fairly long duration do not show any great increase in fibrous tissue.

Autopsies upon diabetic patients should be more numerous. One should never be content with a diagnosis of coma as a cause of death. What caused the coma?

Any physician who knows that his method of treatment will be checked up by an autopsy will unwittingly take more pains with his patient. It is human nature to do better work when one is under supervision, if only his own supervision. Doctors make mistakes, but in general the doctors who have the most autopsies are the ones who err the least. It is insurance for the best sort of treatment during life to stipulate that after death an autopsy shall be performed.

Patients are far more ready today than formerly to grant permission for autopsies and the hereditary element in the disease is a good reason for a request. On its part, the medical profession should do more than it has in the past to conform to proprieties and customs, and to protect the serious responsibilities laid upon undertakers.

A postmortem examination should be performed with as much delicacy and decorum as a surgical operation in an operating room. Hitherto this has not been the case largely because of lack of funds. The room for such examinations should be modernized, more adequately equipped, and should resemble an operating room. A nurse should be in charge and thus provide for the autopsy all the refinements a woman can lend to any medical procedure.

[1] Macleod: Loc. cit., p. 61.
[2] Hédon: Jour. d. Physiol. et de Path. Gén., 1927, **25**, 1.
[3] Jones, Castle, Mulholland, and Bailey: Arch. Int. Med., 1925, **35**, 315.
[4] Labbé: Arch. d. Mal. de l'App. Digest., 1926, **16**, 865.

SECTION V.

THE EXAMINATION OF THE URINE, BLOOD, AND RESPIRATION IN DIABETES.

REVISED WITH THE AID OF HAZEL HUNT
AND ALEXANDER MARBLE, M.D.

A. THE EXAMINATION OF URINE.

1. **The Desirability of Routine Examinations of Urine of All New Patients and of All Old Patients Annually.**—An early diagnosis in diabetes is as important as in tuberculosis. The diagnosis is made largely from the examination of the urine. How infrequent such examinations are is shown by the fact that in an analysis of 200 of my cases it was found that in only 52, or 26 per cent, was there a history of any urine analysis prior to the examination at which the diagnosis was made. The disease usually begins insidiously and its prompt detection depends upon the routine examination of the urine of all patients, rather than upon the examination of the urines of patients who present symptoms of the disease. In fact John[1] found that "among a series of 211 cases of diabetes, only 66 (31 per cent) named any complaint which would lead one to suspect the disease."

In a recent survey of 200 of my cases this same point was brought out, though by no means so strikingly: of the series of 200, there were 21, or 10.5 per cent, without symptoms pointing to the disease. In all acute illnesses urinary examinations should be made for albumin and sugar, and invariably at the last medical visit the doctor should secure a specimen of urine for his own protection. Never allow a new patient to leave the office without obtaining a specimen of urine. Do not trust to the patient's sending a twenty-four-hour specimen. Each has its own value. Gray[2] has emphasized the great advantages which may accrue from examinations of single specimens of urine and has shown that often these are of more service than twenty-four-hour specimens. It is especially

[1] John: Texas State Jour. of Med., 1923, **18**, 512.
[2] Gray: Boston Med. and Surg. Jour., 1923, **188**, 168.

desirable to secure specimens of urine within two hours after a hearty meal.

Such a sample from one of my patients showed 3 per cent sugar, while the specimen only two hours later was sugar-free by Benedict's qualitative test. Gray states: "Dilution is a dangerous mask. By testing separate voidings one can assure that more complete sugar freedom which is the obvious desideratum. Hence the best method alike for early diagnosis, for treatment, and for the doctor's periodic study, is to test every single specimen throughout twenty-four hours. Intermittent glycosuria often occurs at unexpected hours. Casts also are far more constantly found in fresh single specimens than in twenty-four-hour specimens, particularly in diabetic urines. When it is impracticable for the physician to study every sample, it is desirable to investigate a specimen one hour after a hearty meal . . . For patients about to take insulin, single specimens seem especially appropriate to guide the balancing of the dosage against the diet desired." The importance of securing several specimens, particularly in doubtful cases, cannot be overstressed. This was borne out in Case No. 2661 whose specimens as tested in my office at intervals of thirty minutes showed the following by Benedict's test:

	Sugar, per cent.
9.00 A.M.	2.8
9.30 A.M.	0.0
10.00 A.M.	0.0
10.30 A.M.	0.0

Suppose he had gone to different doctors each half hour:

Most cases of diabetes go on for months, many for years, without being diagnosed. Happily this does not appear to be as common as formerly, yet a recent study of 100 consecutive new cases seen in 1927 shows that the average interval between onset and diagnosis was six months.

It is inexcusable to neglect to examine the urine of any case coming for treatment. The wealthy parents of Case No. 1123, built a hospital for their community, but two doctors failed to examine the urine of their child and diabetes was diagnosed by a nurse. Similarly, the parents of Case No. 2568, took the precaution to send their children for medical inspection, prior to an European trip, but urinary examinations were omitted and the diagnosis of diabetes postponed for a year, to the sorrow and chagrin of the doctor.

I attach so much significance to this point that I believe if the physician is unable to secure the urine from the patient he should record this fact for his own self-protection. Practitioners in all branches of medicine should examine the urines of their patients or

demand a recent urinary report. I except no specialist, whether he be surgeon, ophthalmologist, otologist, laryngologist, gynecologist, neurologist, orthopedist, or dentist. All would be incomparably rewarded if they made gratuitous examinations of the urine for albumin and sugar for all patients coming to them. The expense would be trifling, the good done would be enormous. Furthermore, such thoroughness would redound to the credit of those who adopted it. General practitioners should teach their patients, as a matter of routine, to have their own urines and those of their families examined each birthday. This is not fantastic. It is simply a part of the movement to have each member of the community undergo a physical examination each year.

(*a*) **Inexpensive Urinary Examinations.**—Examination of the urine should cost the patient little. Formerly I deprecated the routine examinations made in drug stores, but now I welcome them because such examinations are so inexpensive. The mystery attached to a urinary analysis should be abolished. Recognized essentials alone should find place in an urinary report, which in turn should be expressed in the simplest terms and not be designed to impress the patients with awe. When I see two or even four full pages covered with a single urinary report and padded printed matter, yet showing on the face of it that modern analytical methods were not employed, I blush for the profession. When a urinary report was shown me for which a boy's father had paid $10, it was with considerable satisfaction that I taught the child to do the qualitative Benedict test for sugar, the materials for which can be purchased for 1 cent.

(*b*) **The Importance of a Physician's Laboratory.**—On the other hand, a physician's laboratory and his urinary examinations are often poor. It is not the rule for a physician to quantitate the sugar in the urine even by the fermentation test. The comparison between the outlay which the surgeon is willing to make for the conduct of his practice with that of the physician is most unfavorable to the latter. The surgeon almost invariably takes pride in his equipment, purchasing new apparatus and discarding old with a lavish hand. The physician seldom expends the fraction of this outlay in the development of a laboratory. This should be entirely different. The physician should take as much pride in a well-equipped and neat laboratory as the surgeon in his instrument case.

(*c*) **Causes Which Lead to the Examination of the Urine of Diabetic Patients.**—(1) *Life Insurance Examinations.*—Life insurance examinations led to the detection of sugar in the urine of 14 per cent of 3119 male cases of my series.

The other causes which led to the examination of urine were

those usually recorded in the symptomatology of diabetes, namely, polyuria, polydipsia, loss of weight, rapid gain in weight, weakness, pruritus, pains in the back or legs and polyphagia. (See p. 554.)

2. **The Volume of Urine in Twenty-four Hours.**—The quantity of urine frequently coincides with the quantity of sugar eliminated and von Noorden[1] gives a table to show this relation along with the co-existent specific gravities. (See Table 164.) The connection between volume, specific gravity and sugar percentage is by no means as close as his table would suggest. For comparison, some years ago I added to it figures based on 1127 successive cases of my own.

TABLE 164.—VOLUME OF URINE, SPECIFIC GRAVITY AND PERCENTAGE OF SUGAR COMPARED.

Volume of urine, cc.	Von Noorden.[1] Specific gravity.	Von Noorden.[1] Sugar percentage.	Author.[2] Specific gravity.	Author.[2] Sugar percentage
1,500– 2,500	1025–1030	2–3	1014–1038	2–8
2,500– 4,000	1030–1036	3–5	1010–1044	2–6
4,000– 6,000	1032–1040	4–7	1014–1036	2–8
6,000–10,000	1036–1046	6–9	1006–1036	3–7

But the volume of urine voided in twenty-four hours may give little index to the severity of diabetes. Cases of "diabetes decipiens" are most common. Case No. 8 at onset of treatment showed 1030 cc. of urine with 5 per cent of sugar, and twelve years later 1125 cc. of urine with 2.4 per cent of sugar. Case No. 340 showed 5.8 per cent of sugar in 1860 cc. of urine. Case No. 356 showed 5.8 per cent of sugar in 1035 cc. of urine. In other words, the twenty-four-hour quantity of urine may be normal and yet contain a large amount of sugar. That a patient reports that he is voiding a normal quantity of urine, therefore, is no excuse for the neglect of a urinary examination. However, it is unusual for the urine to be normal in quantity unless the patient is sugar-free, just as it is unusual for a patient long under treatment to have a normal urinary volume. This is particularly true of severe cases who are upon low diets and consuming substitute foods such as broths with their liberal salt content and agar-agar jellies.

There are other exceptions to Table 164. Severe cases of diabetes passing through a period of restricted diet show a steady and daily diminution in the quantity of urine consistent with the restriction of carbohydrate, provided acidosis is absent. On the other hand, if acidosis appears, it is occasionally found that the volume of urine fails to decrease and may rise. The quantity of urine may be quite independent of the amount of sugar which is excreted.

[1] Von Noorden: Loc. cit., p. 325.
[2] Figures in each group based upon 10 successive cases.

Rabinowitch[1] has noted an increase in urinary volume in a group of patients taking insulin whose renal threshold rose since beginning the drug although they exhibited no other signs of renal disease.

So far as I am aware the percentage of sugar as compared with urinary volume through the course of years has not been studied to determine its value in estimating changes in the renal efficiency of any given case.

The greatest volume of urine in twenty-four hours in comparison to the weight of the patient was voided by Case No. 1151, who developed diabetes at the age of three years and came under my care at the age of ten years weighing 18.6 kilos in October, 1916. During the first sixteen hours at the hospital the volume of urine was 7200 cc. and for the following twenty-four hours 7000 cc. If one should calculate on the same basis the total twenty-four-hour quantity of urine for the first day in the hospital it would amount to 10,800 cc., or 58 per cent of the body weight. Per minute he voided 7.5 cc. and per hour per kilogram 24 cc.

The volume of urine should be expressed in cubic centimeters. This enables the percentage of the twenty-four-hour amount of sugar to be most readily calculated. An ounce of urine is actually 29.6 cc., but in clinical work one may reckon it as 30 cc. for the errors in collection of urine more than offset the trifling error in the equivalent. One quart of urine is equivalent to 946 cc. From experience with patients, I believe accurate enough figures are obtainable, except for scientific experiments, if we consider a quart of urine 1000 cc. and I am content with this rule because the error comes in reporting too little rather than too much urine. Naturally, such methods are absolutely barred when accurate work is being done. To avoid the necessity of measuring the urine, wide-mouthed, stoppered bottles graduated in cubic centimeters should be employed. The use of the metric system is essential both in recording the urine and in computing the quantity of sugar, and, indeed, for the diet as well. Most patients are glad to adopt it. The avoirdupois system involves too much labor. Few, if any, instances are recalled of a physician who was accustomed to record the volume of the urine and quantity of sugar by the avoirdupois system who knew the total amount of sugar voided by his patient in twenty-four hours. How could such a physician estimate the quantity of carbohydrate in the diet in grains to the ounce?

3. **The Specific Gravity.**—The specific gravity of the urine in diabetes is usually high, but Case No. 38 showed sugar in the urine when the specific gravity was 1.007. Case No. 1673 showed 0.34

[1] Rabinowitch: Canad. Med. Assn. Jour., 1927, **17**, 685.

per cent sugar in the urine with a specific gravity of 1.006, and Case No. 1151 showed 0.3 per cent sugar with a specific gravity of 1.004, and on two occasions traces of sugar not quantitatable by the Benedict test with a specific gravity of 1.002. In a series of 147 routine examinations of diabetic urine specimens selected for study because the specific gravity was 1.010 or below in each case, John[1] obtained a positive test for sugar in 72.5 per cent. He states that "in many cases, both diabetic and non-diabetic, urine of a low specific gravity contains sugar; and the fact that urine has a high specific gravity does not necessarily indicate the presence of sugar." This is supported by the findings of Podesta.[2] A low specific gravity, therefore, is no more excuse for neglecting to examine the urine than is a normal quantity of urine.

The specific gravity of the urine has taken on increased significance since it has been shown that variations in the specific gravity during the day indicate very satisfactorily the functional power of the kidney. Perhaps no test of renal function is of greal value for the general practitioner or so simply performed.

TABLE 165.—THE FIXATION OF SPECIFIC GRAVITY. CASE NO. 1086.

Time. Oct. 31, 1916.	Volume, c.c.	Specific gravity.	Salt.		Nitrogen.	
			Per cent.	Grams.	Per cent.	Grams.
8 to 10 A.M.	130	1012	0.43	0.74	0.52	0.67
10 to 12 "	430	1008	0.53	2.0	0.32	1.3
12 to 2 P.M.	200	1012	0.4	1.2	0.54	1.1
2 to 4 "	155	1010	0.4	0.93	0.57	0.9
4 to 6 "	240	1010	0.42	1.4	0.43	1.16
6 to 8 "	270	1012	0.47	1.4	0.47	1.26
8 to 8 A.M.	1150	1012	0.57	4.4	0.47	5.4
Totals	2575			12.77		11.79

The fixation of specific gravity is well illustrated in Table 165. The patient, Case No. 1086, was a man, aged sixty-nine years, with prostatic obstruction, and the following test was made ninety-six days subsequent to the removal of the prostate gland by Dr. A. L. Chute. It will be seen that during the whole twenty-four hours the specific gravity varied from 1.008 to 1.012. Along with the figures for the specific gravity are included those for salt and nitrogen. They do not, however, rise and fall with the specific gravity and their variation is much wider than that of the specific gravity. Consequently, they indicate greater renal efficiency. It is well

[1] John: Jour. Am. Med. Assn., 1923, **81**, 1939.

[2] Podesta: Semana Medica, Buenos Aires, 1924, **1**, 1101; Abstr. Jour. Am. Med. Assn., 1924, **83**, 393.

to bear this in mind and not to become too despondent with the results of a two-hour renal test based upon specific gravities alone. Since the greatest excretion, as well as almost the highest percentage, of salt was with the lowest specific gravity, that evidence of functional power should be utilized in drawing conclusions.

4. **Sugars of Normal Urine.**—It has long been known that the urine of presumably normal individuals gives the usual copper reduction tests characteristic of sugar if sufficiently sensitive reagents are used; the amount of these substances is found to vary between 0.01 and 0.2 per cent. The nature of these reducing substances (non-nitrogenous) has been a subject for controversy for years and the question cannot as yet be considered fully settled. S. R. Benedict[1] was the first to observe that in normal people there is often a greater excretion of reducing substances following ingestion of carbohydrate; to this he gave the name "glycuresis." He maintains that the factors which lead to this excretion of a small amount of sugar following a meal are usually the same as those which lead to the concomitant elevation of blood sugar; he is quoted as regarding the sugar in diabetics' urines as representing only a quantitative exaggeration of a preëxisting normal excretion. On the other hand, Folin and Berglund[2] maintain that the sugar of normal urine has no relation to the main carbohydrate metabolism and that it consists of foreign unusable carbohydrate materials found in grains, vegetables, and fruits and in decomposition products resulting from the preparation of foods. Folin believes that "glycuresis" is independent of the blood-sugar level. Many workers have conducted investigations along these lines and much contradictory data has appeared in the literature. The main point of contention has been the question as to whether or not any of the reducing substances are really true glucose. The results of Blatherwick[3] and his coworkers have seemed to show that such is the case and that normal urine does contain a fermentable sugar whose chief source is the main carbohydrate metabolism. On the other hand the work of Host,[4] Greenwald, Gross and Samet,[5] Shaffer and Hartmann,[6] Lund and Wolf[7] and Patterson[8] seem to bear out the view that none of the reducing materials in normal urine is true glucose.

Indeed, the bulk of evidence seems to be piling up on the side of those who maintain that there is no fermentable sugar (specific-

[1] Benedict and Osterberg: Jour. Biol. Chem., 1918, **34**, 217; 1923, **55**, 769.
[2] Folin and Berglund: Jour. Biol. Chem., 1922, **51**, 213.
[3] Blatherwick, Bell, Hill, and Long: Jour. Biol. Chem., 1925, **66**, 801.
[4] Host: Jour. Metab. Res., 1923, **4**, 315.
[5] Greenwald, Gross, and Samet: Jour. Biol. Chem., 1924–1925, **62**, 401.
[6] Shaffer and Hartmann: Jour. Biol. Chem., 1920–1921, **45**, 365.
[7] Lund and Wolf: Biochem. Jour., 1926, **20**, 259.
[8] Patterson: Biochem. Jour., 1926, **20**, 651.

ally, glucose) in normal urine. One of the most recent papers is that of Eagle[1] working at the Johns Hopkins University. He concludes that "glucose is not normally excreted in the urine. What has heretofore been considered to be glucose, fermentable by yeast, is in reality a group of substances which only gradually decompose under the conditions of fermentation, possibly due to bacterial decomposition. Until a certain critical level of blood sugar has been reached, the kidney interposes an absolute barrier against the excretion of glucose. It is only when such large quantities as 100 gm. of glucose are taken that this critical level of blood sugar is exceeded in a certain proportion of normal individuals, and then only does fermentable sugar appear in the urine. Once begun, however, the excretion of glucose continues even after the blood sugar has receded to below this level. It is quite doubtful whether the normal individual, on an average diet, ever shows true glucose in the urine."

5. **Tests for Glucose.**—(Dextrose, $C_6H_{12}O_6$).—It is the presence or absence of glucose in the urine which is important rather than the percentage of sugar, though a knowledge of the latter is essential for careful work. The quantity of sugar in the urine should be recorded in per cent and in grams for the twenty-four hours. The clinic upon diabetes given by Friedrich von Müller at the Boston City Hospital, in which he illustrated the total amount of sugar voided by the patient by exhibiting an equivalent amount of cane-sugar, was most impressive to patient and student. I constantly employ this method in teaching and it never fails that some one in the audience appears astonished at the pound of sugar, more or less, which has been excreted in twenty-four hours. The pound, not the per cent, leaves the desired indelible impression.

In most chronic diseases there is no criterion by which the success or failure of treatment can be readily estimated. Such is not the case in diabetes. One can tell when treatment is successful, for the patient should be free from sugar and acid and be happy and vigorous. While the twenty-four-hour quantity of sugar in the urine is not an absolute measure of diabetes, still in the vast majority of cases it is an accurate index. Taken alone the quantity of sugar eliminated is not of great significance, still less the percentage of a single specimen, but when compared with carbohydrate intake it is possible to determine quite definitely the condition of the patient. It would be deplorable if anyone, because of the above statement, should lay undue stress upon this sign, since the strength, the weight, the mental attitude, the presence or absence of complications, and the acidosis are all important; but it remains true that

[1] Eagle: Jour. Biol. Chem., 1927, **71**, 481.

this is the one feature of the disease which is of almost mathematical accuracy, though we often err in thinking of it alone.

The sugar in the urine of diabetic patients usually varies directly with the quantity of carbohydrate-forming material in the diet, to a lesser extent with the protein, still less with fat, save as that influences the total caloric intake. A change of diet is shown in the urine within a few hours and sugar may appear within a few minutes after food.

(*a*) **Qualitative Tests.**—Many of the qualitatives tests for glucose are excellent, and nearly all have the advantage that although sugar is possibly present in the urine of normal individuals, they fail to demonstrate its presence unless the sugar exists in an amount greater than normal. The Benedict test is the most generally useful. It requires a single solution, keeps indefinitely, and the reaction offers less chance of error in that it is so adjusted as to be rather more sensitive to glucose than the well-known Fehling's solution and is not reduced by creatinine or uric acid or by chloroform which is often used as a urine preservative. Many false positive tests by this method, caused by concentrated urines, may be avoided by the use of slightly more Benedict's solution than originally directed.

Benedict's Test.[1]—The technique of this test has been slightly modified from that first described by Benedict in order to aid in the performance of as many tests as possible at the same time and also to prevent chance, false positive tests. The method of heating the tubes in a water-bath rather than over a free flame, as originally directed by Benedict, was first suggested to me and used by B. H. Ragle.[2] Later we found that Myers and Fine[3] had previously suggested a similar procedure. In the home patients can be taught to use the "teapot method" first described to me by Dr. John A. Peterson of Hingham. The method is so-called because a little teapot, reserved for the purpose, is so convenient for the test and the kitchen stove is far safer than an alcohol lamp over which to heat a test-tube. A more refined method is to use an electric stove or point. A man can complete his test while shaving; it thus becomes a part of the day's routine.

The test is carried out as follows: Eight (not more) drops of the urine to be examined are placed in a test-tube and to this are added 6 cc. (an ordinary teaspoon holds about 5 cc.) of Benedict's solution. The tube is agitated to mix the urine and solution and then placed in water that is already boiling. If a number of tests are to be made

[1] Benedict: Jour. Am. Med. Assn., 1911, **57**, 1193.
[2] Ragle: Boston Med. and Surg. Jour., 1915, **163**, 746.
[3] Myers and Fine: Essentials of Pathological Chemistry, reported from the Post-Graduate, 1912–1913, New York, p. 127.

at once, time may be saved by use of a large water-bath and a wire test-tube rack. After being in the boiling water for five minutes, the tube is removed and examined for evidence of reduction. In the presence of glucose the entire body of the solution will be filled with a precipitate, which may be greenish, yellow or red in color, according to whether the amount of sugar is slight or considerable. As used with urine the test is sufficiently delicate to detect quantities as small as 0.08 or 0.1 per cent sugar. A faint pea-green change in color represents about 0.08 to 0.1 per cent sugar.

This green color changes to a yellowish-green when the urine contains about 0.5 per cent sugar. When the solution loses the greenish tint entirely and becomes yellow or brown, the urine contains over 1 per cent sugar. Above this percentage the color of the solution gives very little aid in estimating the amount of sugar in the urine although large amounts of sugar will produce an orange or a brick-red test. The entire amount of copper in the 6 cc. of solution is reduced (as determined by allowing the test to stand and observing a water-clear supernatant fluid) by a urine of approximately 1.5 per cent glucose content. Rarely urines are tested which give a fluorescent appearance due to a very fine brick-red precipitation of the copper oxide. This seems to occur with severe diabetics who show sugar after eating certain fruits, are on low diets, and void large quantities of urine. Its appearance is related to the rapidity of reduction. It is so slight in amount that one is thrown off guard as to the amount of glucose present in the urine. On titration it is often found that there may be as much as 1 per cent sugar in a urine, which tested qualitatively might be estimated as 0.2 per cent.

The presence of a large amount of phosphate in the urine may produce a flocculent precipitate upon boiling with the copper reagent, but such a false positive test is very easily distinguished by the fact that it is not green but blue and also that it is coarsely flocculent and not in the fine suspension that the oxide of copper exhibits. Another source of falsely positive tests occurs when the urine is concentrated, amounting in twenty-four hours to less than 1000 cc. Under such circumstances creatinine is probably the disturbing factor. A false positive test of this character cannot be distinguished from a true test. The concentration of the urine therefore must be taken into account. Such an error can be excluded by a fermentation test. It should also be remembered that lactose will reduce Benedict's reagent, and positive tests during the latter months of pregnancy are not at all infrequent. Fermentation of such a urine will help to differentiate lactose from glucose but as Castellani and Taylor[1] have pointed out, many

[1] Castellani and Taylor: Jour. Am. Med. Assn., 1926, **86**, 523.

samples of bakers' yeast ferment lactose with gas production so that this test cannot by any means be taken as infallible. They advise indentification of glucose by certain strains of Monilia, which, however, would probably not be readily available for the practitioner.

The chief points to be remembered in the use of the Benedict reagent are: (1) The addition of not more or less than 8 drops of urine, delivered from an unbroken medicine dropper; (2) the use of not less than 5 cc. or more than 8 cc. of Benedict's solution; (3) the transfer of the tube to water actually boiling where it should remain for five minutes; (4) the change in color and transparency of the solution is the criterion for a positive test for sugar.

The formula and directions for preparing the Benedict solution follow. These should be strictly adhered to in preparing the solution.

	Grams or cc.
Copper sulphate (pure crystallized)	17.3
Sodium or potassium citrate	173.0
Sodium carbonate[1] (anhydrous)	100.0
Distilled water to make	1000.0

The citrate and carbonate are dissolved together (with the aid of heat) in about 700 cc. of water. The mixture is then poured (through a filter) if necessary, into a larger beaker or casserole. The copper sulphate (which should be dissolved separately in about 100 cc. of water) is then poured slowly into the first solution, with constant stirring. The mixture is then cooled and diluted to 1 liter. This solution keeps indefinitely.[2]

(*b*) **Quantitative Tests.**—Although none of the quantitative tests for glucose in the urine are as satisfactory as the qualitative tests, there are now available relatively simple and reliable methods. The more accurate of these procedures require a laboratory, but methods sufficiently correct for clinical work can easily be performed by the general practitioner, the nurse, or by more intelligent patients in the home. Such simplification of the treatment of diabetes means everything to the practitioner and to the patient. The highest percentage of sugar found in the urines of my patients was with Case No. 2292. The onset of the disease was in June, 1920. The patient first came for treatment July 23, 1921 at the age of sixteen years and eleven months. The urine voided at this first visit at my office on July 23, 1921, was of specific gravity 1.045 and contained 14 per cent sugar. The quantitative analyses were checked twice by my assistant, Howard F. Root. The following twelve-hour specimen of urine voided during the night, after diet had been restricted, amounted to 1600 cc., with specific gravity of 1.042 and

[1] The crystallized (10 molecules of water) Na^2CO^3 is more soluble; 270 grams of the crystals are equivalent to 100 grams of the anhydrous salt.

[2] Patients in doubt about the quality of their Benedict's solution are taught to test it with orange juice.

contained 8.5 per cent sugar. The patient was later treated with insulin, taking 20 units per day. With this he tolerated a diet of carbohydrate 66 grams, protein 72 grams, fat 154 grams. In January 1928, he reported that he is sugar-free most of the time and that his weight has increased 25 pounds. His diet at that time was carbohydrate 90 grams, protein 90 grams, fat 140 grams, insulin 50 units.

The quantitative tests given below are those which we have found to be most practical:

1. *Original Method of Benedict.*[1]—This original standard method is the one from which the various modifications have been devised. It is now used but little at the New England Deaconess Hospital but it is regarded as the method of choice when quite accurate determinations are desired; for example, it is used to check up the percentage of sugar in rare specimens containing over 10 per cent. The method is based on the fact that in alkaline solution a given quantity of glucose reduces a definite amount of copper, thus decolorizing a certain amount of copper solution. The copper is, however, precipitated as cuprous sulphocyanate, a snow-white compound which is an aid to accurate observation of the disappearance of the last trace of color. The solution for quantitative work, which keeps indefinitely, has the following composition:

"Pure crystallized copper sulphate 18 grams.

"Sodium carbonate, anhydrous 100 grams or 270 grams of the crystalline salt.

"Sodium or potassium citrate 200 grams.

"Potassium sulphocyanide 125 grams, or sodium sulphocyanide 100 grams.

"Five per cent potassium ferrocyanide solution 10 cc.

"Distilled water to make a total volume of 1000 cc.

"With the aid of heat dissolve the carbonate, citrate, and sulphocyanide in approximately 600 cc. of water and filter if necessary. Dissolve the copper sulphate separately in about 100 cc. of water and pour quantitatively the solution into the other liquid, with constant stirring. Add the ferrocyanide solution, cool and dilute to exactly 1 liter. Of the various constituents the copper salt only need be weighed with exactness. Twenty-five cc. of the reagent are reduced by 50 mg. (0.05 gram) of glucose."

The procedure for the estimation is as follows: If the qualitative test has indicated a low percentage of sugar, the urine is used undiluted, otherwise 10 cc. are diluted to 100 cc. and this solution is used for the titration. The urine prepared as above is poured into a 50 cc. burette up to the zero mark.

"Twenty-five cc. of the reagent are measured with a pipette into a porcelain evaporating dish (10 to 15 cm. in diameter), 10 to 20

[1] Benedict, S. R.: Jour. Am. Med. Assn., 1911, **57**, 1193.

grams of crystallized sodium carbonate (or one-half the weight of the anhydrous salt) are added together with a small quantity of powdered pumice stone or talcum, and the mixture heated to boiling over a free flame until the carbonate has entirely dissolved. The diluted urine is now run in from the burette, rather rapidly, until a chalk-white precipitate forms and the blue color of the mixture begins to lessen perceptibly, after which the solution from the burette must be run in, a few drops at a time, until the disappearance of the last trace of blue color which marks the end-point. The solution must be kept vigorously boiling throughout the entire titration."

If the mixture becomes too concentrated during the process, water may be added from time to time to replace the volume lost by evaporation; however, too much emphasis cannot be placed upon the fact that the solution should never be diluted before or during the process to more than the original 25 cc. Moreover, it will be found that in titrating concentrated urines, or urines with small amounts of sugar, a muddy brown or greenish color appears and obscures the end-point entirely. Should this be the case the addition of about 10 grams of calcium carbonate does away with this difficulty. The calculation of the percentage of sugar in the original sample of urine is very simple. The 25 cc. of copper solution are reduced by exactly 0.05 gram of glucose. Therefore the volume of diluted urine drawn out of the burette to effect the reduction contains 50 mg. of sugar.

When the urine is diluted 1 to 10, as in the usual titration of diabetic urines, the formula for calculating the percentage of sugar is the following:

$\frac{0.05}{x} \times 1000$ = percentage in the original sample, wherein x is the number of cubic centimeters of the diluted urine required to reduce 25 cc. of the copper solution.

"In the use of this method chloroform must not be present during the titration. If used as a preservative in the urine it may be removed by boiling a sample for a few minutes, and then diluting to the original volume."

2. *Simplified Benedict Test.*—In this modification, devised by Millard Smith, 5 cc. of a *modified* Benedict's quantitative solution are used instead of the full 25 cc. as outlined in the original method of Benedict. Since this method is no longer used by us to any great extent, it is described only by reference to the third edition of this book.

3. *The Micro-modification of Benedict's Test.*—Also devised by Millard Smith[1] is the method used routinely in the laboratory of the

[1] Smith: Jour. Lab. and Clin. Med., 1922, **7**, 364.

New England Deaconess Hospital. The test can be performed in a minimum of time, is very simple, and if carefully carried out furnishes sufficiently reliable data. It is not necessary to calculate the final percentage of sugar for this can be read directly on the special pipette used for titrating. The method is described in detail below.

The apparatus[1] needed consists of a small ring stand with test-tube clamp, a micro-Bunsen burner or small alcohol lamp, a pyrex test tube (18 by 160 mm.), a Millard Smith pipette No. 2, and one 1 cc. Ostwald pipette.

With the Ostwald pipette transfer 1 cc. of Benedict's original quantitative solution into the test-tube (held in the ring stand clamp) and then add 0.2 to 0.7 gram of anhydrous sodium carbonate. A small well-dried pebble, or a piece of quartz, or a pinch of talcum powder should also be added to prevent bumping.

Heat the mixture to boiling and add the urine from the Smith pipette until reduction is complete as evidenced by the disappearance of the blue color. Read the percentage of sugar directly from the pipette. The approximate strength of the urine, with a slight amount of experience, is easily estimated from the qualitative Benedict test. Urines expected to contain 1 per cent or less of sugar are titrated directly. Those over 1 per cent are diluted ($\frac{1}{10}$ or $\frac{1}{20}$) before titration. All dilutions of the urine reduce, of course, the accuracy of the results obtained due to dilution of the urinary salts.

For *rapid* reduction of the reagent vigorous boiling is essential, which may result in too rapid evaporation. This is avoided by allowing more time for reduction between additions of urine.

The best results are obtained if the solution is kept at the boiling point by manipulation of the flame and the urine added slowly. A very small flame should be employed. *The tendency in this titration of sugar is to go past the end-point. This is because the reduction does not take place as rapidly as the ordinary titrations to which one is accustomed. When nearing the end-point the urine must be added slowly.* In urines of low-sugar content the boiling should be rather vigorous at first in order to maintain a constant volume while the 1 to 2 cc. of urine necessary to give complete reduction are being added. With a moderate amount of practice the regulation of the volume of the boiling solution becomes quite simple.

4. *Polariscopy.*—The determination of the percentage of sugar by means of the polariscope is on the whole convenient and accurate, but has the disadvantages that the instrument is expensive, that the urine must be filtered and sometimes further clarified by the use of infusorial earth, and also that, in the presence of β-oxybutyric

[1] The apparatus may be purchased from many surgical supply houses or from the manufacturers, Emil Greiner Co., 55 Vandam St., New York City.

acid, which is levorotatory, while glucose is dextrorotatory, the error may be considerable, even amounting to as much as 57 grams sugar in twenty-four hours, as in Case No. 235. Although this error can be obviated by determining the levorotatory power of the urine after fermentation and adding this fraction of a percentage to the percentage of sugar obtained before fermentation, the procedure takes too long to be of much aid. We do not use the polariscopic method at all now although it was the routine procedure a few years ago.

5. *Fermentation.*—Physicians who devote only slight attention to diabetes may find the fermentation test to be of value, but it is by no means as satisfactory as the newer micro-chemical methods. Recent tests in our laboratory tend to show that it gives results far from accurate. Directions are given below.

To 100 cc. of urine of known specific gravity, one-fourth of a fresh yeast cake, thoroughly broken up, is added and the whole is set away at a temperature of 85° to 95° F. Twenty-four hours later the urine is tested with Fehling's or Benedict's solution. If a reduction is obtained, it is set aside for further fermentation. Complete fermentation having been proved, the specific gravity is taken after the urine has acquired its original (room) temperature. If the temperature of the urine is 76° F. (room) when the specific gravity is taken at the beginning and end of the test, the result will be more accurate. The difference in specific gravity multiplied by 0.23 gives the percentage. In the performance of the fermentation tests for sugar a few crystals of tartaric acid should be added whenever the urine is alkaline.

The test is most valuable in determining the presence or absence of traces of sugar. At the end of twenty-four hours, if the filtered urine which previously showed a doubtful test for sugar with Fehling's or Benedict's solution shows no reduction upon repetition of the test, it can be assumed that a fermentable substance, presumably glucose, was present.

6. **Tests for Other Sugars.**—Other sugars than glucose are occasionally found in the urine. It is rare that they cause confusion. It is not quite so easy to detect or to exclude them, as would appear from the description of the tests by which they are said to be identified. Of these various sugars lactose is the one most commonly encountered.

(*a*) **Lactose** ($C_{12}H_{22}O_{11}$).—Lactose in the urine may give rise to confusion in the performance of Fehling's or Benedict's tests. Fortunately, the conditions in which it is liable to occur, pregnancy and the lactation period, are usually known to the physician, and it is then not considered of significance. It has also been found in the urines of nurslings. Lactose, like glucose, reduces copper, is

dextrorotatory, but it yields a characteristic osazone with phenylhydrazin and does not ferment with pure yeast (saccharomyces-apiculatus). However, the osazone is very difficult to obtain from the urine and ordinary yeast is not to be depended upon for the fermentation test.

1. *Rubner's Test.*—To 5 cc. of urine in a test-tube, add 1 or 2 grams of lead acetate. Heat until bubbles appear and then add ammonium hydrate until the color changes. A deep yellow or brown color in the solution is distinctive of lactose, whereas in the presence of dextrose the color is a cherry-red.

2. *Mucic Acid Test.*—This test does not distinguish between lactose and galactose, but the latter very rarely occurs. The test is, therefore, of considerable value in differentiating these two sugars from all other reducing sugars. It is performed as follows: To 100 cc. of the urine add 20 cc. of concentrated nitric acid and evaporate the mixture in a broad, shallow glass vessel, upon a boiling water-bath, until the volume of the solution is only 20 cc. At this point the fluid should be clear and a fine, white precipitate of mucic acid should separate. If the percentage of lactose present in the urine is low, it may be necessary to cool the solution and permit it to stand for some time before the preciptate will form. If the specific gravity of the urine is 1.020 or over, it is necessary to use 25 to 35 cc. of nitric acid. Under these conditions the mixture should be evaporated until the remaining volume is approximately equivalent to that of the nitric acid added.

(*b*) **Pentose** ($C_5H_{10}O_5$).—Pentose is occasionally present in the urine. As Rabinowitch[1] states: "though alimentary pentosuria is not infrequently met with, chronic (essential, spontaneous) pentosuria is rare. Less than 50 cases are on record. What is actually known is described in Garrod's[2] classical monograph." From study of his case of chronic pentosuria, Rabinowitch found no indication of diminished sugar tolerance.[3] It may be suspected when Fehling's test, performed in the ordinary way, fails to show reduction upon the second boiling, but later suddenly causes a partial reduction. However, urines containing small quantities of glucose may behave in the same way. Pentose neither ferments nor is it optically active. It may be detected by the Bial test.

Orcinol-hydrochloric Acid (Bial) Test.—Bial's reagent is employed and is as follows:

Orcinol	15 grams
Fuming HCl	500 grams
Ferric chloride (10 per cent)	20 to 30 drops

[1] Rabinowitch: Jour. Clin. Invest., 1926, **2**, 457.

[2] Garrod: Inborn Errors of Metabolism, London, Hodder and Stoughton, 2d ed., 1923.

[3] Levy and Pierson in Am. Jour. Dis. Child., 1927, **33**, 213, report a case in boy of 14 years in whose family reducing substances were present in the urine in 4 generations. Dr. Stephens of the Presbyterian Hospital of New York has had 5 cases.

To 5 cc. of the reagent in a test-tube add 2 to 3 cc. of urine and heat the mixture gently until the first bubbles rise to the surface. Immediately, or upon cooling, the solution becomes green and a flocculent precipitate of the same color may form. This test is more specific than the original orcinol test.

(*c*) **Levulose** ($C_6H_{12}O_6$).—Levulose is frequently present in the urine of severe diabetics. It is not easily identified. It is levorotatory, but so is β-oxybutyric acid, which is found under similar conditions. Levulose ferments with yeast, gives a positive Fehling and Benedict test, and yields the same osazone as does dextrose with phenylhydrazin. Levulose can, however, be differentiated by the Seliwanoff reaction, provided the following precautions are observed: (1) The concentration of the HCl must not be more than 12 per cent; (2) the reaction (red color) and the precipitate must be observed within twenty to thirty seconds of boiling; (3) glucose must not be present in amounts exceeding 2 per cent; and (4) the precipitate must be soluble in alcohol with a bright red color.

1. *Seliwanoff's Test.*—Seliwanoff's reagent is prepared by dissolving 0.05 gram of resorcinol in 100 cc. of dilute (1 to 3) HCl. To 5 cc. of the reagent in a test-tube add a few drops of the urine under examination and heat the mixture to boiling. The presence of levulose is indicated by the production of a red color and the separation of a red precipitate. The latter may be dissolved in alcohol to which it will impart a striking red color.

(*d*) **Maltose** ($C_{12}H_{22}O_{11}$).—Maltose very rarely occurs in human urine, and has not been shown to be of clinical significance. Maltose is powerfully dextrorotatory, is completely fermented by yeast, reduces copper slowly, and yields a characteristic osazone.

(*e*) **Glycuronic Acid** ($C_6H_{10}O_7$).—Glycuronic acid as such is not found in fresh urines, but conjugated glycuronic acids occurring in the urine spontaneously decompose and may cause confusion. Such conjugated glycuronic acids only appear after the ingestion of chloral hydrate, camphor, menthol, turpentine, or phenol in large enough quantities to be of significance. If this point is borne in mind confusion will not arise. Glycuronic acid reduces copper and bismuth, but does not ferment. It may be difficult to detect in the presence of pentose, although one can rely on the characteristic osazone of pentose if differentiation becomes necessary.

(*f*) **Substances Found in the Urine Which Give Rise to Confusion in Testing for Sugar.**—These may be divided into two groups: those in normal urines and those in pathological urines. Very few substances, however, interfere with the accuracy of the modern Benedict's solution although the older Fehling's test may be misleading in more instances. Of these met with in normal urine creatinin and uric acid are the most common.

7. **Methods for the Determination of the Urinary Acids.**—(*a*) **Qualitative Tests.**—1. *Diacetic Acid* (CH_3COCH_2COOH).—The simplest method for the detection of acidosis by urinary examination is Gerhardt's ferric chloride reaction for diacetic acid. The test may be performed as follows: To about 10 cc of the fresh urine carefully add a few drops of an undiluted aqueous solution of ferric chloride, Liquor Ferri Chloridi, U. S. P. A precipitate of ferric phosphate first forms, but upon the addition of a few more drops is dissolved. The depth of the Burgundy-red color obtained is an index to the quantity of diacetic acid present. On account of the merely approximate value of the reaction I now record the intensity of the reaction as follows: +, ++, +++ instead of in four degrees of intensity. Lüthje pointed out the fallacies of this method and Table 166 shows how unreliable Benedict and I have also found it to be.[1]

TABLE 166.—COMPARISON OF DIACETIC ACID AND β-OXYBUTYRIC ACID

Diacetic acid, symbol.	β-oxybutyric acid, grams.
0	5.7 to 11.0
+	7.0 to 14.2
++	8.5 to 55.3
+++	13.3 to 51.0
++++	17.6 to 36.8

It should not be forgotten that if a patient is taking salicylates, antipyrin, cyanates, or acetates, the foregoing test will give a similar reaction, but one that cannot be mistaken if the solution is boiled for two minutes. Diacetic acid is unstable and any color it causes will disappear upon boiling, whereas the red color caused by any of the above substances does not disappear upon boiling. Diabetic patients often take salicylates for pain of one kind or another, and therefore one must always be on the watch for this possibility. I have seen a patient on the verge of coma who was taking salicylates, and at the start confusion arose as to whether the ferric chloride reaction was due to diacetic acid or to salicyluric acid. The vacation of another patient in Europe was abruptly terminated, so far as I can determine, by a falsely positive ferric chloride test due to the oil of wintergreen in an innocent officinal, compound rhubarb pill. As a routine procedure in the laboratory of the New England Deaconess Hospital the sodium nitroprusside test is performed on all urines which give a red color with the Gerhardt test which does not fade upon boiling. In this way acetone bodies masked by the "drug reaction" can be detected.

With the test for diacetic acid the physician must be absolutely at home. It is doubtful if 1 physician in 500 will employ any better

[1] Benedict and Joslin: Carnegie Inst., Washington Pub., **136**, p. 25.

test for acidosis, and only rarely is any other test necessary. It may be helpful to know that if in an emergency the liquor ferri chloridi is not available, ordinary tinctura ferri chloridi will do almost as well.

2. *Acetone* (CH_3COCH_3).—The test for acetone was the first employed for the detection of acid poisoning, but the small rôle which Folin[1] has shown that acetone plays in the total acidosis led me to discard it, believing it better to concentrate time upon the quantitative estimation of the acidosis than to use several qualitative tests. Folin demonstrated that most of the substance supposed to be acetone in the urine is really diacetic acid, and that Legal's test for acetone is really a very delicate test for both diacetic acid and acetone. The different tests for acetone are in reality tests for both acetone and diacetic acid.

Weiland, quoted by L. Blum,[2] says that acetone may amount to 1.67 grams and yet the Gerhardt test for diacetic acid be negative, while at other times the presence of 0.1 gram of acetone in the twenty-four hours is sufficient to make the Gerhardt test positive.

The simplest and most reliable test for acetone plus diacetic acid is a modification of Rothera's test. The reagent is prepared as follows: Dry sodium nitro-prusside is ground to a fine powder and then is thoroughly ground up and mixed with dry ammonium sulphate in the proportions of 0.5 gram of sodium nitroprusside to 200 grams of ammonium sulphate. The resulting mixture has a pale pink color; it is very stable and may be kept indefinitely, thus being much more satisfactory than the usual 5 per cent solution of sodium nitroprusside which should be prepared fresh nearly every time it is used.

To perform the test for acetone proceed as follows: Place 2 or 3 cc. of urine in a test-tube and saturate with the nitroprusside mixture described above; now add a few drops of strong ammonia water and shake. In the presence of acetone a strong purple color is rapidly developed. At the end of two or three minutes the maximum color will have appeared and the test may be read. Since the maximum color slowly turns into a muddy brown, one should read the test before this occurs. A little practice enables one to tell the point of maximum color formation. A positive test is evidenced by a range of color from a faint purplish-pink to a very dark purple. A faint pink may be called 1 plus and a dark purple which does not transmit light a 7 plus. One soon becomes accustomed to making the graduations between these two extremes. Usually the ferric chloride test becomes positive when the nitroprusside test is 5 plus.

[1] Folin: Jour. Biol. Chem., 1907, **3**, 177; Jour. Am. Med. Assn., 1907, **49**, 128; Lab. Manual of Biol. Chem., New York, Appleton & Co., 1925, p. 189.

[2] Blum: Ergebnisse der inneren Medizin und Kinderheilkunde, 1913, **2**, 454.

This is a valuable test in following the course of cases of pernicious vomiting. These are at times quite severe in degree at a stage when the ferric chloride test begins to be positive. It is also of value in watching the disappearance of the final traces of acidosis in treated cases of diabetes or in detecting early tendencies to returning acidosis.

If preferred, the test may be done in the following way: Add 1 to 2 cc. of 10 per cent acetic acid and a small crystal of sodium nitroprusside to 5 cc. of urine in a test tube. Shake, add 2 to 3 cc. of strong ammonia water, and shake again. A purple color indicates diacetic acid and the reaction is read as described above.

3. *β-oxybutyric Acid* ($CH_3CH(OH)CH_2COOH$).—There is no simple qualitative test for β-oxybutyric acid.

(*b*) **Quantitative Tests.**—The determination of the extent of the acidosis is of prime importance in the treatment of any severe case of diabetes. I sympathize with any physician who must treat a severe case of diabetes without a knowledge of the degree of acid poisoning present. Fortunately, comparatively simple methods are at hand which are quite satisfactory in routine treatment; but even most of these simple methods are too complicated for a physician with a large practice who has only a few cases of diabetes in the course of a year.

1. *Reaction of Urine.*—The most easily performed of the urinary tests are concerned with the reaction of the urine. Although the urines of normal individuals are frequently neutral or alkaline, this is seldom the case with urines of diabetics, for the protein-fat diet of the diabetic favors an acid reaction, despite the alkaline salts present in diabetic vegetables.

(*a*) *Total Titratable Acidity.*—The total titratable acidity of the urine is a very good index of the amount of acidosis and runs parallel with the ammonia excretion. The determination is made as follows: Transfer 20 cc of undiluted urine to a small beaker and add 15 grams of neutral potassium oxalate crystals. *Extreme care must be taken that the oxalate is neutral.* Add 3 or 4 drops of 1 per cent phenolphthalein in 95 per cent ethyl alcohol solution and titrate with $\frac{N}{10}$ NaOH to the first *faint* permanent tinge of red, using another beaker containing 20 cc. of the urine as a guide. Calculate the total excretion of acid in terms of $\frac{N}{10}$ NaOH for the twenty-four hours. A normal individual excretes between 200 and 500 cc. of $\frac{N}{10}$ acid bodies in twenty-four hours. Amounts considerably in excess of this quantity indicate acidosis.

It has been proposed to estimate the degree of acidosis by determining the quantity of alkali which it is necessary to give the patient to render the urine alkaline. I do not recommend this method, for I do not approve of giving alkalis to diabetic patients

unnecessarily. It is mentioned to illustrate in a homely way the intensity of the diabetic acidosis. Ordinarily, 5 to 10 grams of sodium bicarbonate will render the normal urine alkaline, but in diabetic patients with an acidosis of moderate severity 20 to 30 grams are required, and in severe cases of acidosis 50 grams daily for a week or more make little impression, and even with doses of over 100 grams sodium bicarbonate in twenty-four hours the urines of patients in coma frequently remain acid. A table has been constructed by von Noorden showing approximately the quantity of acidosis which can be assumed to be present when various quantities of sodium bicarbonate are required to render the urine alkaline.

TABLE 167.—THE RELATION BETWEEN THE QUANTITY OF SODIUM BICARBONATE REQUIRED TO RENDER THE URINE ALKALINE AND THE ACID BODIES PRESENT.

$NaHCO_3$ required to render urine alkaline, grams.	Approximate acidosis in terms of β-oxybutyric acid, grams.
20	Under 15
30 to 40	20 to 30
40 +	30 to 40

Methods of determining the alkali tolerance have been described by Sellards[1] and by Palmer and Henderson.[2]

2. *Ammonia.*—The quantity of ammonia in the urine is a measure of the reaction of the body to counteract the acidosis produced in it. To this extent its estimation gives a more accurate idea of the acid production of the body than any other of the urinary tests at our disposal, which simply show the quantity of acid leaving the body. The test, however, becomes of less value so soon as extraneous alkali is administered, because under such conditions the ingested alkali is used by the body in preference to ammonia. The normal amount of ammonia-nitrogen in the urine varies between 0.5 and 1 gram per day, and the ratio between the ammonia-nitrogen and the total nitrogen in the urine is fairly constant at 1 to 25 (4 per cent). In severe diabetes the ammonia may gradually increase and in Case No. 344 it amounted to 8 grams in one day. The nitrogen upon this same day was 19.2 grams, giving an ammonia-nitrogen : nitrogen ratio of 34.3 per cent. On another day this ratio reached 44.4 per cent, but the absolute quantity of ammonia was only 4.4 grams and the nitrogen 8.7. Case No. 208 had an ammonia nitrogen : nitrogen ratio of 53 per cent when the total nitrogen excretion was 9.2 grams and the ammonia-nitrogen amounted to 4.9 grams. These high ammonia-nitrogen : nitrogen ratios are ordinarily

[1] Sellards: Johns Hopkins Hosp. Bull., 1912, **23**, 289.
[2] Palmer and Henderson: Arch. Int. Med., 1913, **12**, 153.

obtained only when the total quantity of nitrogen in the urine is small. The two procedures which we have employed for the determination of ammonia follow:

(*a*) *Permutit Method.* (Folin and Bell[1]).—This method is based upon the power of permutit to absorb the ammonia from interfering substances in the urine, the subsequent liberation of the ammonia from the permutit by treating with alkali and finally the Nesslerization of the liberated ammonia. This method in detail is as follows:

Transfer 2 grams of permutit[2] to a 200 cc. volumetric flask. Add about 5 cc. of water (no more) and with an Ostwald pipette introduce 1 or 2 cc. of urine, or with a 5 cc. pipette introduce 5 cc. of previously diluted urine, corresponding to 1 or 2 cc. of the original urine. With urines extraordinarily poor in ammonia it may be necessary to use 5 cc. of urine, but in so far as it may be practicable, it is better not to use more than 2 cc. and to employ a weaker standard (0.5 mg. of nitrogen) for the color comparison. Rinse down the added urine by means of 1 to 5 cc. of water, and shake gently but continuously for five minutes. Now rinse the powder to the bottom of the flask by the addition of 25 to 40 cc. of water and decant. Add water once more and decant, but if the urine is rich in bile, it is advisable to wash once or twice more. Add a little (5 cc.) water to the powder, introduce 2 cc. of 10 per cent sodium hydrate, mix, allow to stand about ten minutes and then add more water until the flask is about three-fourths full. Shake for a few seconds and then add 20 cc. of Nessler's reagent prepared as described on p. 448. Mix, and let stand in the stoppered flask for ten minutes or as much longer as may be convenient. Fill up to the mark with water, mix and compare in the colorimeter with the standard. The standard should be made up from a stock solution containing 4.716 grams of ammonium sulphate of high purity plus 11.5 cc. of concentrated HCl (specific gravity, 1.16) per 1000 cc. (This stock solution is used for making the standards for urine urea, urine total nitrogen, blood non-protein nitrogen, and blood urea determinations.) One hundred cc. of the stock solution are diluted to 1000 cc. together with 11.5 cc. of concentrated HCl. Ten cc. of this dilute standard (containing 1 mg. of nitrogen) are placed in a 200 cc. volumetric flask, 2 cc. of 10 per cent NaOH added and the flask filled three-fourths full with water. It is Nesslerized at the

[1] Folin and Bell: Jour. Biol. Chem., 1917, **29**, 329.

[2] Permutit especially prepared for this determination must be used. It may be obtained from the Permutit Company, 30 East 42d Street, New York City by requesting permutit such as prepared for Professor Folin. Different specimens of permutit even from the same company may vary in their power to both take up ammonia and to liberate it in the presence of alkali. One should always test each new preparation of permutit purchased for these two properties in the presence of a known amount of ammonium sulphate which will represent the maximum amount of nitrogen that one is apt to encounter in a determination.

same time as the unknown and with the same amount of Nessler's solution.

The unknown is compared in the colorimeter with the standard which is set at 20 mm., the unknown being moved. The calculation is then

$$\frac{20 \times 1 \times 100}{\text{reading of unknown}} = \text{mgs.}$$

ammonia-nitrogen per 100 cc. of urine, provided 1 cc. of urine has been used for the determination. If 2 or more cc. are used, the final result is divided by the number of cc. of urine used.

(*b*) *Aeration Method.* (Folin[1]).—This method is described in detail in the author's manual.

3. *β-oxybutyric Acid.*—The tests for β-oxybutyric acid are all complicated, because they depend upon the extraction of the acid. Estimation of the β-oxybutyric acid based upon the difference between the quantity of sugar as determined by Fehling's fermentation and polarization tests are inaccurate. They simply suggest the presence of β-oxybutyric acid. It is doubtless unnecessary to call attention here to the fact that β-oxybutyric acid and β-hydroxybutyric acid are synonymous terms. They both refer to the same substance, $CH_3CHOHCH_2COOH$.

Methods available for the determination of β-oxybutyric acid are the following: (*a*) Shaffer's[2] short method, (*b*) method of Folin and Denis,[3] (*c*) Black's method,[4] and (*d*) Van-Slyke-Fitz methods for determination of β-hydroxybutyric acid, diacetic acid, and acetone in urine[5] and blood.[6]

The other acetone bodies may be quantitatively estimated by use of the following methods:

(*a*) Van Slyke and Palmer[7] method for titration of organic acids in the urine, (*b*) Folin's[8] method of determining diacetic acid and acetone in urine and (*c*) Folin's[9] method of determining acetone in urine.

8. **Nitrogen.**—The determination of the nitrogen in the urine is valuable because it furnishes an index to the quantity of protein which the patient is disintegrating. Incidentally, this is the easiest way to determine the quantity of protein in the diet. Since nitrogen constitutes 16 per cent of the protein molecule, we can multiply

[1] Folin: Lab. Man. of Biol. Chem., New York, D. Appleton & Co., 1925, p. 117.
[2] Folin: Ibid., p. 201.
[3] Folin: Ibid., p. 199.
[4] Black: Jour. Biol. Chem., 1908, **5**, 207.
[5] Van Slyke: Jour. Biol. Chem., 1917, **32**, 455.
[6] Van Slyke and Fitz: Ibid., p. 495.
[7] Van Slyke and Palmer: Jour. Biol. Chem., 1920, **41**, 567.
[8] Folin: Loc. cit., p. 197.
[9] Folin and Denis: Loc. cit., p. 195; also Jour. Biol. Chem., 1914, **18**, 263.

the quantity of nitrogen obtained in the urine by 6¼ to obtain the protein which it represents. We shall not be far wrong if to this we add 1 gram of nitrogen to offset the nitrogen of the feces, and consider this total quantity as representing the protein in the food. The determination of the nitrogen is also valuable because it is often useful to know the ammonia-nitrogen:nitrogen ratio as well as the dextrose:nitrogen ratio.

Formerly large quantities of nitrogen were obtained in the urines of diabetic patients, but modern treatment with its restriction of protein makes these excessive quantities rare.

However, I have met with three such examples: Thus, Case No. 632 came to me upon a supposedly restricted diet, and the nitrogen in the urine amounted to 29.25 grams, and now, June, 1927, after fifteen years of diabetes, at the age of forty-six years, shows 12.4 grams in twenty-four hours. The diminution of protein in the diet removed the sugar entirely from the urine, even though 12 grams of carbohydrate were added in the form of oatmeal. Case No. 616 was not sugar-free before her entrance to the hospital, but in the hospital easily became so. The urine upon March 18, 1913, amounted to 6615 cc., and contained 485 grams sugar and 67.9 grams nitrogen. She entered the hospital May 22, 1913, and the urine was free from sugar May 25. Five months subsequently the urine was examined and the quantity of nitrogen in the twenty-four hours amounted to 36 grams. She died in 1917. Case No. 1196 is discussed in connection with the volume of the urine (see p. 530).

A daily analysis for nitrogen is time-consuming, but it is a simple matter to aliquot specimens of urine for a week and then obtain the average nitrogen excretion per day. If albumin is present in the urine to be tested quantitatively for nitrogen, it must be removed before the nitrogen determination is made. To accomplish this, add 1 cc. of Sorenson's reagent (made by adding 56.6 cc. of glacial acetic acid to 118 grams of sodium acetate and diluting to 1000 cc.) to 10 cc. of urine in a pyrex tube graduated at 10 cc. Boil for twenty minutes in a water-bath. Cool, dilute to the original volume of 10 cc., filter, and treat as the test requires. One cc. is equal to 1 cc. of the original urine.

Two simple methods by which the nitrogen in the urine may be determined are referred to here. Each is based upon preliminary digestion of the urine with sulphuric acid-phosphoric acid-copper sulphate mixtures and final determinations of the ammonia content either by distillation and titration or by direct Nesslerization. Both methods have been devised by Professor Folin and co-workers. We use routinely the micro-method and it alone will be described in detail.

(*a*) **A Simplified Macro-Kjeldahl Method for Urine.**[1]—This method is a modification of the Kjeldahl method for the determination of nitrogen in urine which requires very little equipment and by which a urinary nitrogen determination can easily be finished in twenty to twenty-five minutes. It is outlined in full in Folin's manual.

(*b*) **Micro-Kjeldahl Colorimetric Method.**—Dilute 5 cc. of urine to 100 cc., mix, and with an Ostwald pipette transfer 1 cc. of the diluted urine to a large pyrex test-tube graduated at 35 and 50 cc. This pipette must be drained for fifteen seconds against the wall of the test-tube and then blown clean. With an ordinary pipette add 1 cc. of sulphuric acid-phosphoric acid-copper sulphate mixture, together with a pebble or small piece of broken quartzware to prevent bumping.

The acid digestion mixture is the same as that used in the determination of blood non-protein nitrogen (see page 447).

Heat over a micro-burner until water is driven off and fumes become abundant within the tube. This should take place in about two minutes. When filled with fumes, close the mouth of the test-tube with a watch glass and continue the boiling at such a rate that the tube remains filled with fumes yet almost none escape. Within two minutes after closing the mouth of the test-tube the contents should become clear and bluish or light green. Continue the gentle boiling for thirty to sixty seconds longer, provided, however, that the total boiling period, with test-tube closed, must not be less than two minutes. Remove the flame and let cool for a little less than two minutes, then add water almost to the 35 cc. mark.

Transfer 5 cc. of standard ammonium sulphate solution containing 0.2 mg. of nitrogen, the same standard as that used for blood non-protein nitrogen, into another pyrex tube graduated at 35 and 50 cc. Add 1 cc. of the concentrated phosphoric acid-sulphuric acid mixture, to balance the acid in the unknown, and dilute to a volume of about 35 cc. To each tube now add 15 cc. of Nessler's reagent (see page 448), dilute to the 50 cc. mark with distilled water, mix, and compare colorimetrically.

If the unknown Nesslerized digestion mixture is turbid, centrifuge a portion, giving a crystal clear fluid above a white sediment (silica). If the sediment is colored, the Nesslerization was not successful and the determination must be repeated. The standard is set in the colorimeter at 10 mm. and the unknown moved. The calculation is

$$\frac{10 \times 20 \times 0.2}{\text{reading of unknown}} = \text{mg. nitrogen per. cc. of urine.}$$

[1] Folin: A Laboratory Manual of Biological Chemistry, 1925, New York, D. Appleton & Co., p. 197. The method as described above is a modification of Folin's technique.

9. **Albumin.**—The test for albumin in the urine should be performed at frequent intervals during the care of diabetic patients. Too often the diagnosis of diabetes leads to neglect of the general treatment of the case. As a rule when albumin appears, the percentage of sugar falls, even though the percentage of sugar in the blood remains high. Among 50 cases of diabetes of twenty years' duration, 13 showed more than the slightest trace of albumin, whereas among the same number of cases under two years' duration, the number showing albumin was 2.

At the New England Deaconess Hospital we routinely employ two tests for albumin in the urine and consider these to be very satisfactory and reliable. The urine specimen to be examined is thoroughly mixed and a 15 cc. centrifuge tube filled. If urate turbidity is present, the tube is warmed to clear it. After subsequent centrifugation, about one-half of the supernatant urine is poured into a wineglass. To the portion left in the centrifuge tube is added 10 drops of 2 per cent sulpho-salicylic acid (plus 0.5 per cent acetic acid). Any clouding indicates albumin, the amount depending upon the degree of the reaction. Now, underneath the urine in the wineglass is layered a medicine-dropper-full of Robert's reagent (1 volume concentrated HNO_3 and 5 volumes of a saturated solution of $MgSO_4$). If albumin is present, a white zone of precipitate appears at the juncture of the two liquids. The following scheme is used to indicate the amount of albumin present:

SPT—slightest possible trace—precipitate ring or zone visible only with a black background.

VST—very slight trace—visible against any background.

ST—slight trace—visible from above.

T—trace—cannot be seen through when viewed from above.

LT—large trace—flocculent precipitate forms.

The results of the two tests recorded on the charts as $\frac{\text{SPT, VST}}{\text{SPT, VST,}}$ etc., with the reaction obtained in the sulpho-salicylic acid test above the line and that obtained by the Robert's reagent below the line.

The sulpho-salicylic acid test is very sensitive and albumin to the extent of an SPT may often be found in the absence of a positive test by the Roberts' reagent. After emptying the centrifuge tube, the few remaining drops are used for examination of the sediment.

10. **Casts.**—From the time of Külz the irritation of the kidneys in the first stages of diabetic coma has been observed. Over and over again I have seen typical "showers" of casts at the beginning of diabetic coma. They may occur at times when the albumin in the urine amounts to the slightest possible trace. Casts in the urine, even though occurring in showers, do not necessitate the development of fatal coma, for these were found in the urine of

Case No. 765 on December 6–7, 1915, and she lived to enter another state of coma which proved fatal on October 29, 1916. See Table 168. They are of very common occurrence in our patients with coma seen today and treated with insulin.

TABLE 168.—CASE NO. 765. SEVERE ACIDOSIS; "SHOWERS" OF CASTS WITHOUT COMA.

Date.	Vol., c.c.	Albumin.	Diacetic acid.	Ammonia, gms.	Sugar, urine, gms.	Carbohydrate balance, gms.	Soda administered.	Weight, lbs.	Alveolar air, CO_2 mm. Hg.
1915. Dec. 6–7	..	..	..	*3.3*[1]	3.6%	*Showers of granular casts.*			
7–8	1800	Slight trace	++	3.9	25	−20	0	88	26
8–9	1200	Slight trace	+++	2.6	7	−7	0	88	26
9–10	1200	Very slight trace	++	2.4	2	3	0	89	29
10–11	1600	Slightest possible trace	++	2.9	6	−1	0	89	32
11–12	1400	..	++	..	14	16	0	88	33
12–13	900	Slightest possible trace	++	1.5	9	−9	0	89	32

Death in a second attack of coma, October 29, 1916.

11. **Chlorides.**—The importance of a knowledge of the chlorides in the urine is due to the remarkable changes in weight of diabetic patients which are in part related to the excretion and retention of sodium chloride. This subject is discussed under Influence of Sodium Chloride upon the Weight. (See p. 272.)

Folin's Simplified Method.[2]—Solutions required:

1. Standard silver nitrate: Dissolve 29.12 grams of silver nitrate in distilled water and dilute to 1 liter. One cc. is equivalent to 10 mg. of NaCl.

2. Indicator: To 100 grams of ferric ammonium sulphate add 100 cc. of water and 200 cc. of concentrated nitric acid.

3. Standard ammonium sulphocyanate: Dissolve 20 grams of ammonium sulphocyanate in 1 liter of water and mix. Transfer 10 cc. of the standard silver solution to a beaker, add 20 cc. of water and 5 cc. of indicator. Titrate with the sulphocyanate solution until the characteristic reddish end-point is reached. On the basis of the figure obtained, prepare 1 liter of ammonium sulphocyanate solution, which is equivalent to the standard silver nitrate solution.

[1] Ammonia in 14°.

[2] Folin Laboratory Manual of Biological Chemistry, 1925, D. Appleton & Co., New York, p. 167.

With a pipette transfer 5 cc. of urine to a beaker, add 20 cc. of water, 5 cc. of indicator and finally (with a pipette) 10 cc. of silver nitrate solution. While stirring, titrate the surplus with the standard sulphocyanate solution until the first faint, but unmistakable, brown or reddish coloration is obtained. On standing or continued stirring the color may disappear, so the very first end-point must be taken.

Subtract the sulphocyanate used (in cc.) from 10 and multiply by 10. This gives in mg., the amount of NaCl present in 5 cc. of urine. From this figure calculate the amount present in the total twenty-four-hour quantity.

B. THE EXAMINATION OF THE BLOOD.

Due to the introduction of a System of Blood Analysis by Folin and Wu[1] in 1919 we are now able to take a comparatively small sample of blood and make a complete analysis of the blood for sugar, urea, non-protein nitrogen, uric acid, creatin, creatinin, and chlorides. Formerly each determination required as much and sometimes more blood than do all of them at present. A 10 cc. sample of blood will permit a fairly complete chemical analysis. Since all of these tests are seldom required on each sample of blood, even less than 10 cc. suffices. As a routine we precipitate 5 cc. of blood and this requires that about 6 cc. of blood be taken into the syringe. A 21-gauge needle and a 10 cc. syringe may be used.

To prevent the clotting of blood the following methods will be found most useful:

(*a*) Potassium oxalate, 2 mg. per 1 cc. of blood, is placed in the blood bottle (1 ounce, round, wide-mouthed bottles are best) and the blood forced out of the syringe into the bottle with as little loss of time as possible. The bottle should be immediately corked and shaken thoroughly but gently for thirty seconds. Blood drawn in this fashion is ideal for most chemical analyses, including the determination of the carbon-dioxide combining power. It is not best for the determination of blood chlorides. However, oxalated blood loses its sugar content rapidly, particularly if kept at room temperature, and so must be precipitated, preferably within an hour from the time it is drawn. Formaldehyde (40 per cent), 1 drop to each 5 cc. of blood, effectively destroys the glycolytic enzyme and, when used in conjunction with the proper amount of oxalate, preserves blood for from two to four days without loss of sugar. This is helpful to the general practitioner who cannot have his blood-sugar tests done at once, but even so, under such circumstances I should advise use of the fluoride-thymol mixture described below. Bloods

[1] Folin and Wu: Jour. Biol. Chem., 1919, **38**, 81; 1920, **41**, 367.

containing formaldehyde are unsuitable for the determination of urea and non-protein nitrogen. Contrary to the statement of Denis and Aldrich,[1] we have been unable to make these determinations accurately, due to the precipitating effect of the formaldehyde upon the Nessler reagent.

(*b*) Sodium fluoride and thymol (10 to 1), 10 mg. per 1 cc. of blood, are used as described by Sander[2] in place of the oxalate. This anticoagulant mixture preserves blood without decrease in sugar content for several days and is used routinely when immediate analysis is not possible. Blood so preserved cannot be used, however, for any determination on the plasma, because of the hemolysis always produced. We have found that the sodium fluoride distributed by different chemical houses varies markedly in acidity. A neutral salt is necessary. If more than 0.5 cc. $\frac{N}{10}$ NaOH is required to render neutral 100 mg. of the salt, the latter must be neutralized and recrystallized before use.

(*c*) Lithium oxalate impregnated cloth, devised by Folin,[3] furnishes an anticoagulant in a convenient and effective form. We have never used it routinely.

The different chemical determinations are made upon a water-clear filtrate obtained by removing the proteins from the blood. To obtain this filtrate the blood is diluted with 7 volumes of water and then treated with 1 volume of a tungstate solution and 1 volume of a sulphuric acid solution. This precipitates the blood protein which may then be filtered off.

1. **Precipitation of Blood Proteins.**—The solutions required are two: a two-thirds normal (0.667 N) solution of sulphuric acid, which it is best to carefully standardize, and a 10 per cent solution of sodium tungstate.

All brands of sodium tungstate are not equally good. At the present time the large chemical companies are not aware of this fact, and consequently, the reputation of the company or the apparent pure crystalline character of the tungstate is no indication that the tungstate will be suitable for blood work. All brands of tungstate should be carefully titrated to determine if they have the proper degree of alkalinity. Ten cc. of 10 per cent tungstate solution should require not over 0.4 cc. of $\frac{N}{10}$ acid to neutralize it to phenolphthalein. Many tungstates are neutral or acid. It may be positively stated that these will not make effective blood protein precipitates.

In a flask or large tube are placed 7 volumes, usually 35 cc., of distilled water; 1 volume, 5 cc., of blood is then added, followed

[1] Denis and Aldrich: Jour. Biol. Chem., 1920, **44**, 203.
[2] Sander: Jour. Biol. Chem., 1923, **58**, 1.
[3] Folin: Loc. cit. p. 227.

by 1 volume of the 10 per cent tungstate. After mixing, add slowly with shaking 1 volume of the two-thirds normal sulphuric acid. Allow to stand about five minutes or until the coagulum has turned a dull brown color and then filter. The filtrate should be water-clear, and alkaline to Congo red, but neutral or slightly acid to litmus.

2. **Blood-sugar Determinations.**[1] — (*a*) **Original Method of Folin and Wu: Solutions Required.** — 1. *Standard Sugar Solution.*—Dissolve 1 gram of pure anhydrous dextrose in saturated benzoic acid solution and dilute to a volume of 100 cc. Mix, and bottle. If pure dextrose is not available, a standard solution of invert sugar made from cane sugar is equally useful. Transfer exactly 1 gram of cane sugar to a 100 cc. volumetric flask; add 20 cc. of normal hydrochloric acid and let the mixture stand over night at room temperature (or rotate the flask and contents continuously for ten minutes in a water-bath kept at 70° C.). Add 1.68 grams of sodium bicarbonate and about 0.2 grams of sodium acetate. to neutralize the hydrochloric acid. Shake a few minutes to remove most of the carbonic acid and fill to the 100 cc. mark with saturated benzoic acid solution. Then add 5 cc. more of benzoic acid solution (1 gram of cane sugar yields 1.05 grams of invert sugar) and mix. Transfer to a bottle; shake well, and stopper tightly. The stock solution made in either way keeps indefinitely. Two standard sugar solutions should be on hand: (1) A solution containing 1 mg. of sugar per 10 cc. (5 cc. of the stock solution diluted to 500 cc. with a saturated benzoic acid solution); (2) a solution containing 2 mg. of sugar per 10 cc. (5 cc. of the stock solution diluted to 250 cc.). The invert sugar has the advantage that it can be easily prepared from cane sugar, which is pure. The keeping quality of such solutions should be less good than those made from glucose, but we have encountered no trouble on that score. When good quality glucose is available, it is of course, the one to use.

2. *Alkaline Copper Solution.*—Dissolve 40 grams of anhydrous sodium carbonate in about 400 cc. of water and transfer to a liter flask. Add 7.5 grams of tartaric acid and when the latter has dissolved add 4.5 grams of crystallized copper sulphate; mix, and make up to a volume of 1 liter. If the carbonate used is impure, a sediment may be formed in the course of a week or so. If this happens, decant the clear solution into another bottle.

3. *Sugar Reagent.*[2]—Dissolve 150 grams of sodium molybdate,

[1] A new technic for blood sugar determination which appears to indicate very closely the true glucose content of blood, has been presented recently by Benedict in the Jour. Biol. Chem., 1928, **76**, 457.

[2] These new directions will be found described by Folin: Jour Biol. Chem., 1926, **67**, 357.

$Na_2MO_4 : 2H_2O$, in 300 cc. of distilled water in a 500 cc. beaker. Filter through a 15 cm. quantitative filter paper into a liter flask, washing the filter with 75 cc. of water. To the sodium molybdate solution in the flask add several drops (0.1 to 0.2 cc.) of bromine water and shake for a minute until the bromine has dissolved. Let stand for an hour to complete the oxidation produced by the hypobromite. Then add, with shaking, 225 cc. of 85 per cent phosphoric acid. The surplus bromine is set free and imparts a yellow color to the solution. After all the phosphoric acid has been added, add also 150 cc. of cooled 25 per cent H_2SO_4 (1 volume of concentrated H_2SO_4 to 3 volumes of water). Remove the surplus bromine by means of a moderately rapid air current. The aëration will take about one-half hour. Finally add 75 cc. of 99 per cent acetic acid, mix, and dilute to a volume of 1 liter.

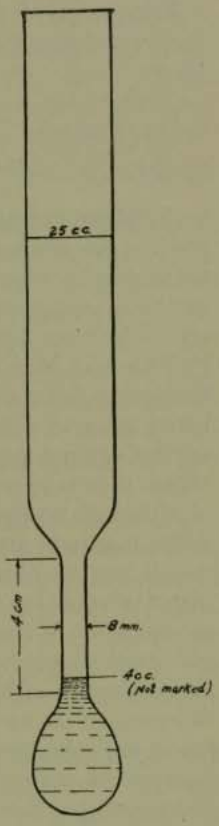


FIG. 31.—Blood-sugar tube.[1]

4. *Blood Sugar Tubes.*—See Fig. 31.

5. *The Determination.*—Transfer 2 cc. of the tungstic acid blood filtrate to a blood sugar test-tube, and to two other similar test tubes (graduated at 25 cc.) add 2 cc. of standard sugar solution containing respectively 0.2 and 0.4 mg. of dextrose. To each tube add 2 cc. of the alkaline copper solution. The surface of the mixtures must now have reached the constricted part of the tube. If the bulb of the tube is too large for the volume (4 cc.) a little, but not more than 0.5 cc. of a diluted (1 to 1) alkaline copper solution may be added. If this does not suffice to bring the contents to the narrow part, the tube should be discarded. Test-tubes having so small a capacity that 4 cc. fills them above the neck should also be discarded. Transfer the tubes to a boiling water-bath and heat for eight minutes. Add to each test-tube 2 cc. of the sugar reagent, transfer to a cold water bath and allow to cool without shaking for two to three minutes. The cuprous oxide dissolves rather slowly if the amount is large, but the whole, up to the amount given by 0.8 mg. of dextrose, dissolves usually within two minutes. When the

[1] Test-tubes of the sort, shown in Fig. 31 with and without graduation, are now made by The Emil Greiner Company, 55 Vandam Street, New York, and can also be obtained from Arthur H. Thomas Company, West Washington Square, Philadelphia.

cuprous oxide is dissolved, dilute the resulting blue solutions to the 25 cc. mark, insert a rubber stopper, and mix. It is essential that adequate attention be given to this mixing because the greater part of the blue color is formed in the bulb of the tube.

The two standards given representing 0.2 and 0.4 mg. of glucose are adequate for practically all cases. They cover the range from about 70 to nearly 400 mg. of glucose per 100 cc. of blood.

The standard nearest to the unknown in color is set at 20 mm. in the colorimeter and the unknown moved. The calculation is then:

$$\frac{20 \times 0.2 \times 500}{\text{reading of unknown.}} = \text{mg. glucose per 100 cc. of blood when standard No. 1 is used.}$$

$$\frac{20 \times 0.4 \times 500}{\text{reading of unknown.}} = \text{mg. glucose per 100 cc. of blood when standard No. 2 is used.}$$

(*b*) **Micro-chemical Methods for Analysis of Blood.**—Since the introduction of methods for determining the sugar content of blood, many modifications have arisen with the idea of providing accurate methods applicable for small quantities of blood. Such micro-methods have been described by Bang,[1] Hagedorn[2] and Jensen,[3] Pollock and McEllroy,[4] Haden,[5] Isaacson and Baum,[6] Kramer and Gittleman,[7] Randles and Grigg,[8] and Byrd.[9] Orent[10] has recently listed most of the methods now available together with references to the orginal papers. Folin[11] has devised a new micro-method which is now in press.

Although accuracy must necessarily be sacrificed to some extent when methods are thus modified, under some conditions the data which can be obtained from small amounts of blood are of great importance. In the New England Deaconess Hospital a micro-modification of the Folin-Wu method is used.[12] Analyses are made by this method only on children and in cases of diabetic coma where a great number of bloods have to be taken. The blood sugar can be determined on as little as 0.05 cc. of blood. A 1 to 10 dilution is made and the proteins precipitated by tungstic acid. By centrifugation a water clear liquid is obtained which corresponds in character to the Folin-Wu protein-free filtrate. Special tubes made for us by the Emil Greiner Company, New York City, are

[1] Bang: Biochem. Ztschr., 1913, **57**, 300.
[2] Hagedorn: Acta Med. Scand., 1920, **53**, 672; Biochem. Ztschr., 1920, **107**, 248.
[3] Jensen: Biochem. Ztschr., 1923, **135**, 46.
[4] Pollock and McEllroy: Am. Jour. Med. Sci., 1922, **163**, 571.
[5] Haden: Jour. Biol. Chem., 1923, **56**, 469.
[6] Isaacson and Baum: Jour. Lab. and Clin. Med., 1922, **7**, 357.
[7] Kramer and Gittleman: Jour. Am. Med. Assn., 1923, **81**, 1171.
[8] Randles and Grigg: Jour. Am. Med. Assn., 1924, **82**, 684.
[9] Byrd: Jour. Lab. and Clin. Med., 1925, **11**, 67.
[10] Orent: Jour. Lab. and Clin. Med., 1927, **12**, 432.
[11] Folin: To be published, Jour. Biol. Chem., 1928.
[12] Hunt: Boston Med. and Surg. Jour., 1926, **195**, 502.

used for the dilution and color comparison. The results which have been obtained in the laboratory of the New England Deaconess Hospital compare very favorably with the analyses made on larger amounts of blood and are well within the range necessary for clinical investigation. All reagents are those used in the Folin-Wu method (page 442) except the sodium tungstate solution. The method used is as follows:

Transfer 0.05 cc. of blood taken from the ear or the finger to a small centrifuge tube containing 0.4 cc. of sodium tungstate solution (1.25 per cent) and rinse the pipette once with the mixture. With the same pipette add 0.05 cc. of two-thirds normal sulphuric acid. Mix thoroughly and centrifuge. (The small tube is placed in a larger centrifuge tube to do this.) The resulting supernatant liquid is water clear.

Transfer 0.1 cc. of the clear supernatant liquid to a graduated tube B. To a similar tube A add 0.1 cc. of standard sugar solution (1 cc. = 0.2 mgs. glucose). To each tube add 0.1 cc. of alkaline copper solution and place in a boiling water-bath for six minutes. To each tube add 0.1 cc. of the sugar reagent and cool. Dilute the standard to the mark with water and invert once, closing the tube with the finger. Dilute the unknown to the lowest graduation on the tube and then add water drop by drop until the color of the unknown solution exactly matches the color of the standard. The sugar percentage is read directly from the tube.

(*c*) **Bedside Method.**—A "bedside method," a modification of the Folin-Wu technique, was devised by Kiefer[1] in the Deaconess Hospital laboratory. It furnishes a reliable and fairly convenient method of determining the blood sugar when laboratory facilities are not available. It does not require the use of a centrifuge as does the micro method described above. The complete outfit can be carried in a case somewhat smaller than that of the usual portable typewriter.

3. **Non-protein Nitrogen.**—The remarkable efficiency of the kidneys of patients with diabetes has always impressed me, and the onset of renal disease in cases of diabetes of long duration has been far less frequent than most of us would anticipate. Proof of this is shown by the moderate changes of blood-pressure in cases of diabetes over long periods of time. (See p. 699.) On the other hand, in beginning coma renal involvement has always seemed to the author to be marked. Today the question arises as to whether this may not have been in part due to the alkaline treatment at such times, which forced an excessive quantity of acid through the kidneys. The increasing duration of life of patients with diabetes

[1] Kiefer: Jour. Am. Med. Assn., 1925, **84**, 589.

will show in a few years whether this is accompanied by a greater incidence of renal complications. Other evidence will be forthcoming upon the effect of high blood-sugar percentages over long periods of time upon the kidneys, as a result of insulin.

TABLE 169.—NON-PROTEIN NITROGEN IN DIABETES.

Non-protein nitrogen in 100 cc. of blood, mgms.	Number of analyses.	Age in years.		Phthalein tests.			Albumin present, per cent.	Blood-pressure.		Acidosis present, per cent.	Blood sugar.	
		Average.	Range.	Number.	Average.	Range.		Systolic average.	Diastolic average.		Average, per cent.	Range, per cent.
						1916[1]						
16–20	2	32	25–39	1	58	...	0	130	83	100	0.33	0.09–0.57
21–30	12	47	26–68	6	51	28–60	67	144	87	33	0.19	0.11–0.40
31–40	13	50	19–69	6	45	20–60	77	153	91	54	0.24	0.12–0.33
41 and over	9	50	22–69	4	34	5–56	89	152	80	40	0.20	0.10–0.50
						1922[2]						
16–20	4	31	16–51	1	42	...		146	77	0	0.21	0.17–0.29
21–30	43	40	9–69	17	51	26–80		130	78	21	0.19	0.05–0.45
31–40	55	41	7–73	30	55	22–90		129	79	18	0.21	0.06–0.39
41 and over	22	50	14–69	15	46	26–75		143	81	5	0.25	0.05–0.42

The non-protein nitrogen of the blood varies in normal individuals between 20 and 40 mg. per 100 cc. blood. Table 169 shows a small number of analyses of non-protein nitrogen in two series of diabetics which were abnormal. Thus, of 36 analyses in 1916, there were but one-fourth (9) with 41 mg. non-protein nitrogen or over; of 124 analyses in 1922, but one-sixth (22). These figures confirm the impression of the relatively good function of the kidneys above mentioned. Both series of data show increasing non-protein nitrogen with advancing age. Acidosis appears to have exerted little influence in the cases tabulated above. As is to be expected there is a general tendency for the phenolphthalein excretion to decrease as the non-protein nitrogen increases. In the earlier series of data the blood-pressure also rises with the non-protein nitrogen. The fact that the greatest average blood-pressure in the 1922 series (146 mm. Hg.) occurred when the non-protein nitrogen was between 16 and 20 mgs. does not invalidate this statement, because of the small number of determinations. The blood sugar appears to have no relation whatsoever to the non-protein nitrogen as shown by the average values and the ranges of the blood sugars.

Of the 63 cases of diabetic coma treated by us[3] between April, 1923, and February, 1927, there are 51 in which are recorded estimations of the non-protein nitrogen during one or more of the first three days of coma (*i. e.*, days spent in the hospital). Of these 51

[1] 30 cases, 36 analyses.
[2] 100 cases, 124 analyses.
[3] Joslin, Root, and White: Med. Clin. of North America, 1927, **10**, 1281.

there were 24 cases in which the non-protein nitrogen rose to 41 mgs. per 100 cc. of blood or over and of these in 18 cases the non-protein nitrogen was 50 mgs. or over. In Case No. 4978, a girl, aged eighteen years, actual nitrogen retention, with a non-protein nitrogen of 106 mgs., with oliguria and a rising blood-pressure, and with a large trace of urinary albumin, followed without warning in the wake of original diabetic coma and presented a very confusing diagnostic picture. The cause of nitrogen retention is still unknown.

An ante mortem rise in non-protein nitrogen occurred in Case No. 3079, who entered the hospital on April 2, 1923, with gangrene and septicemia due to streptococcus hemolyticus. The changes in non-protein nitrogen, blood sugar, and glycosuria which occurred in twenty-four hours are shown in Table 170. Death occurred one hour after the last observation. The influence of "renal bloc" upon the percentage of sugar in the blood has been noted by Fuller.[1] It is certainly true that one often encounters falling percentages of urinary sugar as coma advances. Fasting or inability to take food may in part account for this phenomenon, but undoubtedly "renal bloc" is one of the factors.

TABLE 170.—CASE NO. 3079. ANTE MORTEM RISE IN NON-PROTEIN NITROGEN.

Date.	Diacetic acid.	Sugar in urine, gms.	Diet in grams.				Non-protein nitrogen, mgs.	Blood sugar, per cent.	Blood CO_2 vols. per cent.	Insulin, units.
			C.	P.	F.	Cals.				
1923.										
Apr. 2	..	..	..	..	..	...	35.4	0.40	58	
	Amputation		left leg		half way		between knee and ankle.			
2–3	0	21	60	17	2	326	....	....	..	5
3–4	0	46	62	37	38	738	....	....	..	10
4–5	0	45	74	42	44	860	....	....	..	20
5–6	0	0	..	..	..	...	75.0[2]	0.50		

(*a*) **Determination of Blood Non-protein Nitrogen.**—The tungstic acid filtrate is used in this method which is part of "The System of Blood Analysis of Folin and Wu." The filtrate is first digested with a digestion mixture similar to that used in the urine macro-Kjeldahl method for nitrogen determination. The digested mixture is then Nesslerized directly with a Nessler reagent specially modified by Folin and Wu. The solutions needed follow:

1. *Digestion Mixture.* — Mix 300 cc. of phosphoric acid syrup (about 85 per cent H_3PO_4) with 100 cc. of concentrated sulphuric

[1] Fuller: Jour. Metabl. Research, 1922, **1**, 609.

[2] Blood specimen taken one hour before death. Death occurred 4.30 P.M. April 5, due to streptococcus hemolyticus septicemia. No coma. Blood culture taken on admission and before operation.

acid. Transfer to a tall cylinder, cover, and set aside for sedimentation of calcium sulphate. In the course of a week or so the top of the liquid may be used. To 100 cc. of the clear acid add 10 cc. of 6 per cent copper sulphate solution and 100 cc. of water.

2. *Nessler's Reagent (Modified).* — Transfer 150 grams of potassium iodide and 110 grams of iodine to a 500 cc. Florence flask; add 100 cc. of water and an excess of metallic mercury, 140 to 150 grams. Shake the flask continuously and vigorously for seven to fifteen minutes or until the iodine has nearly dissolved. The solution becomes quite hot. When the red iodine solution has begun to become visibly pale, though still red, cool in running water and continue the shaking until the red color of the iodine has been replaced by the greenish color of the double iodide. This whole operation usually does not take more than fifteen minutes. Now separate the solution from the surplus mercury by decantation and washing with liberal quantities of distilled water. Dilute the solution and washings to a volume of 2 liters. If the cooling is begun in time, the resulting reagent is clear enough for immediate dilution with 10 per cent (2.5 normal) alkali and water, and the finished solution can at once be used for Nesslerizations.

The final Nessler solution is prepared from the above stock solution as follows. From completely saturated caustic soda solution containing about 55 grams of NaOH per 100 cc. decant the clear supernatant liquid and dilute to a concentration of 10 per cent. (It is worth while to determine by titration that a 10 per cent solution has been obtained within an error of not over 5 per cent.) Introduce into a large bottle 3500 cc. of 10 per cent sodium hydroxide solution, add 750 cc of the double iodide (stock Nessler's) solution and 750 cc. of distilled water, giving 5 liters of Nessler's solution. This solution may be used for urine nitrogen, urine ammonia, urine urea, blood non-protein nitrogen and blood urea Nesslerizations.

3. *Standard Nitrogen Solution.* — Weigh out accurately 0.4716 gram of especially purified ammonium sulphate and dissolve in exactly 100 cc. of $\frac{N}{10}$ HCl. This stock solution contains 1 mg. N per cc. To prepare for use dilute 20 cc. of this to 500 cc. with distilled water. Five cc. of this contain 0.2 mg. N.

4. *Apparatus Needed.* — (1) Blood non-protein nitrogen pyrex tubes (200 x 25 mm.) graduated at 35 cc. and 50 cc. These may be obtained at any of the large chemicalware supply houses by asking for Folin non-protein nitrogen digestion tubes; (2) a ring stand with test-tube clamp with which to hold the digestion tubes; (3) microbunsen burner.

The Determination.—Introduce 5 cc. of the protein-free blood filtrate into a dry NPN test-tube. Add 1 cc. of the digestion mix-

ture. Add a dry quartz pebble and boil vigorously over a microburner until the characteristic dense acid fumes begin to fill the test-tube. This is usually accomplished in from three to seven minutes. When the fumes are unmistakable, cut down the size of the flame so that the contents of the tube are just visibly boiling and close the mouth of the test-tube with a watch-glass. Continue the heating very gently for two minutes from the time the fumes began to be unmistakable, even if the solution has become clear and colorless at the end of twenty to forty seconds. If the oxidation is not visibly finished at the end of two minutes the heating must be continued until the solution is nearly colorless. Such cases are very rare; the oxidation is almost invariably finished within the first minute. Allow the contents to cool for seventy to ninety seconds and then add 15 to 25 cc. of water. Cool further, approximately to room temperature, and add water to the 35 cc. mark.

To prepare the standard, transfer 5 cc. of the standard nitrogen solution (containing 0.2 mg. N.) to a non-protein nitrogen tube, add 1 cc. of the digestion mixture, and dilute to the 35 cc. mark with water. To each tube—standard and unknown—add 15 cc. of Nessler's solution, mix, and compare colorimetrically. If the standard is set at 10 mm., calculate as follows:

$$\frac{10 \times 0.2 \times 200}{\text{reading of unknown}} = \text{mgs. NPN per 100 cc. of blood.}$$

4. **Chlorides.**—The determination of the chlorides in the blood gains importance from the fact that the water content of the body in diabetes varies so rapidly and to so great an extent. This is in addition to the value which such determinations have in the dietetic management of cases of nephritis and hypertension, complications not uncommon in diabetes.

This determination should be done upon serum or upon plasma separated from blood to which sodium citrate has been added as an anticoagulant. The method devised by Whitehorn[1] is used routinely. It will be found to be simple and reliable and is considered so by Folin.[2] In preparing the protein-free filtrate from plasma only one-half as many cubic centimeters each of 10 per cent sodium tungstate and $\frac{2}{3}$N. sulphuric acid are used as cubic centimeters of plasma avilable. It is well to note that the use of sodium citrate rather than oxalate as an anticoagulant in securing the blood renders the end-point more easily detected. The actual method itself depends upon direct titration with KCNS of the excess of a known amount of silver nitrate solution added to 10 cc. of tungstic acid filtrate.

[1] Whitehorn: Jour. Biol. Chem., 1921, **45**, 449.
[2] Folin: Lab. Man. of Biol. Chem., New York, D. Appleton & Co., 1925, p. 295.

Practically all available methods for the determination of the blood chlorides are discussed by Short and Gellis[1] and by Leiboff[2] in recent articles on the subject.

5. **Lipids.**—The blood of diabetic patients can advantageously be examined for its contents of lipids. It is true, one seldom sees cases with 16.3 per cent of blood fat as Case No. 786, and in fact, I have had no other among the 1962 analyses made in my laboratory. One reason for this may be that less fat is given now than formerly and another that the blood is examined for the lipids before instead of after a meal. Formerly of the cases examined, an increase was found in 26, a normal state in 2, and a decrease in none. Recently under insulin treatment we have found 60 per cent of 116 cases to have normal or subnormal cholesterol values. The blood fat should be normal in all cases of diabetes and no case of diabetes should be considered well treated otherwise. When carbohydrate and protein are unassimilated, they appear in the urine, but when fat fails of assimilation, it collects in the blood.

The normal variation of the lipids in the blood and the changes which they undergo have been described on p. 239.

The method used for the determination of blood lipids is that of Bloor, Pelkan and Allen.[3]

The lipids are extracted from blood plasma with hot alcohol-ether. The extract is saponified, the cholesterol extracted with chloroform and the soaps with hot alcohol. Cholesterol is determined colorimetrically and fatty acids nephelometrically. The procedure is as follows:

Extraction.—Two cc. of blood plasma are run in a slow stream of drops into a 50 cc. volumetric flask containing about 35 cc. of alcohol-ether (3 to 1 both redistilled) mixture, which is kept in constant motion by rotating the flask. The solution is raised to boiling by immersion in a boiling water-bath (with constant shaking to prevent super-heating), cooled to room temperature, made up to volume with alcohol-ether, mixed and filtered. The extract if placed in tightly-stoppered bottles in the dark will keep several months. Ten cc. of the extract are transferred to a 100 cc. Erlenmeyer flask (non-soluble glass is preferable), 0.1 cc. of concentrated NaOH made from sodium is added and the mixture evaporated nearly to dryness on a water-bath. Great care should be taken in this procedure, the original description of the authors being consulted for details. When the volume has been reduced to a minimum and the odor of alcohol has completely disappeared, the flask is cooled and 0.1 cc. of dilute sulphuric acid (25 per cent) is added and the contents well mixed

[1] Short and Gellis: Jour. Biol. Chem., 1927, **73**, 219.
[2] Leiboff: Jour. Lab. and Clin. Med., 1927, **12**, 702.
[3] Bloor, Pelkan, and Allen: Jour. Biol. Chem., 1922, **52**, 191.

to insure even distribution over the bottom of the flask. The flask is now heated on the water-bath until all traces of moisture have disappeared from its walls.

Separation and Determination of Cholesterol.—After cooling, 10 cc. of dry chloroform are added and after standing for ten minutes the extract is poured through a 55 mm. hardened filter into another small flask and the extraction twice repeated with 5 cc. of chloroform. The combined filtrate is evaporated down to 2 or 3 cc. and then transferred to a 10 cc. glass stoppered graduated cylinder, and made up to 5 cc. with chloroform washings from the flask. The cholesterol is determined by the use of the Liebermann Burchard reaction as follows: One cc. of acetic anhydride and 0.2 cc. of pure concentrated sulphuric acid are added to the chloroform extract in the cylinder, the cylinder is stoppered and cautiously mixed well. The cylinder is allowed to stand for fifteen minutes exposed to the same light by which readings are later to be made. The solution is then transferred to the colorimeter cup and compared with a suitable standard similarly prepared from pure cholesterol. The standard cholesterol for this purpose contains ordinarily 0.5 mg. of cholesterol in 5 cc. of chloroform.

Determination of Fatty Acid.—The residue in the small flasks, after the extraction with chloroform, is treated with boiling alcohol for the extraction of fatty acids and the hot alcohol extract is poured through the small hardened filter which was used in filtering the chloroform, into a small Erlenmeyer flask. The combined filtrates, after two extractions with boiling alcohol, are evaporated to a small volume, transferred to a small glass-stoppered cylinder and diluted to 5 cc. with alcohol washings from the flask. The alcoholic extract thus prepared is poured, with stirring, through a small funnel with a capillary stem into 100 cc. of distilled water in a 200 cc. beaker and the cylinder rinsed once with the mixture. Ten cc. of dilute hydrochloric acid (1 to 4 dilution) are added with stirring and after standing not less than three or more than ten minutes the turbid solution is compared in a nephelometer with a suitable standard similarly prepared from oleic and palmitic acid. The standard ordinarily used contains 2 mgs. of a mixture of 60 per cent oleic and 40 per cent palmitic acid per 5 cc. For directions for using a nephelometer consult the description prepared by Bloor.[1]

6. **Acetone in the Blood.**—It sometimes occurs that acidosis is present yet is not disclosed by the simple ferric chloride test for diacetic acid in the urine. Under such circumstances the test for acetone in the urine may be made, or better still, a qualitative test for acetone in the blood. The description of such a test follows.

[1] Bloor: Jour. Biol. Chem., 1914, **17**, 378.

(*a*) **Wishart Method for Detection of Acetone in the Blood.**—The blood is drawn into a syringe or tube containing a few crystals of potassium oxalate, then centrifuged for five minutes at medium speed. The test is made on the plasma with as little delay as possible, as there is liable to be some loss of acetone on standing.

To 4 drops of plasma add solid ammonium sulphate until plasma is thoroughly saturated and protein precipitated; then add 2 drops of a freshly made 5 per cent solution of sodium nitroprusside and 2 drops of concentrated ammonium hydrate. Thoroughly mix. If the test is positive, in from one to ten minutes a color develops which runs all the way from a pale lavendar to that of a deep permanganate hue, in this way indicating whether much or little acetone is present. This is an adaptation to the plasma of the Rothera nitroprusside reaction as ordinarily used for urine. It is said to be sensitive to 1 part in 20,000.

The acetone reagent described on page 431 may be used in this test and is recommended because of its stability. The plasma is saturated with the reagent and a few drops of strong ammonia water are added.

(*b*) **Van Slyke-Fitz Methods for Determination of β-hydroxybutyric Acid and Acetone in Urine and Blood.** (See p. 435.)

7. **Carbon Dioxide in Blood Plasma.**—Whether in health or in disease, the reactions of the body remain nearly constant and the blood not only conforms to this general law but helps to enforce it. This end is accomplished in the presence of acidosis: (1) by removing the CO_2 from the blood by way of the lungs to make way for the stronger acid; (2) by combining of the acid through the buffer; and (3) by saving of alkali through the excretion of acid phosphate through the kidneys.

The blood plasma normally contains a certain amount of bicarbonate ($NaHCO_3$). An idea of the amount of bicarbonate can be obtained by measuring the quantity of CO_2 which is set free when a stronger acid, such as sulphuric acid or lactic acid is added to the blood. The CO_2 thus obtained ("CO_2 content") is expressed as volume of CO_2 per 100 cc. of blood (volumes per cent). Normal venous bloods contain between 48 and 58 volumes per cent of CO_2 and normal arterial bloods between 46 and 52 volumes per cent of CO_2. Despite the introduction of an acid, the blood preserves its normal degree of alkalinity to a certain point through the buffer action of the alkali (chiefly sodium bicarbonate) of the plasma and the proteins, especially hemoglobin. Just how much a reserve in alkalinity a given blood plasma may possess is comparatively easily learned by exposing the blood to an atmosphere of CO_2 until it has become saturated and then measuring the amount of CO_2 which has been taken up. This gives the alkali reserve capacity (combin-

ing power) of the blood for CO_2 of which the normal varies between 55 and 75 volumes per cent with an average of 60 to 65 volumes per cent. Values of 20 volumes per cent or lower we choose arbitrarily to call "coma figures." Both (1) the actual CO_2 content in volumes per cent of the blood and (2) the CO_2 combining power (alkaline reserve) of the blood expressed also in volumes per cent are measures of its alkalinity. The second value is the one with which one usually deals in the routine of the clinic because the method of determination is simpler.

In the laboratory of the New England Deaconess Hospital we routinely use the standard method of Van Slyke[1] for determination of the carbon dioxide combining power of the blood plasma. Since the whole method depends upon the use of the special Van Slyke pipette,[2] no detailed description of the procedure need be given here.

If one can take time for determinations of the actual CO_2 content of the blood, certain other information can be obtained which is of value in the interpretation of states of acidosis. For this purpose one makes use of the CO_2 diagram of Haggard and Henderson[3] (see Fig. 32).

In this diagram the ordinates express the CO_2 in volumes per cent and the abscissæ express tensions of CO_2 in mm. of mercury. The points (*a*), (*b*), and (*c*) were obtained by exposing samples of blood (venous or arterial blood may be used) to different atmospheres of air and CO_2 in saturators in a water-bath at body temperature until equilibrium was reached and then determining by means of a Van Slyke or other apparatus the amount of CO_2 taken up in each saturator. The free-hand curve drawn through these three points is called the CO_2 Dissociation Curve. This curve represents the combination of CO_2 and blood over the range of changing tensions of CO_2 that may exist in the body, and since the amount of CO_2 carried by blood is chiefly concerned with the amount of alkali present in the blood, the level of the CO_2 curve is of interest in determining whether an acidosis, alkalosis, or a normal state exists at the time the observations are made. If the level of the curve falls below the zone now considered as normal for CO_2 curves, *acidosis*, as the term is now used, exists although the actual reaction of the blood may be kept normal down to quite low levels of the curve through the action of the lungs in blowing off CO_2 by means of increased ventilation. If a curve is obtained having a level above

[1] Van Slyke: Jour. Biol. Chem., 1917, **30**, 347, cf; also Van Slyke and Stadie: Jour. Biol. Chem., 1921, **49**, 1, for description of a newer type of pipette.

[2] Apparatus may be purchased from many surgical supply houses or from the Emil Greiner Company, 55 Vandam Street, New York City.

[3] This diagram as well as the discussion which follows has been taken almost bodily from a letter written to me by Dr. Arlie Bock of the Massachusetts General Hospital. For his kindness in allowing me to do this I am most grateful.

that of the normal zone an excess of alkali is present in the blood and the condition is known as *alkalosis*.

"In Fig. 32, the method of plotting the amount of CO_2 in arterial blood is also shown. Arterial blood is obtained by puncture of the radial or brachial artery, the amount of CO_2 which it contains is determined immediately, precautions being taken to exclude loss of CO_2 from the blood, and the value obtained is then placed on a

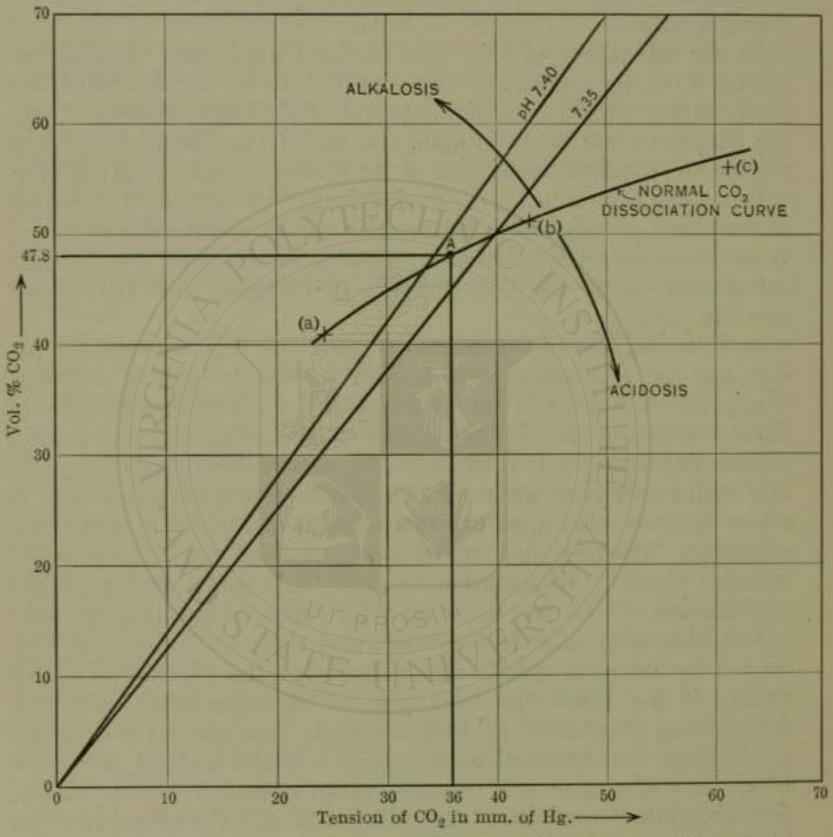


FIG. 32.—Reconstructed CO_2 diagram of Haggard and Henderson. (After Bock.)

CO_2 dissociation curve determined either from the same sample of arterial blood or of venous blood drawn simultaneously with the arterial sample. The point on the curve at which this value falls is known as the "A" point. In the case given in Fig. 32, the value is 47.8 volumes per cent. An ordinate drawn from this point on the curve to the base line shows that the tension at which this amount of CO_2 in arterial blood existed in the body must have

been about 36 mm. of mercury. In patients not subject to cardiac or pulmonary disease, the tension of CO_2 in arterial blood is the same as that of the CO_2 in the alveolar air, so that in the above case the tension of CO_2 in the alveolar air at the time the observation was made was 36 mm. of mercury."

From facts thus obtained two other deductions can easily be drawn: namely, (1) the pH or hydrogen-ion concentration of the

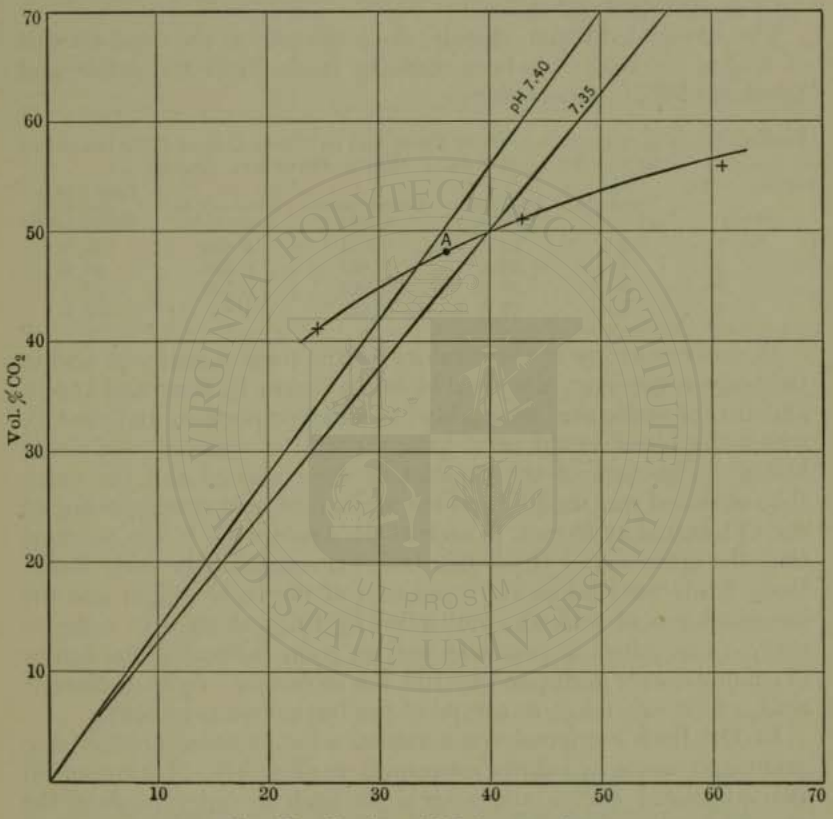


FIG. 33.—Tension of CO_2 in mm. of Hg.

blood and (2) the total amount of acid in the body. The first deduction is possible since we know from L. J. Henderson's original observations that the reaction of the blood depends upon the ratio of the free CO_2, or the CO_2 in solution in blood, to the combined CO_2 in the form of sodium bicarbonate as expressed in the ratio $\frac{NaHCO_3}{H_2CO_3}$. Given the total CO_2 in arterial blood and the tension at which it

exists, as in the above case, we can determine the value of the ratio of free to combined CO_2 because the amount of free CO_2 is directly dependent upon the tension or pressure at which it exists in the blood. Instead of making this calculation for each determination we can calculate, by means of the Hasselbalch formula, a series of pH values and express them by the straight lines shown in Fig. 33 (labeled pH 7.40 and pH 7.35). A pH line passing through the A point on the curve thus would give the reaction of the blood at the time of the observation.

The second deduction, namely, the estimation of the total amount of acid in the body, has been made by Bock, Field and Adair[1] and tabulated for 4 cases as follows:

TABLE 171.—CALCULATIONS OF BODY FLUID AND OF TOTAL ACID IN FOUR DIABETICS RECOVERING FROM COMA. (BOCK, FIELD AND ADAIR.)

Case.	Weight in kg.	Body fluid in liters.	Concentration of acid.	Total acid in gram mols.	Total acid in grams, diacetic acid.
No. 1	32	22.5	0.031	0.698	71.0
2	42	28.8	0.031	0.892	91.0
3	40	28.0	0.027	0.757	77.2
4	39	27.3	0.037	1.01	103.0

In order to arrive at these values for the total quantity of acid in the body, a specimen of normal blood was taken by them and known amounts of acetic acid were added to different portions and the CO_2 which the blood would take up at 40 mm. of mercury was determined. The data of the experiment were plotted and the curve thus obtained was used to find the amount of acid corresponding to the CO_2 bound at 40 mm. in each of the 4 patients. It was assumed that the acids were evenly distributed throughout the body fluids. Body fluids were taken as 70 per cent of the body weight and the concentration of acid was multiplied by this volume. In order to express the values in grams as well as gram molecules, the figures of column 4 were multiplied by 103, the molecular weight of diacetic acid, which was taken as a type of the foreign acids present.

In Dr. Bock's original communication he enclosed another diagram and wrote as follows concerning it (Fig. 34): "I have added two additional curves and several pH lines in order to show the general level of the CO_2 curve in diabetic coma, the low level to which the arterial CO_2 may fall in this condition, the change in pH from a normal of 7.37 to 7.20, and to indicate the response of the blood and body in general to insulin therapy. The rise in the level of the curve is due to the amount of alkali released from its combination with non-volatile acids such as those of the ketone group and thus made available for combination with CO_2." The diagram is given below.

[1] Bock, Field and Adair: Jour. Metab. Res., 1923, **4**, 27.

8. **The Hydrogen-ion Concentration of the Blood.**—Human blood is slightly alkaline, having an hydrogen-ion concentration a little less than that of pure water. The hydrogen-ion concentration—pH— of oxalated normal blood is pH 7.35. In clinical acidosis the values for the oxalated blood may fall to pH 7.1, and Bock has found as low as pH 7.03 in diabetic coma. In artificially produced acidosis in dogs the pH may go as low as pH 6.9. A

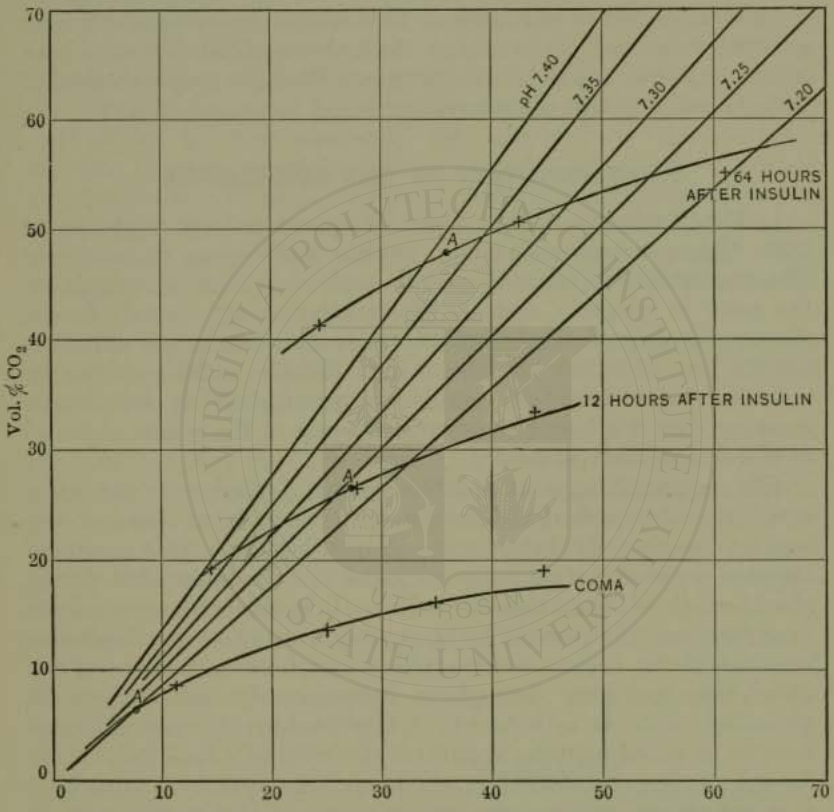


FIG. 34.—Diagram showing CO_2 dissociation curves in acidosis. (Bock.)

reaction of pH 7.6 or higher would be obtained only after the administration of alkalis. The buffer action of the carbonates of the plasma and the protein of the whole blood enables the blood to take up considerable amounts of acids or alkalis without appreciable change in hydrogen-ion concentration. Until practically all the plasma bicarbonate is taken up by acid, little or no change occurs in the pH of the blood. After this point rapid changes in pH occur.

In the determination of the pH of the blood one may use electrometric, colorimetric, or gasometric methods. (1) Electrometric methods are complicated and require expert technical skill. (2) Colorimetric methods, using dye or buffer standards, are widely used. The methods of Cullen[1] and of Hastings and Sendroy[2] are perhaps the best known. They are simple but under certain conditions require the application of correction factors to insure accuracy. (3) Gasometric methods by CO_2 analyses are illustrated in the method described by Eisenman.[3] A combination colorimetric and gasometric procedure has been devised by Austin, Stadie, and Robinson;[4] it is said to be more accurate than the simple method of Cullen, but it is also more complicated.

C. EXAMINATION OF THE RESPIRATION.

1. **The Technique.**—Two types of apparatus are employed to learn the exchange of carbon dioxide and oxygen in man: (1) The respiration calorimeter and the respiration chamber, which are the same in principle, and (2) the respiration apparatus. In the closed chamber of the calorimeter and the respiration chamber, the oxygen admitted and the carbon dioxide withdrawn can be accurately determined in periods from one-half to one hour's duration, but it is better to take the average of the results obtained in three successive periods.

The respiration apparatus differs from the calorimeter and respiration chamber in that the patient is not in a closed chamber, but instead breathes through a nose- or mouth-piece. This is advantageous because the exchange of gases can be determined during short periods of fifteen minutes or less. It is disadvantageous, however, because, the periods being so short, errors at the beginning and end of the periods are magnified, and further, because of the individual breathing through a nose-piece or mouth-piece an abnormal state is introduced. Unfortunately, in each form of mouth- or nose-breathing apparatus the error of a leak falls chiefly on the oxygen, because the patient and the apparatus constitute a closed circuit, and any diminution in gas in this circuit must be offset by the addition of oxygen. A more troublesome source of error and one difficult to avoid arises from the possibility of the patient exhaling carbon dioxide, which has previously accumulated in the body, at a more rapid rate than corresponds with the oxygen

[1] Cullen: Jour. Biol. Chem., 1922, **52**, 501. Cf. also Myers, Schmitz, and Booker: Jour. Biol. Chem., 1923, **57**, 209.

[2] Hastings and Sendroy: Jour. Biol. Chem., 1924, **61**, 695.

[3] Eisenman: Jour. Biol. Chem., 1927, **71**, 611.

[4] Austin, Stadie, and Robinson: Jour. Biol. Chem., 1925, **66**, 505.

inhaled. The patient is said to "pump out" carbon dioxide. This error could only occur in the relatively short periods which are employed with the respiratory apparatus. There is also another error due to carbon dioxide which is lost by cutaneous respiration, and it has been calculated that this would lower the quotient 0.01 to 0.015. This also occurs only with the respiratory apparatus.

Many forms of apparatus have been invented to measure the basal metabolism of man and it is gratifying that the tendency is all in the way of simplification. In the routine and investigative work at the New England Deaconess Hospital the Tissot apparatus was formerly employed but with the introduction by Benedict[1] in 1923 of the "student apparatus" the older method was discarded. As yet it has not seemed justifiable to expend the money for a basal metabolism test of each diabetic. A single observation, with the necessary control tests on the same day, should not be given as much weight as the labor of securing the data would warrant. The variations in the metabolism of diabetics are far less than in the metabolism of patients with thyroid disease.

2. **The Respiratory Quotient.**—The relation which the volume of carbon dioxide exhaled bears to the volume of oxygen inhaled constitutes the respiratory quotient. The respiratory quotient has been discussed at length on page 306 to which the reader is referred. During the combustion of a food in the body a definite quantity of oxygen is consumed and carbon dioxide produced. The relation which the volumes of carbon dioxide and oxygen bear to one another constitutes the theoretical respiratory quotient of the substance. I will insert here examples showing how the respiratory quotient of alcohol and milk may be theoretically calculated, because the computations are based on different methods.

The oxidation of alcohol (C_2H_5OH) requires 3 molecules of oxygen, $3(O_2)$, for its complete combustion, as is indicated in the following equation:

$$\begin{matrix} & C_2 & & & \text{Volume } 2(CO_2) & \\ C_2H_5OH = & H_4 & +3(O_2) = 3(H_2O) + 2(CO_2). & \dfrac{\text{Volume } 2(CO_2)}{\text{Volume } 3(O_2)} = 0.67, & \text{respiratory} \\ & H\text{–}O\text{–}H & & & \text{quotient of alcohol.} \end{matrix}$$

The calculation of the theoretical respiratory quotient of milk is dependent upon the fact that milk is made up of known quantities of milk-sugar, fat, and protein, and that the quantities of oxygen consumed and carbon dioxide given off in the combustion of each of these substances have been determined. These values, as well as some others, are shown in Table 172.

[1] Benedict and Benedict: Boston Med. and Surg. Jour., 1923, **188**, 567.

TABLE 172.—RESPIRATORY QUOTIENTS FOR PROTEIN, FATS, CARBOHYDRATES,[1] AND ALCOHOL.

Materials.	Oxygen required to oxidize 1 gram.		Produced in the oxidation of 1 gram.			Respiratory quotient $\frac{CO_2 \text{ cc.}}{O_2 \text{ cc.}}$	Heat.			
	Weight, gms.	Volume, cc.	Carbon dioxide.		Heat, cal.		Per gram of oxygen, cal.	Per liter of oxygen, cal.	Per gram of carbon dioxide, cal.	Per liter of carbon dioxide, cal.
			Weight, gms.	Volume, cc.						
Starch	1.185	829.3	1.629	829.3	4.20	1.000	3.54	5.06	2.58	5.06
Cane-sugar	1.122	785.5	1.543	785.5	3.96	1.000	3.53	5.04	2.57	5.04
Milk-sugar[2]	1.066	746.2	1.466	746.2	3.74	1.000	3.51	5.01	2.55	5.01
Animal fat	2.876	2013.2	2.811	1431.1	9.50	0.711	3.30	4.72	3.38	6.64
Human fat	2.844	1990.8	2.790	1420.4	9.54	0.713	3.35	4.79	3.42	6.72
Protein[3]	1.367	956.9	1.520	773.8	4.40[4]	0.809	3.22	4.60	2.89	5.69
β-oxybutyric acid	1.368	968.0	1.286	860.0	4.69	0.889	3.40	4.85	2.78	5.46
Alcohol	2.085	1459.5	1.911	972.9	7.10	0.667	3.41	4.86	3.72	7.30

[1] Benedict and Joslin: Metabolism in Diabetes Mellitus, Carnegie Institution of Washington, Publication No. 136, p. 166.

[2] These values apply likewise to dextrose and levulose.

[3] While this computation is based upon meat protein, the values will be essentially the same for all proteins. These values represent quantities found when burning protein not in a calorimetric bomb, but in the animal body.

[4] The heat of combustion of protein averages 5.65 calories per gram; deducting the unoxidized material in the urine, the heat per gram would be 4.40 calories. For discussion of this point, see Atwater and Bryant, Storrs (Connecticut) Agr. Exp. Sta. Rept., 1899, p. 73. Since this value has to deal with protein actually burned, it is not to be confused with the value 4.1 commonly used to calculate the calories from ingested protein of which a portion is assumed to be excreted undigested in the feces.

One liter of milk may be considered to contain 50 grams of carbohydrate, 40 grams of fat, and 33 grams protein.

C. (50 grams × 746.2) = 37,310.0 cc. CO_2
F. (40 grams × 1431.1) = 57,244.0 cc. CO_2
P. (33 grams × 773.8) = 25,535.4 cc. CO_2

120,089.4 cc. CO_2

C. (50 grams × 746.2) = 37,310.0 cc. O_2
F. (40 grams × 2013.2) = 80,528.0 cc. O_2
P. (33 grams × 956.9) = 31,577.7 cc. O_2

149,415.7 cc. O_2

$$\frac{120{,}089.4 \text{ cc. } CO_2}{149{,}415.7 \text{ cc. } O_2} = 0.803, \text{ respiratory quotient of milk.}$$

The calculations to determine the respiratory quotient of an individual are still simpler, and are shown in an experiment discussed under the Total Metabolism in the following paragraph.

3. **The Total Metabolism.**—The total metabolism, with its variations in diabetic patients at different stages of the disease, has been discussed, beginning on page 254. The calculations by which the total metabolism of an individual can be determined when the oxygen consumed and the carbon dioxide exhaled are known are illustrated in the data of the following experiment (Table 173).

TABLE 173.—NORMAL INDIVIDUAL (E. P. J.). FASTING EXPERIMENT DECEMBER 23, 1914. WEIGHT, 65 KILOS. HEIGHT, 177.8 CM.

Period.	Duration, min.	Duration, sec.	CO_2 per min. cc.	O_2 per min. cc.	Respiratory quotient.	Calories per kilo per 24°.	Variation standard H. & B.	Variation from DuBois.
1	15	6	152	192	0.79	20.40		....
2	14	59	150	194	0.77	20.51	−14%	−20%
3	15	0	153	196	0.78	20.77		....
				Average =	0.78			

Total calories. per 24 hours = 1336.

First, the calculation of the respiratory quotient of this individual should be determined, and this is done as follows:

$$\frac{\text{Volume } CO_2}{\text{Volume } O_2} = \frac{152 \text{ cc.}}{192 \text{ cc.}} = 0.79, \text{ respiratory quotient.}$$

Since the body weight was 65 kilograms and 192 cc. O_2 were inhaled for the whole body per minute, 2.95 cc. (192 cc. O_2 ÷ 65 kilos) were inhaled per kilo per minute, and as there are fourteen hundred and forty minutes in twenty-four hours 4284 cc. or 4.284 liters oxygen (1440 × 2.95) were consumed per kilogram body weight per twenty-four hours. In order to express in terms of calories

the heat which any consumption of oxygen represents, Williams, Riche and Lusk have constructed a useful table (see Table 174) showing the caloric value of a liter of oxygen for different non-protein respiratory quotients. The term "non-protein respiratory quotient" is explained in a later paragraph.

TABLE 174.—THE CALORIC VALUE OF ONE LITER OF OXYGEN FOR VARIOUS NON-PROTEIN RESPIRATORY QUOTIENTS AND THE PROPORTIONS OF THE ENERGY FROM CARBOHYDRATE AND FAT METABOLISM TO BE ASSIGNED TO CARBOHYDRATE AND FAT RESPECTIVELY. (WILLIAMS, RICHE AND LUSK.[1])

Respiratory quotient.	Calories for 1 liter O_2. Number.	Log.	Carbohydrate, per cent.	Fat, per cent.
0.70	4.686	0.67080	0	100.0
0.71	4.690	0.67116	1.4	98.6
0.72	4.702	0.67231	4.8	95.2
0.73	4.714	0.67346	8.2	91.8
0.74	4.727	0.67460	11.6	88.4
0.75	4.739	0.67574	15.0	85.0
0.76	4.752	0.67688	18.4	81.6
0.77	4.764	0.67801	21.8	78.2
0.78	4.776	0.67913	25.2	74.8
0.79	4.789	0.68024	28.6	71.4
0.80	4.801	0.68136	32.0	68.0
0.81	4.813	0.68247	35.4	64.6
0.82	4.825	0.68358	38.8	61.2
0.83	4.838	0.68469	42.2	57.8
0.84	4.850	0.68578	45.6	54.4
0.85	4.863	0.68690	49.2	51.0
0.86	4.875	0.68800	52.0	47.6
0.87	4.887	0.68910	55.4	44.2
0.88	4.900	0.69019	59.8	40.8
0.89	4.912	0.69128	62.6	37.4
0.90	4.924	0.69230	66.0	34.0
0.91	4.936	0.69343	69.4	30.6
0.92	4.948	0.69450	72.8	27.2
0.93	4.960	0.69557	76.2	23.8
0.94	4.973	0.69664	79.6	20.4
0.95	4.985	0.69771	83.0	17.0
0.96	4.997	0.69878	86.4	13.6
0.97	5.010	0.69985	89.8	10.2
0.98	5.022	0.70092	93.2	6.8
0.99	5.034	0.70199	96.4	3.4
1.00	5.047	0.70307	100.0	0.0

Consulting this table of Williams, Riche and Lusk, it will be seen that the equivalent in calories for 1 liter of O_2 for a non-protein respiratory quotient of 0.79 is 4.789. (As a matter of fact, the respiratory quotient above obtained is not the exact non-protein respiratory quotient, but this may be neglected unless the nitrogen excretion is distinctly abnormal.)[2] If we multiply 4.789 calories by the total number of liters of O_2 consumed per day, the number

[1] Williams, Riche and Lusk: Jour. Biol. Chem., 1912, **12**, 357.

[2] It will be remembered that the respiratory quotient of protein is 0.81 which is nearly that here obtained for the total metabolism.

of calories per kilo per twenty-four hours is obtained, which would be in this case (4.789 × 4.284) 20.5 calories. It should be stated that this actually represents the metabolism for a period of fifteen minutes when the individual was under complete relaxation, and as quiet as possible. It by no means represents the average metabolism for the day. Even with this extreme basis of repose maintained during the experiment the weight of the oxygen inhaled was 550 grams and of the carbon dioxide exhaled 424 grams in the twenty-four hours.

4. **The Non-protein Respiratory Quotient.**—If the nitrogen in the urine is known, one can calculate the amount of oxygen employed by the body for the oxidation of the protein which it represents, and correspondingly, the amount of carbon dioxide simultaneously produced. If these computed figures are subtracted from the total oxygen and carbon dioxide obtained by direct experiment, the remainders represent the oxygen absorbed and carbon dioxide produced by the non-protein respiratory metabolism. The relation of these to one another constitutes the non-protein respiratory quotient. In the table of Williams, Riche and Lusk the proportions of the total energy from the katabolism of carbohydrate and fat assumed as produced from the two materials respectively for any known non-protein respiratory quotient between 0.70 and 1 are given. Thus, a respiratory quotient of 0.70 shows that 100 per cent fat and no carbohydrate was oxidized, and a respiratory quotient of 1 shows exactly the reverse.

The calculations necessary for the determination of the non-protein respiratory quotient of an individual are given below. The example chosen for this purpose is that of a man undergoing a prolonged fast at the Nutrition Laboratory. (See p. 362 for the complete table.)

	Respiratory quotient.		Quantities oxidized.			Calories.
Time	Actual.	Non-protein.	Protein, gms.	Carb., gms.	Fat, gms.	per kilo. per 24 hrs.
5th day of fast .	0.73[1]	0.72	62	15	133	28

The values used for the computation of the above data were as follows:

CO_2	O_2	Nitrogen.
cc. per min.	cc. per min.	grams per 24 hours
175	240	10.41

10.41 grams nitrogen represent the nitrogen excreted per twenty-four hours or fourteen hundred and forty minutes, and $\left(\frac{10.41 \text{ gms.}}{1440 \text{ min.}}\right)$ 0.0072 gram is the excreted nitrogen per minute.

[1] Calculated for twenty-four hours.

One gram of protein nitrogen, representing 6.0 grams body protein,[1] produces in its combustion 4750 cc. CO_2, and consumes in its combustion 5910 cc. O_2. Therefore (4750 × 0.0072) 34.20 cc. CO_2 are produced per minute, and (5910 × 0.0072) 42.55 cc. O_2 are consumed per minute, as a result of the protein metabolism.

In the experiments conducted that day, the total CO_2 eliminated per minute was estimated at 175 cc., and the total O_2 consumed per minute at 240 cc. These two amounts represented the total metabolism of protein, fat and carbohydrate for the day. If the oxygen and carbon dioxide per minute derived from nitrogen, which represents the protein metabolism, are subtracted from the total oxygen absorbed and carbon dioxide produced per minute, the remainders show the non-protein metabolism, or the metabolism which is based on the oxidation of fat and carbohydrate.

175 cc. CO_2 per min.	=	total metabolism.		240 cc. O_2 per min.	=	total metabolism.
34 " "	=	protein metabolism.		43 " "	=	protein metabolism.
141 " "	=	non-protein metabolism.		197 " "	=	non-protein metabolism.

$$\frac{\text{Volume 141 cc. } CO_2}{\text{Volume 197 cc. } O_2.} = 0.72, \text{ non-protein respiratory quotient.}$$

Consequently 4.8 per cent of the non-protein metabolism was due to carbohydrate and 95.2 per cent due to fat, according to Table 174.

5. **Theoretical Respiratory Quotients as Calculated from the Diet.**—The theoretical respiratory quotient of a normal individual living upon protein and carbohydrate can be calculated as shown in the following table:

TABLE 175.—THEORETICAL RESPIRATORY QUOTIENTS.

Diet.[2]	Cal.	O_2.	CO_2.	Respiratory quotient.
Protein, 100 grams . .	414	95.69	77.38	
Carbohydrate, 563 grams .	2365	466.73	466.73	
		562.42	544.11	0.967

The theoretical respiratory quotient of a diabetic individual in which the carbohydrate in the diet has been replaced by fat has been calculated by Magnus-Levy, and he has also inserted the deductions which must be made on account, (1) of 60 grams of dextrose, and (2) 20 grams of β-oxybutyric acid lost in the urine during the same period.

[1] In estimating the quantity of body protein burned from the nitrogen in the urine the equivalent 6 should be employed instead of 6.25.

[2] Magnus-Levy: Ztschr. f. klin. Med., 1905, **56**, 83.

TABLE 176.—THEORETICAL RESPIRATORY QUOTIENTS.

Diet.[1]	Calories.	O_2 liters.	CO_2 liters.	Respiratory quotient.
Protein, 100 grams	414	89.2	72.0	
Fat, 250 grams	2365	504.9	356.8	
	2779	594.1	428.8	0.722
Dextrose, 60 grams	225.6	44.8	44.8	
	2554	549.3	384.0	0.699
β-oxybutyric, 20 grams	91	19.3	17.2	
	2463	530.0	366.8	0.692

Lusk[2] has calculated that when the dextrose-nitrogen ratio is 3.65 to 1, the quotient of protein is 0.632. The formation and excretion of acetone bodies also tend to lower the quotient, but such acid substances may react with sodium bicarbonate to set free carbon dioxide, so that the precise theoretical value of the quotient in diabetes cannot be determined. The actual observations in phlorizinized dogs and human patients with the 3.65 ratio are found to meet the theoretical expectations with quotients approximating 0.69.

6. **The Carbon Dioxide Tension of the Alveolar Air.**—The introduction of simple methods for the detection of acidosis by determination of the CO_2 in the alveolar air has been of inestimable value. In 1907, I spent a week in Naunyn's laboratory with Magnus-Levy in order to learn to study acidosis by familiarizing myself with the latter's method for the estimation of β-hydroxybutyric acid. The analysis was most time-consuming, as was also the quantitative test for ammonia by the Schlösing method, then commonly in use, which demanded an interval of three days even after the twenty-four-hour quantity of urine had been collected. The technic of Folin in 1912, and of others soon reduced this latter process to less than half an hour, but even then the result obtained respresented the average excretion for the preceding twenty-four hours, and in the presence of approaching coma the data were obtained too late. Therefore newer methods which enable the acidosis to be quantitatively estimated promptly have proved most helpful in treatment. At present three such methods are available for the detection of the CO_2 in the alveolar air, the Plesch-Higgins, the Fridericia and the Marriott. Probably the Plesch-Higgins is the most accurate, and those familiar with it in large hospitals prefer it. However, the other two methods are quite satisfactory, and the technic of either one can be learned by physician or nurse in a few minutes.

[1] The values used by Magnus-Levy for O_2 and CO_2 vary somewhat from those given in Table 175.

[2] Lusk: Arch Int. Med., 1915, **15**, 939.

In the discussion of the carbon dioxide tension of the blood plasma, reference is made to the fact that the carbon dioxide of the blood diffuses so readily into the alveolar air of the lungs that the estimation of the latter in nearly all cases gives an index of the former. Because of the simplicity of the determination of the carbon dioxide in the alveolar air, it is today the best quantitative method which the physician has for the estimation of the acidosis of the patient. It is only fair to state, however, that at the present time at the New England Deaconess Hospital we determine the alveolar CO_2 only rarely. In ordinary patients we depend upon the ferric chloride test in the urine as a gauge of possible acidosis; in coma patients we determine the CO_2 combining power of the blood plasma at suitable intervals.

Normally, the carbon dioxide tension of the alveolar air varies between 38 and 45 mm. mercury, 5.3 to 6.3 per cent. If abnormal acids are present in the blood, these displace a proportionate amount of carbon dioxide, and as the carbon dioxide tension in the alveolar air bears a direct relation to that in the blood, it is evident that the carbon dioxide in the alveolar air will vary likewise. A low carbon dioxide tension of the alveolar air therefore indicates an acidosis. If the carbon dioxide tension lies between 38 and 32 mm. mercury a slight acidosis is present, between 32 and 28 a moderate acidosis, and if it falls below 25 mm. Hg. the acidosis is extreme. The lowest value with recovery in my group of cases has been 8 and the lowest obtained in the series was 5, and that occurred in a patient in coma.

Hornor[1] found in an analysis of 300 observations of the alveolar CO_2 tension of my cases that when the carbon dioxide tension of the alveolar air was less than 25 mm. mercury the ammonia was 3 grams or more, when the carbon dioxide tension varied between 25 and 33 mercury the urinary ammonia varied between 3.7 grams and 1.15 grams, and when the carbon dioxide tension was 33 mm. mercury or over the ammonia was less than 2 grams. He also studied the carbohydrate balance in these cases, and learned that it was invariably negative when patients showed a tension of less than 25 mm. mercury, and in three-quarters of the cases was negative when the tension was between 25 and 33 mm. mercury, but that at a higher tension the carbohydrate balance was usually positive and invariably so when the carbon dioxide tension was above 36 mm. mercury. The ferric chloride reaction was also observed, and was found to vary from negative to strongly positive, not only when the carbon dioxide tension of the alveolar air was at 36 mm., but also at 23 mm.

Case No. 1120, a child with onset of diabetes at the age of six

[1] Hornor: Boston Med. and Surg. Jour., 1916, **175**, 148.

years, entered the hospital eight months later as he was recovering from definite diabetic coma. Under treatment he thoroughly recovered from acidosis, but upon repeated trials increase of food led to the return of both sugar and acidosis. In one of these attempts to build up his nutrition severe acidosis occurred on a diet containing no carbohydrate, 42 grams protein and 70 grams fat. Typical hyperpnea without cyanosis developed and repeated observations showed the CO_2 tension of the alveolar air to be 15 mm. Hg. By fasting and without the use of alkalis the patient promptly came out of this state, but he later died from inanition without a trace of acidosis, representing the third mortality from inanition which I had had at that time.

(*a*) **Fridericia**[1] **Method.**—This method possesses the advantages of being simple and involving the use of apparatus which may be easily transported to the bedside. One hundred cc. of alveolar air are collected in a closed chamber and then cooled from the temperature of the body to that of the room. The carbon dioxide in this air is then absorbed with a 20 per cent aqueous solution of potassium hydrate, thereby creating a partial vacuum which in turn is equalized with water. This water is then subjected to atmospheric pressure, when the amount of carbon dioxide replaced by water can be read in percentage of atmospheric air by reading the height in cm. to which the column of water has risen in the closed 100 cc. chamber. This percentage may be changed to mm. of mercury pressure by multiplying by the difference between barometric pressure at the time of the test, and this varies in Boston between 770 mm., and 750 mm., and the tension of aqueous vapor at 37.5° C., which is 48 mm. mercury. This will make a factor which lies between 722 and 702. As the reading of 760 is much the more common at sea level, for clinical purposes the factor 715 ± may be used satisfactorily. The patient should be in the same position and quiet for ten minutes prior to the performance of the test.

At the end of a normal inspiration the patient places his lips entirely about the outside of the mouthpiece *A* (Fig. 35) and forcibly blows out all the air left in his lungs through the apparatus, the corks *C* and *D* being open so that there is a free passage from *A* to *B*. Before the patient begins the next inspiration and sucks back air already blown into the tube the stopcock *C* is closed. Care should be taken to hold the apparatus always by tube *Y* to avoid temperature variations in tube *X*. The apparatus is now immersed in a glass tank of water at room temperature and allowed to remain there five minutes. At the end of five minutes it is removed from the water-bath, always being held by tube *Y* and about 10 cc. of 20

[1] Fridericia: Berlin. klin. Wchnschr., 1914, **51**, Pt. 2, 1268.

per cent sodium hydroxide solution is poured in through tube *Y* at opening *B*. A small amount of this solution runs over into tube *X*. Stopcock *D* is then turned to the left (counter clockwise) so that it is no longer connected with *X* or *Y*, thus making a closed chamber of *X*. The tube is now inverted and shaken several times so that

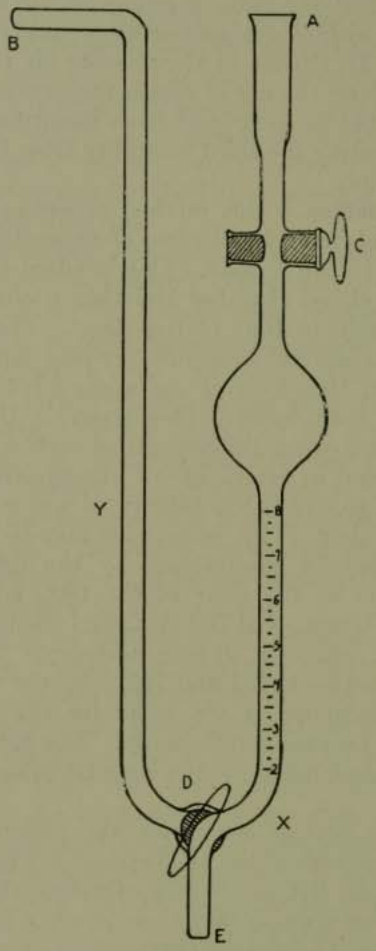


FIG. 35.—Fridericia apparatus.

every surface of the chamber *X* is touched by alkaline solution. By opening stopcock *D* more sodium hydroxide is run into tube *X* and after closing the stopcock again the apparatus is inverted and shaken as before. This procedure is repeated three times. By turning stopcock *D* further to the left a continuous passage is made between *Y* and *E* and the sodium hydroxide in tube *Y* is allowed to flow into the sink. The apparatus is then replaced in the water-

bath and when under water the stopcock D is turned further around until water flows up through E into chamber X. The apparatus is allowed to stand immersed in the water-bath for two minutes. At the end of that time the apparatus is raised until the meniscus of the fluid in tube X is exactly level with the surface of the water in the water-bath. This level is read on the calibrated scale of tube X. This reading represents the percentage of CO_2 in the alveolar air. It may be expressed as CO_2 tension in mm. of mercury by use of the following table.

TABLE 177.—FRIDERICIA READING.

Reading, volume per cent.	CO_2 tension.	Reading, volume per cent.	CO_2 tension.
2.0	14	4.9	35
2.1	15	5.0	36
2.2	16	5.1	36
2.3	16	5.2	37
2.4	17	5.3	38
2.5	18	5.4	39
2.6	19	5.5	39
2.7	19	5.6	40
2.8	20	5.7	41
2.9	21	5.8	41
3.0	21	5.9	42
3.1	22	6.0	43
3.2	23	6.1	44
3.3	24	6.2	44
3.4	24	6.3	45
3.5	25	6.4	46
3.6	26	6.5	46
3.7	26	6.6	47
3.8	27	6.7	48
3.9	28	6.8	49
4.0	29	6.9	49
4.1	29	7.0	50
4.2	30	7.1	51
4.3	31	7.2	51
4.4	31	7.3	52
4.5	32	7.4	53
4.6	33	7.5	54
4.7	34	7.6	55
4.8	34	7.7	56

The apparatus is prepared for the next test by opening cock C so that A to B is a continuous passage. The fluid in the apparatus is allowed to escape. Orifice B is put under the faucet and cold water allowed to run through the apparatus, taking care to shake sufficiently at the time, so that water touches all of the inside of the apparatus. Repeat. Then pour through orifice B about 10 cc. of 4 per cent solution of boric acid. Rinse the apparatus very thoroughly with this acid so that there shall be no alkali remaining adherent to its sides. Wash again with cold water. Leave the apparatus so that the cocks to A and B are open, thereby allowing any water in the apparatus to drain out.

From the above it will be seen that the apparatus necessary is,

first, the Fridericia appliance,[1] a glass tank, whose depth is equal to the length of the Fridericia apparatus, a wash bottle containing 20 per cent solution of sodium hydrate and another wash bottle containing 4 per cent solution of boric acid. It is convenient to add an indicator, such as alizarin or litmus, to the alkaline and acid fluids.

(*b*) **Marriott's Method.**[2]—A very simple method has been devised by Marriott for the determination of the CO_2 in the alveolar air. For details of the procedure the reader is referred to the author's original description. The apparatus is portable and the test requires but a few moments for execution.

The method depends on the fact that if a current of air containing carbon dioxide is passed through a solution of sodium carbonate or bicarbonate until the solution is saturated, the final solution will contain sodium bicarbonate and dissolved carbon dioxide. The reaction of such a solution will depend on the relative amounts of the alkaline bicarbonate and the acid carbon dioxide present. This, in turn, will depend on the tension of carbon dioxide in the air with which the mixture has been saturated and *will be independent of the volume of air blown through, provided saturation has once been attained.* High tensions of carbon dioxide change the reaction of the solution toward the acid side. Low tensions have the reverse effect; hence the reaction of such a solution is a measure of the tension of carbon dioxide in the air with which it has been saturated. The reaction of such a solution may be determined by adding to it an indicator such as phenolsulphonephthalein. Standard solutions of a given reaction for comparison may be prepared by mixing acid and alkaline phosphates in definite proportions. Such solutions may be kept unaltered for long periods of time.

In normal adults at rest, the carbon dioxide tension in the alveolar air, determined as described above, varies from 40 to 45 mm. Tensions between 30 and 35 mm. are indicative of a mild degree of acidosis. When the tension is as low as 20 mm., the individual may be considered in imminent danger. In coma, associated with acidosis, the tension may be as low as 8 or 10 mm. In infants, the tension of carbon dioxide is from 3 to 5 mm. lower than in adults.

"Alveolar" air collected as described above, is essentially air which has come in equilibrium with the venous blood in the pulmonary capillaries. The tension of carbon dioxide is approximately that in the venous blood. "Alveolar" air collected by the Haldane or Fridericia methods is air which has come in approximate equilibrium with the arterial blood, and hence is of a carbon dioxide tension from 10 to 20 per cent lower.

[1] Apparatus may be purchased from Emil Greiner, 55 Vandam Street, New York.

[2] Marriott: Jour. Am. Med. Assn., 1916, **66**, 1594.

SECTION VI.

THE DIET IN HEALTH AND IN DIABETES.

A. THE DIET OF NORMAL INDIVIDUALS.

1. **Caloric Needs of the Body.**—The metabolism of normal individuals varies greatly, as Lavoisier, 1743–1794, was the first to prove by experiments in respiratory metabolism. A normal ration for a man weighing 70 kilograms (154 pounds) when at moderate work would contain approximately 2800 calories, but if he weighed 60 kilograms (132 pounds), 2400 calories, or 40 calories per kilogram body weight. Individuals with sedentary occupations require far less, and I agree with Chittenden, about 2100 calories, or 30 calories per kilogram body weight. By a calorie is understood the amount of heat necessary to raise the temperature of 1 kilogram of water 1° C., or what is approximately the equivalent, 1 pound of water 4° F.[1] The heat liberated by 1 gram of various foodstuffs during this combustion in the body is shown in the following table. In clinical diabetic computations the decimals may be omitted:

TABLE 178.—CALORIC VALUES OF FOODS.

1 gram.	Calories.		Calories.
Carbohydrate	4	actually	4.1
Protein	4	"	4.1
Fat	9	"	9.3
Alcohol	7	"	7.1

The caloric needs of the body vary not only from day to day and hour to hour, but from moment to moment. It is convenient to remember that 1 calorie per kilogram body weight per hour represented the metabolism of a group of normal individuals at the Nutrition Laboratory while at rest in a horizontal position and 1.2 calories per kilogram per hour while sitting in a chair. In other words, 20 per cent more energy was required by these individuals to sit in a chair than to lie on a couch. If the subject is asleep lying down and awake sitting up, the difference may be

[1] This is a large calorie, often written with a capital C; a small calorie deals with 1 gram instead of 1 kilogram.

35 to 40 per cent. On the other hand, if the greatest possible care is taken to be as quiet when erect as when horizontal, the difference may be only 8 per cent. If the individual is in a comfortable steamer chair or propped up in a semi-reclining position with a back-rest, the metabolism is 3 per cent less than when lying flat in bed.[1] At the Nutrition Laboratory 89 normal men at rest eliminated on the average 25.5 calories per kilo body weight per twenty-four hours, the total output per twenty-four hours being 1609 calories, and 68 normal women eliminated on the average 24.9 calories, calculated per kilogram of body weight per twenty-four hours, a total output of 1355 calories for the twenty-four hours of the day. Too often in dietetic computations it is assumed that the caloric needs of the body can be accurately estimated. As a matter of fact, the error in such computations is considerable, and it is absurd to expect to compute the needs of the individual when up and about, whether normal or diabetic, more closely than within 10 to 20 per cent of the real value. The reason for this is apparent if one observes the attitudes and motions of individuals in a street car. The one is quiet, the other restless, the one avoids exertion, the other is all activity. In disease these differences of habit and disposition are accentuated. One patient with 40 calories per kilogram body weight will gain pounds, the other will barely hold her own weight. A diabetic patient, Case No. 1541, confined to her bed with hemiplegia for a year remained sugar-free, held her weight constant and the diet, accurately weighed by a trained nurse for the entire period, amounted to 20 calories per kilogram body weight for twenty-four hours.

As an illustration of the amount of work which can be performed by 1 calorie of energy, I learn from my friend, Prof. Benedict, that the expenditure of 1 calorie of heat is required to rise from a sitting position in front of a door, turn the key in the door, and sit down. A single 16-candle-power carbon lamp gives off in heat the equivalent of about 45 calories per hour, which represents a little less than the basal metabolism of an adult weighing 50 kilograms.

Standards of basal metabolism for age, sex and height have been created in the last few years. The two most commonly employed are those of Harris and Benedict of the Nutrition Laboratory and of DuBois of the Cornell Laboratory. A description of the manner in which these standards were made and of the method by which the metabolism of an individual can be determined or predicted is described on pp. 256 and 461.

It is desirable for us all to visualize calories and to that end various concrete examples of what calories derived from food will enable an individual to do are given.

[1] Sonderstrom, Meyer and DuBois: Arch. Int. Med., 1916, **17**, 872.

To walk one hour on a level road at the rate of 2.7 miles an hour requires 160 calories above that of the resting metabolism (Lusk). The amount of energy expended in walking on a level road can be calculated with more accuracy as follows: If the individual weighs 60 kilograms and walks 1000 meters (3281 feet) he is said to have travelled (60 × 1000) 60,000 horizontal kilogram-meters. For each horizontal kilogram-meter 0.0005 calories are required. This would represent an expenditure of (60,000 × 0.0005) 30 calories, which should be added to the resting metabolism of the individual during the time required to walk the given distance. A man weighing 60 kilograms who walks 4 miles an hour would expend [60 (kilograms) × 4 (miles) × 1609.3 (meters in 1 mile) × 0.0005 (calories per horizontal kilogram-meter)] 193 calories. To this figure should be added 60 calories, on the basis of 1 calorie per kilogram body weight per hour, which would have been expended by the individual at rest if one desires to obtain the total expenditure of heat. The basis for calculations of this type is direct measurement. It should be remembered that the weight—60 kilograms —represents the naked weight of the individual plus the weight of his clothes. If a pack weighing 5 kilograms is carried, then the calculations must be on the basis of 65 kilograms.

If the individual ascends a height, the calculations are somewhat different. The unit is the vertical kilogram-meter. The weight of an individual in kilograms multiplied by the height ascended in meters gives the vertical kilogram-meters. The heat equivalent of the mechanical work evolved in 426.5 vertical-meters is 1 calorie. Thus, if an individual of 60 kilograms body weight walks up 10 flights of stairs each 3 meters high, he would expend $\left(\frac{60 \times 10 \times 3}{426.5}\right)$ 4.2 calories. As the mechanical efficiency of the body is only about 20 per cent, it is necessary to multiply this figure by 5 in order to determine the actual energy expended (4.2 × 5) namely, 21 calories. Here we are dealing with figures based on estimate and not on direct experimentation. To this figure must be added the calories necessary for horizontal progression, as well as the calories required during the same period of resting metabolism. Two calories might, therefore, be added for the forward progression, and 3 calories more for the three minutes of time of resting metabolism. In other words, a man of 60 kilograms walking up 10 flights of stairs each 3 meters (10 feet) high, in three minutes would expend the heat equivalent of 26 calories or about 3 calories per flight. This would in effect double his basal metabolism.

The metabolism of a group of men standing was 12 per cent more

than when in the horizontal position, according to Smith.[1] He also found that walking at 2 miles an hour nearly doubled the standing requirement and at 4 miles an hour increased it threefold.

The basal metabolism of a fasting individual weighing 60 kilograms (132 pounds) has been determined by Benedict (see pp. 362 and 363) and found to vary between 1845 and 1318 calories during the thirty-one days of the fast. Not only did the total calories decrease as the fast progressed, but the calories per kilogram decreased as well. How important a rôle undernutrition plays in the metabolism has already been discussed at length, (See pp. 299 to 306).

It has been estimated that an individual weighing 70 kilograms (154 pounds) requires, under the varying conditions set forth in Table 179, the given number of calories.

TABLE 179.—CALORIES REQUIRED DURING TWENTY-FOUR HOURS BY AN ADULT WEIGHING 70 KILOGRAMS (154 POUNDS).

Condition.	Calories per kilogram body weight.	Calories per pound body weight.	Total calories.
At rest	25–30	11–14	1750–2100
Light work	35–40	16–18	2450–2800
Moderate work	40–45	18–20	2800–3150
Hard work	45–60	20–27	3150–4200

Farmers in various parts of the United States have been shown to consume on an average 3500 calories. One is apt to forget that an individual doing heavy work requires additional calories only for the actual period of that work and not for the entire twenty-four hours. With the cessation of work the metabolism falls abruptly. Furthermore, the actual period of heavy work is short and represented by minutes rather than hours. If of a pessimistic nature one has only to watch street laborers to be convinced, though a far more enjoyable and as scientific a proof is furnished by the minutes spent in actual play by the teams of football. In an entire game, the minutes in which the ball was in play numbered eleven instead of the supposed four quarters of fifteen minutes each according to the stop watch observations of the late Prof. Harold C. Ernst, and Mr. Robert Fisher tells me that in the Boston College—Holy Cross game of 1922 the ball was in play eleven minutes and twenty-three seconds. Carpenter[2] found 30 calories per hour additional were required by a typist when writing at the rate of 50 words a minute compared with sitting still and reading.

[1] Smith, H. M.: Gaseous Exchange and Physiological Requirements for Level and Grade Walking, Carnegie Inst., Washington, D. C., Pub. No. 309.

[2] Carpenter: Jour. Biol. Chem., 1911, **9**, 231.

Normal boys twelve or thirteen years of age have been shown by DuBois[1] to produce 25 per cent more heat than adults when compared according to his linear formula of body surface. Gephart[2] in a study of the dietary at St. Paul's School came to the conclusion that the boys whose average ages were between thirteen years and six months and sixteen years and one month ate approximately 5000 calories daily, but this is difficult for me to believe, because for eight to ten hours in the day the boys are asleep and for at least six hours more they are reasonably quiet at their studies or meals. I think that an estimate of 3000 calories would be more conservative. For these same boys, the calculated basal metabolism would amount to about 1700 calories. It is, therefore, evident that children require proportionately more food per kilogram or pound body weight. The metabolism of girls has been found to differ from that of boys or women. Standard tables for the estimation of the metabolism of infants, boys, and girls are still unsatisfactory. This is especially true for girls and is set forth in the discussion of the basal metabolism of diabetic girls in Carnegie Monograph, No. 323, p. 90.

2. **Composition of the Diet.**—The ordinary diet for a man at moderate work would contain about 400 grams of carbohydrate, 100 grams of protein (equivalent to 16 grams of nitrogen, approximately eliminated as 14 grams in the urine and 2 in the feces) and 100 grams of fat. This would amount to 2900 calories in the twenty-four hours, or about 40 calories per kilogram for an individual weighing 70 kilograms. These figures would be proportionately reduced both for those of lower body weight and for those with lighter occupations, who would require nearer 30 calories per kilogram. As age advances the metabolism requirements are lessened, thus if 1677 calories are required for basal metabolic needs at thirty years, 1542 are required at fifty and 1407 at seventy years of age. The Harris and Benedict data for these figures are shown in Table 180.

TABLE 180.—DECREASING METABOLIC NEEDS WITH ADVANCING YEARS. HARRIS AND BENEDICT PREDICTION TABLES.[3]

Male, age in years	30	50	70
Height 170 cm.	648	513	378
Weight 70 kg.	1029	1029	1029
Calories in twenty-four hours	1677	1542	1407

[1] DuBois: Arch. Int. Med., 1916, **17**, 887.

[2] Gephart: Boston Med. and Surg. Jour., 1917, **176**, 17.

[3] For the simple method of calculating the metabolism by the Harris and Benedict standard, see p. 959; also consult p. 960 for DuBois' methods.

TABLE 181.—THE PROPORTION OF CARBOHYDRATE, PROTEIN AND FAT IN THE NORMAL DIET.

Food.	Quantity, grams.	Calories, per gram.	Total calories.
Carbohydrate	400	4	1600
Protein	100	4	400
Fat	100	9	900

The figures given above are very different from the old Voit standard in which the carbohydrate was placed at 500 grams, the protein at 125 grams, and the fat at 55 grams. The more I observe the diets of non-diabetic patients, the more I have come to believe that adults eat less than has generally been supposed. The figures given above are high rather than low. Students in one university which I visited evidently ate below their requirements, and the reason was possibly attributable to the cafeteria system. At boarding houses they would have been more free to take liberal portions. The World War, here as elsewhere, rendered less necessary the teachings of Chittenden[1] upon the dangers of overnutrition and the fashions, at least for women, have done still more. People care more for their money than for surplus food.

3. **Carbohydrate.**—From the preceding statements it will be seen that 55 per cent of the energy of the diet of the normal individual consists of carbohydrate. These figures are only approximate, but they leave no doubt as to how large a place sugar and starch occupy in the daily ration. (See p. 475.) What percentage of carbohydrate is furnished by sugar is problematical.[2] We do know, however, that the average individual in the United States was supposed to consume 103 pounds of cane sugar during the year 1923. This would amount to 127.2 grams or 0.28 pounds per day, which would amount to more than one-fourth of the carbohydrate calories.

The carbohydrate intake of healthy children has also been investigated by Holt and Fales. Among 100 healthy children from one to eighteen years of age, they found that the quantity of carbohydrate taken per kilogram body weight averaged 10 grams. "Of this 51 per cent was sugar, including lactose, saccharose and fructose, and 49 per cent was starch. The carbohydrate in the diet of the infant is almost all sugar, that of the nursing infant entirely lactose, that of the artificially fed infant usually a mixture of lactose with saccharose or maltose and dextrins."[3]

On account of the possible importance of the variety of sugars ingested, the table of Holt and Fales is inserted; to it I have added a column showing the percentage of fruit sugar to the total sugar in the diet.

[1] Chittenden: Physiological Economy in Nutrition, New York, 1904, p. 474.

[2] Mendel estimates that sugar constitutes about one-fifth of the requisite food intake, 2500 calories, of our population. See Mendel: Our Changing Food Habits, etc. New York, George H. Doran Company, 1927.

[3] Holt and Fales: Am. Jour. Dis. Children, 1922, **24**, 44.

TABLE 182.—AVERAGE AMOUNTS OF DIFFERENT SUGARS TAKEN.[1] BOTH SEXES—AVERAGE GRAMS DAILY.

Age, years.	No. of cases.	Lactose.	Saccharose.	Fruit sugars.[2]	Other sugars.	Total sugars.	Fruit sugars, per cent of total.
1– 2	7	30	9	24	..	63	38
2– 3	11	33	19	40	2[3]	94	43
3– 4	10	34	12	27	..	73	37
4– 5	12	36	26	24	1[4]	87	28
5– 6	10	35	39	37	3[5]	114	32
6– 7	8	29	55	33	..	117	28
7– 8	5	24	69	38	1[5]	132	29
8– 9	9	40	64	57	..	161	35
9–10	9	39	76	43	1[3]	159	27
10–11	9	44	53	59	..	156	38
11–12	4	42	59	44	5[4]	150	29
12–13	3	48	48	35	..	131	27

The proportion of carbohydrate in the normal diet varies in different countries, reaching its maximum in the tropics and its minimum in the arctic zones. According to Carrasco Formiguera,[6] less sugar but more bread is eaten in Spain than in the United States. The people in India take 848 grams carbohydrate daily, while the Eskimos get along very comfortably upon 52 grams. Table 183

TABLE 183.—VARIATIONS IN DIET ACCORDING TO RACE.

Race.	Weight, kilos.	Protein, gm.	Carbohydrate, gm.	Fat, gm.	Total calories.
Eskimo	65	282	52	141	2604
Bengali	50	52	484	27	2390
European	70	118	512	65	3055
American[7]	70	100	400	100	2900

is arranged by modifying somewhat a similar table of Lusk's.[8] It shows well the adaptability of different races to different diets. That the Eskimos live upon 52 grams of carbohydrate daily should greatly encourage diabetic patients. All who treat diabetics should be very thankful that there is a race of Eskimos through whom proof is afforded that it is perfectly possible to maintain life on a diet in which carbohydrate is largely replaced by fat.[9] Eskimos are

[1] Holt and Fales: Am. Jour. Dis. Child., 1922, **24**, 44.

[2] This includes all sugars occurring in fruit taken; largely fructose, but includes considerable saccharose and occasionally very small amounts of starch.

[3] Honey (levulose and dextrose).

[4] Maltose.

[5] Honey and maltose.

[6] Carrasco Formiguera: Loc. cit., 427.

[7] Added by E. P. J.

[8] Lusk: The Fundamental Basis of Nutrition, New Haven, Yale University Press, 1914, p. 31.

[9] It must be acknowledged, however, that today the Danish Government supplies the Eskimo with more than this quantity of carbohydrate. Krogh: A Study of the Diet and Metabolism of Eskimos, Copenhagen, 1913.

otherwise also dietetically valuable. Thomas[1] writes that the Greenland Eskimo, on a carnivorous diet, exhibits no increased tendency to vascular and renal disease. This diet furnishes him with vitamins adequate for protection against scurvy and rickets, while the Labrador Eskimo, whose meat is cooked and whose diet includes many prepared, dried, and canned articles, is very subject to both these maladies.

The composition of the diet also varies in the same race from time to time and this has been interestingly described by Mendel.[2] Attention has already been called to the increase in the consumption of sugar in the United States during the last century. Rübner noted that the consumption of meat per capita in Germany had risen three and one-half times during a hundred years prior to the World War. The effects of undernutrition during the war were manifest in the lowering of diabetic mortality, but the total dietary restriction obscures the results of qualitative changes. (See p. 125.)

4. **Protein.**—The protein burned in the metabolism of a healthy individual from day to day depends chiefly on the protein supplied by the diet. Muscular exercise has little effect upon it, since that is dependent upon carbohydrate directly or indirectly. Even in the early days of fasting the protein metabolism changes but little from that in health. With a diet rich in carbohydrate and fat and low in protein the protein metabolism is easily brought to less than 50 grams per day, but with an excess of protein in the diet it may rise to 150 or 200 grams. A liver well stored with glycogen protects the body protein of a fasting man for a day equally as well as does carbohydrate in the diet. On the second day, since the glycogen is nearly exhausted, the protection is distinctly less.

The nitrogenous metabolism as measured by the excretion of nitrogen in the urine and in the stools was lowered to a minimum by Millard Smith,[3] who lived upon a diet essentially free from protein but excessive in calories in the form of carbohydrate and fat. At the end of twenty-four days the nitrogen in the urine was 1.58 grams, the lowest yet recorded. He summarizes all previous experiments of this nature. Despite the prolonged restriction in diet he remained in good condition—good proof that the energy requirement of the muscle cells can be supplied by carbohydrate and fat. The total nitrogen lost in the twenty-four days averaged 3.34 grams per day.

"The influence of the available supply of body fat upon the

[1] Thomas: Health of a Carnivorous Race—A Study of the Eskimo, Jour. Am. Med. Assn., 1927, **88**, 1559.

[2] Mendel: Changes of the Food Supply and Their Relation to Nutrition, New Haven, Yale University Press, 1916.

[3] Smith: Boston Med. and Surg. Jour., 1927, **196**, 649; also Jour. Biol. Chem., 1926, **68**, 15.

protein metabolism of fasting," as stated by Sherman, [1] "is shown by the following observations of Falck, on the protein metabolism of two fasting dogs—the one lean, the other fat." (See Table 184.) The fat dog was healthy thirty-five days after the lean dog died.

TABLE 184.—THE EFFECT OF FASTING UPON THE PROTEIN METABOLISM OF A LEAN AND A FAT DOG.

Falck's lean dog.		Falck's fat dog.	
Fasting days.	Grams protein catabolized per day.	Fasting days.	Grams protein catabolized per day.
1– 4	26.1	1– 6	29.9
5– 8	24.6	7–12	26.7
9–12	33.9	13–18	26.1
13–16	38.0	19–24	22.3
17–20	31.9	25–29	20.0
21–24	3.9	30–34	16.8
		35–38	15.7
		40–44	13.0
On the twenty-fifth day the dog died		45–50	13.6
		55–60	12.2
		Dog still healthy after sixty days.	

The quantity of protein in the normal diet is somewhat below 100 grams. Presumably patients visiting a physician and consequently not in perfect health would be living upon a somewhat restricted diet. Even allowing for this, the values, 8 to 14 grams, which represent the usual urinary nitrogen excretion of my non-diabetic adults, is lower than might be expected from older writers. and is continuing to decrease. This is obvious from reading the menu of a noted chain of restaurants. Emerson and Larimore[2] say the per capita meat consumption has fallen from 179 pounds to 155 pounds in the years 1909 to 1924.

Prof. Cannon writes me that he has "reports from 46 different students who have lived carefully and made thorough reports of their conditions during four days, on the last of which unusual exercise was taken. The average excretion of nitrogen for these 46 students, on the four days in succession, was 12, 12.16, 12.38, and 12.29 grams." If we raise the nitrogen by allowing the difference for that eliminated in the feces, the total elimination of nitrogen would be 14 grams, and this would represent the equivalent of 88 grams protein ($14 \times 6.25 = 88$) as the normal metabolism of these students. Denis and Borgstrom[3] found the average intake of 233 medical students in New Orleans to be 76.1 grams and Beard and Lovener[4] in Cleveland in a similar survey found the protein to

[1] Sherman: Chemistry of Food and Nutrition, the Macmillan Company, 1919, p. 205.

[2] Emerson and Larimore: Arch. Int. Med., 1924, **34**, 585.

[3] Denis and Borgstrom: Jour. Biol. Chem., 1924, **61**, 109.

[4] Beard and Lovener: Am. Jour. Phys., 1927, **82**, 577.

be 76.7 grams. A group of 12 students in the International Young Men's Christian Association College, at Springfield, Massachusetts, excreted 13 to 14 grams nitrogen in the urine daily while upon an unrestricted diet. It will be found of great advantage to accustom oneself to estimate the protein content of the diet of patients in terms of nitrogen as well as in protein, and to control one's calculations by determining the nitrogen in the urine. Such controls, however, will not be of value if the patient is undergoing rapid changes of diet or weight, or partakes freely of soups made of meat extracts.

When Prof. Chittenden's[1] epoch-making studies appeared, many felt that he went to extremes, but today his statements appear very moderate. He wrote "Food requirements must with necessity vary with changing conditions. . . all the results so far obtained in this investigation with a great variety of persons point to the conclusion that the real demands of the body for protein food do not exceed 50 per cent of the amount generally consumed. Half of the 118 grams of protein food called for daily in ordinary dietary standards is quite sufficient to meet all the real physiological needs of the body. . . "

Low protein diets are perfectly compatible with life and the more abundant the supply of carbohydrate and fat and the more frequent the protein meals the lower they can be reduced. The fact that Karl Thomas could reduce his total protein metabolism to between 2 and 3 grams daily is not proof that it is desirable to do so any more than I would advise little Mary and little Elizabeth, less than a year and a half and a half year old, respectively, to live on 1 gram protein per kilogram, though this is possible. Two-thirds of a gram of protein per kilogram body weight appears to be a safe minimum. It is not a wise minimum when allowance must be made for growth, repair of injuries, convalescence from disease, and heavy muscular work. The possibility of maintenance of nitrogenous equilibrium upon a very low-protein intake has been demonstrated for diabetics by Newburgh and Marsh, see p. 603 and Petrén, see p. 607.

From a recent investigation Lyall[2] also concludes that nitrogen equilibrium is possible on a low-protein diet if carbohydrate and fat can be utilized in sufficient quantities. He states that although very high-protein diets are undesirable on account of their power of sugar production and their specific dynamic action, no evidence has been found that protein diets up to 2 grams per kilo have any deleterious effect on sugar tolerance. Furthermore, he states, contrary to Petrén, that protein was not found to increase ketosis.

[1] Chittenden: Loc. cit., p. 416.
[2] Lyall: Quart. Jour. Med., 1927, **20**, 115.

He considers his results to bear out the ketogenic-antiketogenic ratio of Shaffer and Woodyatt.

The term protein is a broad one, and until recent years in dietary programs comparatively little account has been taken of its components. The old formula for hemoglobin, $C_{758}H_{1203}O_{228}N_{195}FeS_3+P$, though by no means accurate, gives some idea of its complexity. The individual nitrogenous substances (amino-acids) which are found in protein are nineteen in number, and the different proteins vary in the percentages of each of these present. The complete proteins—namely, those which are essential for constructing the different parts of the body—contain the same amino-acids and such proteins are represented by milk, meat, fish and egg proteins. In gelatin and some vegetable foods, important amino-acids are lacking and it is, therefore, essential that such incomplete proteins shall not be furnished diabetic patients, particularly children, when on a low diet. Osborne and Mendel[1] have carefully studied the value which various proteins exercised upon growth and have shown that whereas upon milk or a mixed diet young rats grew normally, if a single incomplete protein—gliadin—was given, they appeared well, but remained dwarfs, and resumed normal growth only when returned to milk or mixed diet.

The quantity of protein necessary to keep in nitrogenous equilibrium has been found by Thomas[2] to vary according to the source.

TABLE 185.—RELATIVE QUANTITIES OF PROTEIN REQUIRED TO MAINTAIN NITROGENOUS EQUILIBRIUM.

Protein.	Gm.
Meat	38
Milk	31
Rice	34
Indian corn	102
Potato	38
Bean	54
Bread	76

Furthermore, a possibility exists that protein may be formed in the body from the addition of nitrogen to the decomposition products of sugar (methyl-glyoxal, lactic acid, pyruvic acid) in the form of alanin.

5. **Fat.**—The quantity of fat in the normal diet varies, partly from choice and partly from economic reasons. In general, in those cases where the carbohydrate in the diet is high, the fat is low, and *vice versa*. The Voit standard placed the fat at 55 grams, but a series of 1300 dietary studies of families, carried out among different races and in different countries, showed that the average

[1] Osborne and Mendel: Jour. Biol. Chem., 1913, **15**, 311; 1915, **23**, 439; 1916, **24**, 37; 1916, **25**, 1; 1916, **26**, 1 and 293.

[2] Cited by Lusk: Loc. cit., p. 416.

quantity of fat eaten was about 135 grams (4.5 ounces) per person per day, the variation recorded being from 45 to 390 grams per person per day.[1] [2]

The more agreeable varieties of fat, such as butter, cream and oil, are expensive foods, counterbalanced to some extent, it is true, by their not being wasted. Fat is also concentrated food, not only because it has twice the caloric value of either carbohydrate or protein, but because it occurs more frequently in pure form. Oil, butter, and lard contain little water, whereas, except for pure sugar and starch, most carbohydrates and proteins are diluted five to ten times with water.

The chief source of error in calculating the total caloric value of the diet and especially of the diabetic diet is in the estimation of fat. Thus for many years I have considered that, on an average, lean meat and fish contained 10 per cent fat and have taught patients to reckon 3 grams of fat to each ounce of meat or fish. This figure is unquestionably correct for poultry and very lean meat, and is very high for most varieties of fish, such varieties as cod, haddock and flounder containing only 1 per cent, but an analysis of a mixture of ten portions of cooked meat exactly identical with similar portions about to be served patients at the New England Deaconess Hospital was made at the Nutrition Laboratory, and showed 14.4 per cent fat. It is, therefore, better to reckon 5 grams of fat to the ounce of meat when the patient is taking several varieties.

Bacon is variously estimated, but I have adopted 50 per cent as an average value for the fat in cooked bacon. Analyses from different sources show the fat of cooked bacon varies from 37 to 79 per cent. Portions of bacon lose varying quantities of weight in the cooking, as shown in the following table:

TABLE 186.—LOSS OF WEIGHT OF BACON DURING COOKING.

Uncooked, grams.	Cooked, grams.	Loss.	
		Grams.	Per cent.
80	46	34	43
200	100	100	50
50	17	33	66
60	23	37	62
30	10	20	67
110	30	81	73
240	41	199	83

Through the courtesy of Dr. Katherine Blunt, I am now able to insert an extensive series of analyses of bacon. These make it

[1] Holmes and Lang: Fats and Their Economical Use in the Home, U. S. Dept. Agriculture, 1916, Bulletin No. 469.

[2] Anderson and Mendel: Jour. Biol. Chem. 1928, **76**, 729. The character of the body fat is markedly influenced by diet. When fats in the form of oil are fed, the body fat resembles food fat. When carbohydrates or proteins are fed, the body fat produced is of a harder type, *i. e.* the iodine numbers are lower.

very evident that our caloric values for bacon must be very crude unless all the fat in the frying pan is utilized. The protein appears to vary even more than the fat in the cooked bacon. Figures like these upset our preconceived ideas about dietary values and show the necessity of carefully arranged dietary studies upon diabetic patients.

TABLE 187.—COMPOSITION OF VERY FAT BACON COOKED (KATHERINE BLUNT).

	Fat, per cent.	Protein, per cent.	Ash, per cent.	Water, per cent.	Loss by cooking, per cent.
Much cooked	61.9	30.3	7.7	0.3	82
	64.5	28.1	6.2	0.3	79
Lightly cooked	71.4	21.8	2.7	1.9	65
	75.2	18.5	...	2.6	69
	80.3	12.0	2.1	2.8	58

Eggs in some cities by law must weigh 1½ pounds a dozen, and average 60 grams (2 ounces) apiece. Such eggs contain approximately 6 grams of protein and 6 grams of fat. How gross our caloric reckonings are is obvious if a collection of eggs is weighed and the minimum and maximum weights noted. The weight of the heaviest egg was 72 per cent more than that of the lightest. (See Table 188.)

TABLE 188.—VARIATIONS IN WEIGHTS OF EGGS WITH THE SHELLS.

Number eggs weighed.	Minimum, grams.	Maximum, grams.	Variation, per cent.
9	52	63	21
12	40	62	55
11	56	63	12
12	51	69	35
12	48	66	38

The weight of egg shells is usually about 7 grams.

These examples will serve to show that doctors, nurses and patients should not take their dietetic calculations of calories too seriously, and that carbohydrate, protein, fat, and calories should be recorded in whole numbers and not in decimals. Ladd and Palmer[1] and also Rabinowitch[2] have illustrated this well.

In metabolism experiments upon diabetic patients a method for the indirect determination of the energy values of foods and excreta, described by Benedict and Fox,[3] will be found useful.

An egg contains cholesterol, 0.38 gram in each one according to Professor Bloor. He looks askance at this insoluble and unexcretable chemical, but I do not yet banish them from the diabetic's table, for fear they will cause arteriosclerosis, although I often reduce the number to one egg daily for patients over fifty years of age. (See p. 687.)

[1] Ladd and Palmer: Am. Jour. Med. Sci., 1923, **166**, 157.
[2] Rabinowitch: Canadian Med. Assn. Jour., 1925, **15**, 1106.
[3] Benedict and Fox: Jour. Biol. Chem., 1925, **66**, 783.

6. **Caloric Values Which Every Doctor Should Know by Heart.**—The quantity of carbohydrate, protein, and fat found in an ordinary diet must be known by a physician if he wishes to treat a case of diabetes successfully. If he cannot calculate the diet he will lose the respect of his patient. The value of the different foods in the diet can be calculated easily from the diet Table 189. This is purposely simple, because a diet chart, to be useful, must be easily remembered. With these food values as a basis it is possible to give a rough estimate of the value and composition of almost any food. Various foods are also classified according to the content of carbohydrate (see p. 500) in 5, 10, 15 and 20 per cent groups, and the lists are so arranged that those first in each group contain the least, those at the end the most. This is a practical and sufficiently accurate arrangement, because except in the most exact experiments the errors in the preparation of the food are too great to warrant closer reckoning. It is practically impossible, except when accurate analyses of the diet are made, to reckon the carbohydrate for the twenty-four hours closer than within 5 to 10 grams, and we had best acknowledge that fact. It is really surprising, however, how reliable the figures are if we do not push the matter to extremes. For example, the protein was analyzed in 10 portions of cooked lean meat, similar to 10 other portions served the same day at the New England Deaconess Hospital. In these analyses it was found that the protein content was 30 per cent.

TABLE 189.—FOOD VALUES IMPORTANT IN THE TREATMENT OF DIABETES.

30 grams (1 oz.) Contain approximately.	Carbohydrates, grams.	Protein, grams.	Fat, grams.	Calories.
Oatmeal, dry weight	20	5	2	118
Shredded wheat	23	3	0	104
Uneeda biscuits, two	10	1	1	53
Cream, 40%	1	1	12	116
Cream, 20%	1	1	6	62
Milk	1.5	1	1	19
Brazil nuts	2	5	20	208
Oysters, six	4	6	1	49
Meat (cooked, lean)	0	8	5	77
Chicken (cooked, lean)	0	8	3	59
Bacon	0	5	15	155
Cheese	0	8	11	131
Egg (one)	0	6	6	78
Vegetables 5% group (mixture)	1	0.5	0	6
Vegetables 10% group (mixture)	2	0.5	0	10
Potato	6	1	0	28
Bread	18	3	0	84
Butter	0	0	25	225
Oil	0	0	30	270
Fish, cod, haddock (cooked)	0	6	0	24
Broth	0	0.7	0	3

The only safe way for diabetic patients at the commencement of their training is to weigh their food. After a few days of weighing, patients can select utensils which conform to the size of the portions of their own special diets and use these exclusively. As a matter of fact practically all of my patients use scales at one time or another in the course of treatment. The variety which has served me best is the 500-gram scale manufactured by John Chatillon and Sons, 85 Cliff Street, New York City. These scales have been of great service to diabetics.

So small a quantity of carbohydrate was allowable for diabetic patients prior to the introduction of insulin that it was dangerous to rely upon approximate portions of foods; today this is often permissible. It is, however, of great advantage to utilize foods which are of standard size. In this respect a shredded wheat biscuit with its content of carbohydrate 23 grams, protein 3 grams, fat 0 is ideal and so are the Uneeda biscuits so commonly in use in this neighborhood. In Cleveland John utilizes a roll which is of uniform size in that city. A saucerful of cereal is equivalent to about carbohydrate 20 grams, protein 5 grams; a large portion of 5 per cent vegetables to about carbohydrate 5 grams; which is the equivalent of one Uneeda biscuit; a small orange or one-half a small grapefruit, a saucerful of strawberries, or one-half a banana contain about carbohydrate, 10 grams. Bread is indefinite and so are potatoes. To obviate the difficulty with bread I sometimes give my patients a bread block. This is merely a piece of wood 3 by $2\frac{1}{2}$ by $\frac{3}{4}$ inches ($7.6 \times 6.3 \times 1.9$ cm.) in size. As white bread is light and dry and contains a high per cent of carbohydrate and the coarse breads are heavy and moist and contain a low per cent of carbohydrate, one can almost more safely prescribe a bread block of bread than a weighed quantity of bread. It will be noted that the bread block is thick so as to minimize error which would be considerable if the bread block were cut as the conventional slice of bread.

A glass of milk, 240 cc., contains carbohydrate 12 grams, protein 8 grams, fat 8 grams. It is not so very different from a small orange plus an egg, more because of its rapid absorption than because of qualities inherent in the lactose and casein, although each is theoretically (?) less utilizable by the diabetic.

In order to illustrate the errors which easily rise from general statements about foods, the accompanying illustration, Fig. 36 is inserted. It shows: (1) How readily errors may occur in estimating the food values of the diet unless definite quantities of foodstuffs are prescribed; (2) the absurdity of reckoning food values to the fraction of a gram unless actual analyses of each food as served are made.[1]

[1] Ladd and Palmer: Am. Jour. Med. Sci., 1923, **166**, 157.

Errors in eggs may compensate themselves, because the eggs average about 60 grams (and must so average in some communities); errors in potatoes, oranges and grapefruit must necessarily be very great. The largest of the three potatoes is actually a small potato; the potato weighing 60 grams is about the size of an egg; the oranges

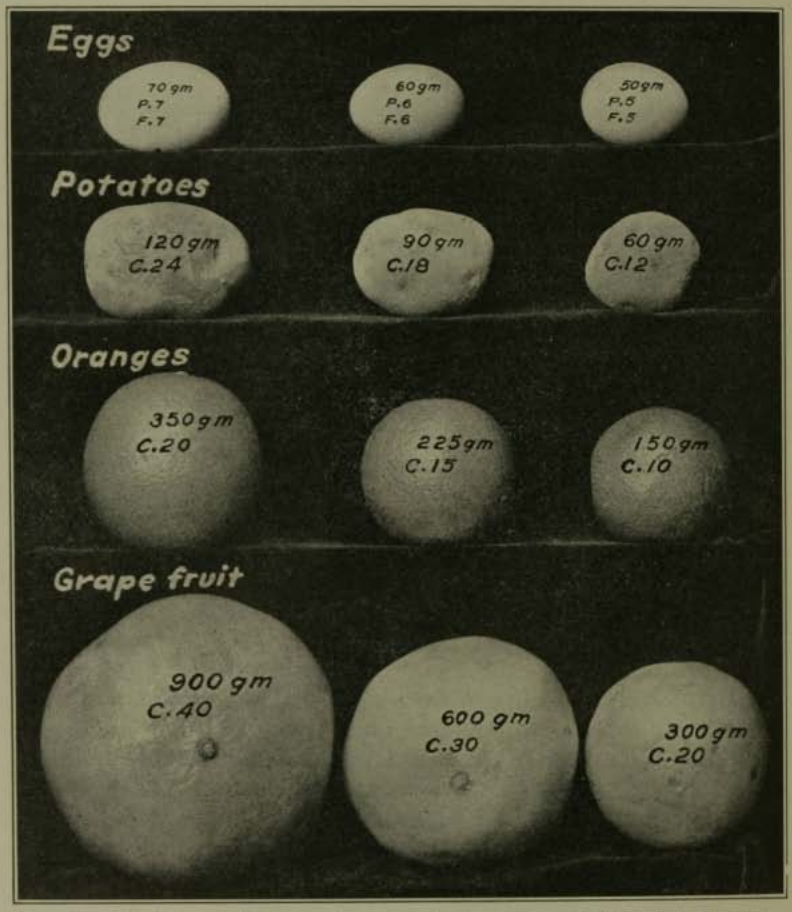


FIG. 36.—Variations in the sizes of common foods. *C.* = carbohydrate; *P.* = protein; *F.* = fat. The food values recorded are for gross weights and only approximate.

from left to right are sold under the trade names of 126, 170 and 250 (to the box) and the grapefruit under the trade names of 28, 64 and 96 (to the box).

It is partly on account of the ease with which large errors in the carbohydrate content of food may occur that it is desirable to give

to patients with a low carbohydrate tolerance their carbohydrate in the form of 5 per cent vegetables exclusively, for an error in weighing, reaching 120 grams (4 ounces), would amount only to a few grams of carbohydrate.

7. **Vitamins.**[1]—In recent years the importance in the diet of certain food substances other than protein, carbohydrate, fat, salts, and water has become widely recognized so that now the matter is one of popular interest. To these substances McCollum gave the name "vitamins" and this term, though somewhat unsatisfactory, is now commonly used. Palmer[2] points out that "accessory food substance" is not a good designation since it suggests that these materials are not indispensable. Most of our knowledge in this field we owe to the researches of Eijkman, Hopkins, Osborne, Mendel, McCollum, and Evans. The present classification of the vitamins is as follows:

Vitamin A.—Vitamin A is fat-soluble and is found in abundance in butter fat, milk, egg yolk, and to a less extent in the leaves of food plants, although more in the green leaves rich in chlorophyl,[3] and in the germ of cereal grains. Bolted flour, degerminated corn meal, polished rice, starch, glucose, cane sugar, and beet sugar contain little, if any, of this substance. Lack of vitamin A causes xerophthalmia and perhaps is detrimental to growth and health in general.

Vitamin B.—Vitamin B is water-soluble and is present to a great extent in milk and grain. It is considered to prevent beri-beri, a disease in which the chief symptom is peripheral neuritis resulting in paralysis. Vitamin B is also growth- and health-promoting.[4]

Vitamin C.—Vitamin C is water-soluble and is abundant in fresh cow's milk and in many fresh fruits and vegetables. Lack of this vitamin causes scurvy. This principle received its first application as long ago as 1747 when James Lind, a British Navy surgeon, proved that orange and lemon juice prevented and cured this disease, formerly so common in long sea voyages.

Vitamin D.—Vitamin D is found in abundance in the liver of fishes, chiefly the cod. Recently it has been shown that ultra-violet rays can produce the same physiological results as vitamin D obtained in cod-liver oil, and that irradiation of various inert substances imparts to them a like action. This vitamin is associated with the metabolism of calcium and phosphorus and its deficiency leads to rickets.

Vitamin E.—Vitamin E is found in whole wheat, wheat germ, lettuce, meat, rolled oats, dried alfalfa, and to some extent in milk fat.

[1] McCollum and Simmonds: The Newer Knowledge of Nutrition, 3d ed., N. Y., Macmillan Company, 1925.

[2] Palmer: Metabolism in Nelson's Loose Leaf Medicine, Revised November, 1926, **3**, 33.

[3] Dye, Medlock, and Christ: Jour. Biol. Chem., 1927, **74**, 95.

[4] In rats potent combinations promoting growth are lettuce and liver, liver and yeast or yeast and lettuce. Osburne and Mendel: Carnegie Inst. Year Book. 1926–27, No. 26, 351.

In experimental animals, at least, this vitamin confers fertility and its lack causes sterility. This vitamin is widely distributed in human dietaries so that its deficiency may be eliminated as a factor in the nutrition of man.

Diabetics need not fear lack of vitamins A, B, C, and E, because of the abundance of cream, butter, meat and green vegetables in the routine diet. Nearly all my children are given cod-liver oil daily and many take liver once a week.

However, avitiminosis in the course of diabetes has been observed by Wohl.[1] The patient was under the care of her mother who restricted the food intake whenever glycosuria appeared. "The main articles of diet were cereals, such as rice, occasionally eggs and chicken, canned vegetables, small amounts of milk and butter. The patient received this diet for a year. She lost 50 pounds from the beginning of her illness. 'Muscle soreness,' nausea, and occasional vomiting with epigastric distress were early symptoms, later inability to walk without assistance. The face was of whitish, slightly cyanotic tinge, pinched, and the right cheek was edematous. Photophobia was present. The skin of the extremities was moist and very sensitive to touch. The finger nails were brittle. The subcutaneous tissues over the tibias were edematous and the ankles swollen.

"The eyes showed opaque, dull, dry corneas. The mother said that when the patient cried, tears did not appear. The lower eyelids on both sides were edematous, the mucous membrane pale and dry."

B. THE DIET OF DIABETIC INDIVIDUALS.

1. **Caloric Needs of the Diabetic.**—The diet of the diabetic patient should contain, except for brief intervals, the minimum number of calories which the normal individual would require under similar conditions. Many normal individuals are living upon less than 30 calories per kilogram, and repeatedly one sees diabetic patients over fifty years of age who live upon less for long periods of time. Table 190 shows the wide variation in calories per kilogram body weight of those of my diabetic cases whose metabolism was tested between 1908 and 1917. In Table 191 the variations in basal metabolism, respiratory quotient, weight, and percentage of sugar in the blood are shown before and after treatment with insulin when it was first introduced.

If the physician allows his patient to go untreated and excrete sugar and β-oxybutyric acid in the urine instead of burning these substances in the body, he must add for each gram of sugar so lost

[1] Wohl: Jour. Am. Med. Assn., 1926, **87**, 901.

4 calories (actually 4.1) and for each gram of β-oxybutyric acid 5 calories (actually 4.693). The figure of 5 calories for 1 gram of β-oxybutyric acid is used because, along with this acid, a certain amount of acetone and diacetic acid also escape so that the allowance of 5 calories for all three is undoubtedly too low rather than too high. Case No. 344., p. 433, shows the importance of the loss of acid bodies as well as of sugar.

TABLE 190.—POSTABSORPTIVE METABOLISM OF ADULT DIABETICS ARRANGED ACCORDING TO CALORIES PER KILOGRAM BODY WEIGHT.

Calories per kilogram body weight per 24 hours.	Average calories per kilogram body weight per 24 hours.	Number of observation days.	Number of cases.	Average basal metabolism. By days, per cent.	By cases, per cent.
15 to 20	19	33	18	−16	−13
21 to 25	23	175	61	−11	− 9
26 to 30	28	122	45	0	+ 1
31 to 35	32	51	25	+15	+14
36 to 40	38	16	5	+14	+18
41	41	1	1	+22	+22

The average calories per kilogram body weight per twenty-four hours for all days and all cases was 26 calories.

And this is not all, for when acidosis is extreme, Benedict and I have shown that the metabolism is increased about 15 per cent, and consequently more calories are required to meet this demand. It is seldom one can obtain definite knowledge of a patient's diet before treatment is begun, but with Case No. 1147, the figures appeared reliable, though they show an attempt to lower the carbohydrate in the food before she came to me for treatment. This patient was a lady, aged thirty-five years, with diabetes of two and a half years' duration, who lost 66 pounds in a little more than this interval. On October 6, 1916, the volume of urine was estimated at 6000 cc., and the sugar was found to be 5 per cent or 300 grams—the equivalent of a loss of 1200 calories in twenty-four hours. She reported her daily diet to have been as shown in Table 192.

After a two weeks' stay in the hospital she felt more content with a diet of 1600 calories than she did upon her diet at entrance, and her weight was constant during the last four days. It is obvious that the saving of food entailed hereby would be considerable. It is the diet of the *untreated* diabetic which is expensive.

The use of national foods in the treatment of diabetic patients of foreign birth has been investigated by Stern and Reyner[1] of the Boston Dispensary. They have adapted the Italian, Jewish, and Armenian menus to diabetic requirements.

[1] Stern and Reyner: Jour. Am. Med. Assn., 1927, **88**, 316.

TABLE 191.—BASAL METABOLISM AND RESPIRATORY QUOTIENT OF DIABETIC PATIENTS BEFORE AND AFTER TREATMENT WITH INSULIN.

Case No.	Date before treatment, 1922.	No. of days treated.	Age, yrs.	Height (net), cm.	Weight (net), kg.	Gain in weight.		Calories per 24 hours.		Gain in calories.		Respiratory quotient.		Blood sugar.	
						Actual kg.	Per cent	Before.	After.	Actual cals.	Per cent.	Before.	After.	Before, per cent.	After, per cent.
632[1]	Dec. 1	18	41	177	49.6	0.3	0.6	1115	1186	71	6.4	0.76	0.79	0.14	0.13
866	Oct. 14	101	39	186	39.9	3.1	7.8	854	977	123	14.4	0.80	0.81	0.12	0.17
1542[1]	Oct. 4	111	42	164	33.6	2.6	7.7	903	1033	130	14.4	0.78	0.76	0.31	0.26
1889[3]	Nov. 13	68	17	156	28.4	2.9	10.2	849	1031	182	21.4	0.86	0.83	0.16	0.20
1970[4]	Dec. 4	51	52	156	51.7	0.5	1.0	1198	1204	6	0.5	0.83	0.78	0.24	0.20
2256[1]	Nov. 9	98	18	165	23.1	3.4	14.7	821	887	66	8.0	0.76	0.78	0.31	0.19
2448[1]	Oct. 20	52	19	172	43.5	6.3	14.5	1355	1341	−14	−1.0	0.76	0.82	0.28	0.14
2687[1]	Dec. 11	37	25	164	43.2	−0.1	−0.2	1119	1303	184	16.4	0.75	0.83	0.24	0.27
2729[5]	Nov. 7	35	22	181	48.2	0.8	1.7	954	1012	58	6.1	0.78	0.81	0.22	0.14
2801[6]	Oct. 19	88	15	161	38.0	1.5	4.0	1090	1352	262	24.0	0.76	0.79	0.35	0.39
2972[7]	Dec. 21	34	67	151	33.7	2.1	6.2	931	921	−10	−1.1	0.79	0.75	0.25	0.22
	Average	**63**	**33**	**167**	**39.4**	**2.1**	**5.3**	**1017**	**1113**	**96**	**9.4**	**0.79**	**0.80**	**0.24**	**0.21**

[1] Alive July, 1927. [2] Died March, 1923, erysipelas. [3] Died, February, 1927, coma, either of acidosis or hypoglycemia.
[4] Died May, 1925, myocarditis. [5] Died November, 1923, coma. [6] Died August, 1923, coma. [7] Died May, 1926, accident.

TABLE 192.—ESTIMATED DIET OF A WOMAN, CASE NO. 1147, PRIOR TO TREATMENT.

Food grams.	Carbohydrate, grams.	Protein, grams.	Fat, grams.
Eggs, 12	0	72	72
5 per cent. vegetables, 450	15	8	0
Milk, 2000	96	64	64
40 per cent. cream, 240	8	8	96
Butter, 90	0	0	75
Meat, 120	0	32	20
Bread, 100	60	10	0
Totals	179	194	327
	4	4	9
Total calories	716	776	2943

Total calories 4435 ÷ 72 (kilograms) = approximately 60 calories per kilogram body weight.

2. **Carbohydrate.**—The total carbohydrate in the diet of diabetic patients under treatment is almost invariably restricted, but with insulin one tries to prescribe about 100 grams or eventually more, and even at first if patients are seen soon after onset of the disease. This is a decrease approximately to 25 per cent of the normal carbohydrate ration. This alters so radically the composition of the normal diet that if the changes are rapidly made the result would be indigestion in a normal individual and still more in the unstable diabetic. Indigestion will all the more readily occur unless the patient is warned against replacement of the calories lost by a sudden undue increase in fat and protein. One of the great advantages of fasting and undernutrition was the avoidance of indigestion at the beginning of treatment.

The character of the carbohydrate has comparatively little effect upon its assimilability. It is true that levulose behaves under certain conditions in a manner peculiar to itself, but as a rule its effect is not noticeably distinguishable, perhaps because not sufficiently investigated. For a discussion of the behavior of levulose in diabetes see pp. 343 and 619. Various methods have been employed to test the assimilation of the different carbohydrates and the evidence is presented in the following paragraphs. The results of oral tests have been described already. (See p. 202.)

(*a*) **The Assimilability of Starch and the Various Sugars.**—The assimilability of sugar can be tested by the oral, subcutaneous, and intravenous methods of administration, and Allen[1] has pointed out in detail the striking differences which result. The oral method is convenient, but inaccurate on account of variation in the rate of absorption. The intravenous method merely gives the saturation limit of the blood and tissues for sugar which can take

[1] Allen: Glycosuria and Diabetes, Harvard University Press, 1913.

place without sugar overflowing the kidneys, and hence is affected by slight variations in renal permeability. The subcutaneous test is really the best test of the power of the body to utilize sugar. By it errors in absorption are minimized, the liver avoided, and the actual efficiency of the tissues in storing or burning the sugar is determined.

The relations of the tests are brought out interestingly by the case of levulose. "The oral tolerance of levulose is not much less than that of dextrose, because the liver stops nearly all levulose. The intravenous tolerance of levulose is approximately the same as that of dextrose, for the value represents a more immediate saturation limit. The subcutaneous tolerance of levulose is a very small fraction of that of dextrose, because this method tests the power of the general tissue to utilize levulose, and this power is easily exceeded." In other words, the intravenous method shows the saturation limit, the oral method furnishes a test for the hepatic function, and the subcutaneous method shows the utilization by the tissues.

Blumenthal[1] found that the amount of sugar injected into a rabbit sufficient to cause glycosuria varied between 1.8 and 2.8 grams per rabbit (about 0.8 gram per kilo) in injections lasting from one to two minutes, and he records that the saturation limits of dextrose and levulose are almost equal. For galactose it is much less; for saccharose and lactose it is very small. Comessatti[2] found the tolerance to be between 2 and 2.5 grams of dextrose; by having rabbits run in a treadmill the tolerance was raised about 20 per cent. Glucose is so frequently given today by the intravenous route that excellent opportunities are afforded for studying its effect. So far as glycosuria is concerned, one hears nothing; emphasis is rather placed on the danger of reactions if the glucose infusions are not freshly prepared, properly buffered, and carefully given.

The rate of injection is an important factor. Woodyatt, Sansum, and Wilder[3] have urged very strongly the importance of time in determining sugar tolerance. Tolerance must be measured and expressed in grams of glucose or other sugar per kilogram of body weight per hour of time. They point out that sugars administered by the stomach take varying lengths of time to be absorbed, according to the motility of the stomach and intestines, and even if sugars are given subcutaneously or by any other route which demands absorption as a prelude to their entering the blood, the rates at which they enter the blood will depend upon the rates at which they are

[1] Blumenthal: Hofmeister Beiträge, 1905, **6**, 329.
[2] Comessatti: Hofmeister Beiträge, 1906–1907, **9**, 67.
[3] Woodyatt, Sansum, and Wilder: Jour. Am. Med. Assn., 1915, **65**, 2067.

absorbed.[1] They have devised a method by which solutions of the various sugars can be easily and painlessly injected into animals or man for hours at a time. Recently Wilder used the procedure effectively in the patient with hypoglycemic reactions caused by metastatic carcinoma of the islands of Langerhans into the liver. By the use of these methods, they found that a man can utilize 0.85 grams of glucose per kilogram of body weight per hour for from six to twelve hours without producing any glycosuria, or even diuresis. In other words, a man weighing 70 kilograms when resting comfortably in bed may and did receive and utilize 60 grams of glucose by vein per hour without glycosuria. This would amount to 252 calories per hour. As not more than one-third of the caloric value of the glucose would be required for the basal metabolism, the balance must be stored. This apparently is the normal tolerance limit for glucose. In cases of exophthalmic goiter, the intravenous tolerance was found to be as low as 0.65 grams per kilogram per hour. For lactose it was nearly zero. If twice the normal tolerance limit for glucose—that is 1.7 grams per kilogram per hour—are given about 10 per cent of the same is lost in the urine, but if glucose is given at a rate faster than 2 grams per kilogram per hour, 50 per cent of all the glucose injected appears in the urine when constant conditions have been secured.

In a normal individual, the greatest rate of glycosuria which can be produced by feeding any quantity of glucose by mouth is limited, and at most approximates that which is produced by an intravenous injection at the rate of 1.8 kilogram per hour. Hence it would be reasonable to believe that when sugar is given by mouth in health, it is never absorbed faster than at this rate.

The above investigators also found that when glucose was given at rates exceeding 0.85 gram per kilogram per hour and the glucose begins to accumulate in the tissues and pass out into the urine, it carries water with it. When the sugar is given at the rate of 5.4 grams per kilogram per hour marked diuresis results—thus, in a dog the urine output rises rapidly to the vicinity of 350 cc. per hour. If each hour the dog received enough water to make good the loss, this rate of diuresis or a higher one could be maintained for long periods of time. If enough water is not given to counterbalance the urinary loss, the volume of urine decreases, the dog suffers from thirst and death may ensue. On the other hand, if too much water is given with the hourly injections of glucose of 5.4 grams per kilogram per hour, there is danger of stopping the heart mechanically. In giving intravenous injections of glucose

[1] The ratio in the rate absorption of glucose, fructose, and dehydroxy-acetone is of the order 100:51:65. Cori and Cori: Jour. Biol. Chem., 1928, **76**, 755.

there are then two things to avoid: Too great dehydration and heart failure from imposing too much mechanical work.

1. *Glucose.*—The tolerance for glucose is apparently unaffected by season or sex, and there is no constant difference for the various races. It is interesting that children are supposed to have a far higher tolerance than adults, but Allen's experiments with young animals were to the contrary. The increased tolerance in children might be explained by their increased activity. In general, the tolerance for glucose, like that of other carbohydrates, varies inversely with the rapidity of its absorption. Its assimilation is increased in fever. The occasional appearance of glycosuria in fever is considered by Allen not to invalidate this statement, because that is a toxic glycosuria. Actual increased temperature favors tolerance, possibly by rendering the kidneys less permeable, but chiefly by increasing utilization in the tissues. The influence of muscular work in increasing the tolerance for dextrose has been proved by experiments upon animals and is analogous to the effect of work upon the assimilation of carbohydrates in general. Glycosuria may be produced experimentally by intravenous, subcutaneous, and intraperitoneal administration of sugar, though not normally by oral administration even when as much as 200 grams are taken, according to Folin and Berglund. It is not produced by rectal injections.

Various methods have been employed to test the presence of diabetes by the administration of glucose.

Higgins[1] has studied the time at which the various sugars begin to be burned in the body by the change in the gaseous exchange and especially in the respiratory quotient. He found that glucose and maltose were not utilized as food as soon as the other sugars —sucrose, lactose, and levulose—for the former begin to be burned in twenty to thirty minutes, but the latter within ten minutes. He further observed a distinct difference in men between the metabolism of glucose and of levulose and galactose.

We often erroneously think of an excess of sugar in the blood as being removed by the kidneys. As a matter of fact, this is not the case, for the kidneys remove only a trifle of the excess of the sugar. They by no means regulate the percentage of sugar in the blood. By far the greater portion of the sugar is removed from the blood by the tissues as Kleiner and Meltzer[2] have so beautifully demonstrated and Woodyatt, Sansum and Wilder have confirmed.

2. *Saccharose.*—LeGoff[3] found that saccharosuria and glycosuria resulted in 100 per cent of the cases after 100 grams cane sugar

[1] Higgins: Jour. Phys., 1916, **41**, 258.

[2] Kleiner and Meltzer: Am. Jour. Phys., 1914, **33**, xvii, Jour. Exp. Med., 1916, **23**, 507; Proc. Soc. Exp. Biol. and Med., 1914, **12**, 58.

[3] Cit. by Allen: Compt. rend. de l'Acad. des Sc., 1911, **157**, 1785.

were administered orally. This probably explains why glucose instead of saccharose is employed in making carbohydrate tolerance tests. Caution must be exercised in the interpretation of such tests in the light of the more recent work of Folin and Berglund.

Saccharose has little place in the diet of primitive races, and Allen has pointed out a possible connection between the increased use of saccharose and the increased incidence of diabetes. (See p. 166.)

3. *Lactose.*—The poor assimilation of lactose is remarkable because it is the one distinctly normal sugar. This lack of assimilation holds in diabetes as well as in health. It is perhaps due to the fact that lactose is broken up into galactose and dextrose before it is absorbed. Folin and Berglund[1] write instructively as follows: "Almost all authorities assign a much higher limit of assimilation for milk-sugar than for galactose, 100 to 150 grams for the former, against 20 to 40 grams for the latter. It is certainly true that much more sugar is excreted from 100 grams of galactose than from 200 grams of lactose, but with respect to the assimilation limits based on quantitative sugar determinations and glycuresis there is scarcely any difference between the two. Ten grams of milk-sugar, corresponding approximately to the amount taken with a single glass of milk, is sufficient to produce a temporary, but unmistakable increase in the sugar of the urine.

"The interesting fact about the sugar excretion after lactose ingestion is that *lactose* (as well as galactose) is present in the urine unless the amount taken is very small—less than 30 grams. This is instructive, for *it indicates that there is no mechanism in the digestive tract for preventing the absorption of soluble but incompletely digested carbohydrate materials. If such are not absorbed it is only because the activity of the endocellular enzymes is capable of accomplishing the hydrolysis during the transit of soluble carbohydrates through the mucous membrane of the intestine.* In the case of lactose the endocellular hydrolytic activity is easily exceeded, and this disaccharide is absorbed. Lactose, as such, is supposed to be unusable, and it is customary to refer to the occasional occurrence of milk-sugar in the urine of pregnant women as proof of how completely unassimilable milk-sugar really is.

"We do not think that the question of the assimilability of milk-sugar can yet be considered as definitely settled. The old experiments based on the injection of known quantities of milk-sugar into the blood and finding the whole of it in the urine can no longer be considered conclusive, because under such conditions the sugar in the urine would be increased by virtue of superimposed glycosuria. Our own experiments have not furnished conclusive evidence, but

[1] Folin and Berglund: Jour. Biol. Chem., 1922, **51**, 251.

the fact that the excretion of milk-sugar comes to a definite end in the course of a few hours suggests that a part of the absorbed lactose may be utilized. The question of whether or not some lactose is utilized seemed to us unimportant in comparison with the problem of why milk-sugar taken by mouth results in less total sugar excretion than is obtained from the galactose corresponding to the same quantity of milk-sugar. One hundred grams of galactose will give twice as much sugar in the urine as 200 grams of lactose. Our attempts to solve this problem have yielded extraordinarily interesting results, but our investigation is not yet completed, and the statements and interpretations here given we explicitly consider only as a preliminary communication. When the hydrolysis of the milk-sugar during absorption from the intestinal tract is quantitative, as it presumably is in normal infants, then the giving of milk-sugar is the same as the giving of equal quantities of galactose and glucose. The difference between the adult and the nursing infant with reference to the power of splitting lactose can be eliminated by giving pure glucose and pure galactose— equal amounts of each. This was done, the subject taking 100 grams of galactose plus 100 grams of glucose and the sugar excretion was less than one-fifth as great from the mixture of the two sugars as from the milk-sugar and is less than one-tenth as great as the excretion obtained from 100 grams of galactose when taken alone. The figures are 0.37, 2.8 and 5.7 grams, respectively.

"The results given show that the extent to which galactose is retained and utilized by the human organism depends on the quantity of available glucose."

4. *Galactose.* — All agree that galactose is poorly assimilated, and yet it is fermented with more difficulty than either dextrose or levulose. It is on a par with glucose or levulose as a glycogen former. It scarcely increases the percentage of blood sugar, but 100 grams of galactose may yield as much as 10 grams of sugar in the urine, whereas 200 grams of glucose will not yield a trace.

5. *Maltose.* — Maltose to the amount of 200 grams has extremely little effect on the level of the blood sugar of normals and no effect upon the sugar in the urine. It is commonly agreed that maltose is tolerated less well by diabetics than any other form of sugar.

6. *Levulose.* — (See also p. 343.) Levulose does not cause an increase in the percentage of blood sugar (whole blood) even when 200 grams are taken. Folin and Berglund found a slight increase in the plasma, from 0.102 per cent to 0.110 per cent. Frequently, glycuresis was observed lasting for several hours, but this was proved *not* to be due to levulose. Later experiments made probable that this glycuresis was caused by decomposition products of the levulose to which Folin and Berglund ascribe the nausea and diarrhea and

indeed the laxative effects of various sugars—maple sugar, molasses, and certain candies. Although levulose was not demonstrated in the urine, it was found in the blood at the height of its absorption from the digestive tract and the above authors conclude that the slight rise of sugar in the plasma from 0.098 per cent before to 0.112 per cent, twenty minutes after its ingestion, is made up one-third by levulose. The assimilation limits for levulose are so high that they can scarcely be exceeded.

Folin's and Berglund's interpretation of the fate of absorbed fructose is as follows: "The liver retains fructose as well as every other usable sugar to a greater extent in proportion to its weight than do the general tissues such as the muscles. But such retentions by the liver are never even approximately quantitative, and a large fraction of absorbed sugar, possibly the greater part, gets by this organ. Other tissues, such as the muscles, take up sugar from the plasma of arterial blood, and it is this general absorption which prevents excessive accumulations of sugar in the blood. But tissue sugar like blood sugar is normally and predominantly glucose, partly because the major part of our carbohydrate food is made up of glucose, partly because all other usable sugars are gradually converted into this essential sugar. The tissues being relatively well stored with glucose and empty of other sugars, such as fructose, may well be able to absorb these other sugars from the blood so nearly completely that the venous blood used for our analyses shows only traces. The glycogen formation may or may not begin immediately, and at all events need not be the immediate cause for the rapid disappearance of levulose from the blood."

7. *Dextrin.*—Dextrin given in large doses produced no increase in the level of the blood sugar and no increase in the level of the preformed sugar of the urine but the urine did contain an abundance of the dextrin. The elimination of dextrin was at its height the morning of the day following the ingestion of dextrin and continued for four days. Evidently dextrin or a dextrin-like product had been absorbed from the digestive tract and only slowly found its way into the urine. Since it was not found in the blood, presumably it was absorbed by the tissues and was gradually released and eliminated later.[1]

8. *Inulin.*—Inulin is a polysaccharide of levulose and in this respect comparable with starch, which is a polysaccharid of dextrose. For discussion see p. 629.

9. *Algæ.*—The nutritive value of the carbohydrate in lichens and algæ was investigated by Mary Swartz. Lichens and algæ have been used as food by man from the earliest times, being

[1] Folin and Berglund: Loc. cit., p. 431.

resorted to particularly when there is scarcity of cereal crops or in famine. Tons of marine algæ are eaten annually in various parts of the world particularly in Japan. Irish moss is the most common food of this type in the American dietary, being employed in the making of blanc mange. Dulse is particularly used in Scotland and is quite abundant in New England where it is dried and eaten as a relish.

Of the 10 species of marine algæ studied by Swartz the hemicelluloses which they contained were made up chiefly of pentosans and galactans. When these hemicelluloses are injected into an animal subcutaneously or intraperitoneally, they are excreted through the kidneys and can be recovered unaltered in the urine. The pentosan of dulse is completely eliminated in four or five days, and the carbohydrates of Irish moss, salep and sinistrin, in one to three days. Feeding experiments show that these hemicelluloses most readily attacked by bacteria disappear most completely from the alimentary tract. The average coefficient of digestibility for man is, in the case of the pentosan of dulse and the mannan of salep, 99 per cent notwithstanding their apparent resistance to amylolytic enzymes and the hydrolyzing influence of the gastric juice; their disappearance seems, therefore, directly attributable to bacterial activity, and the possibility of sugar formation by this agency having been demonstrated, it remains to be shown by means of respiration experiments to what extent materials so hydrolyzed can serve as true nutrients for the organism.

In striking contrast to the above hemicelluloses stand the galactans, (of which agar agar is an example), with their high degree of resistance to bacterial decomposition; they show in man, an average digestibility of approximately 25 per cent, in dogs of 45 per cent. It is manifestly impossible to treat of the digestibility of hemicelluloses as a class, in view of such diversity in the groups. Not only must each type receive special consideration, but distinction must be drawn between soluble and insoluble forms, as is illustrated by the pentosans, the ratio of the digestibility coefficient of the former to the latter being approximately 100 to 50 in man, and 75 to 25 in dogs.[1] In general their disappearance from the alimentary tract appears to be proportional to their decomposition by microörganisms, and thus there is little justification for any especial claim as a source of energy and nutrition. Their bulk makes them of value in constipation and they also serve as a source of inorganic salts.

10. *Mushrooms.*—"The value of the mushroom is in its flavor, for it is seen to have no extractable carbohydrate, and Mendel[2]

[1] Swartz, Mary D.: Trans. Conn. Acad. Arts and Sciences, 1911, **16**, 247.
[2] Mendel: Am. Jour. Phys., 1898, **1**, 225.

has shown that its nitrogen does not occur as protein, but in an unavailable form."[1]

(*b*) **The Estimation of the Carbohydrate in the Diabetic Diet.**—The quantity of carbohydrate in the various foods is easily calculated and far more simply than is usually thought. This is not true if one desires scientific accuracy, for in that event analyses of the food given the patient must be made. In any estimation of carbohydrate in the diabetic diet one must not overlook the possibility of 58 grams of carbohydrate being formed out of 100 grams of protein and 10 grams out of the glycerol of 100 grams of fat. The "total glucose" value of the three foodstuffs would be, therefore, 100 grams C. × 100 per cent + 100 grams P. × 58 per cent + 100 grams F. × 10 per cent. Such calculations, of course, are based upon the assumption that the D to N ratio of 3.65 to 1 is a reliable index of the carbohydrate-forming power of protein and that only the glycerol of the fat turns to sugar. There is certainly doubt in this matter, and I believe it is safer to be guided by the carbohydrate quantity of the diet and the total calories with protein limited to a range of 3 grams to 0.66 gram per kilogram body weight according to the age of the patient and the condition of the kidneys.

(*c*) **Carbohydrate in Vegetables.**—*Loss in Cooking.*—It would appear perplexing to determine the amount of carbohydrate in each of the various vegetables which the patient eats in twenty-four hours. Diabetic patients have too much to do in their daily work to be encumbered with unnecessary details of arithmetic. An attempt to force accuracy to the extent of a gram may result in loss of accuracy to the extent of an ounce by the patients' giving up weighing entirely.

For convenience I have classified the vegetables and fruits which enter into the diabetic diet under four headings—those containing approximately 5 per cent, 10 per cent, 15 per cent, and 20 per cent carbohydrate. Wagner and Warkany[2] have tested vegetables for their content of carbohydrate by various biological tests, comparing the same with white bread. Considerable variation from the tables were found, but these do not seem to me to be essential. The rate of absorption of the food in any such test is of importance. (See Table 193.)

It is true that there is considerable variation in each group, but the average content is not far from that represented, the error being on the lower side. This does not hold for string beans, for often trouble occurs from the beans having developed into maturity, thus greatly increasing their content in carbohydrate. Canned

[1] Wardall, Ruth A.: Jour. Am. Med. Assn., 1917, **69**, 1859.
[2] Wagner and Warkany: Ztschr. f. Kinderheilk., 1927, **44**, 322.

string beans usually contain smaller beans than fresh string beans and for this reason are placed in the 5 per cent group. So with many of the other vegetables, the more advanced the stage of development, the more carbohydrate. Many an unexplained trace of sugar in the urine has undoubtedly occurred in this way. The carbohydrate content of peas is also most variable.

TABLE 193.—FOODS ARRANGED APPROXIMATELY ACCORDING TO CONTENT OF CARBOHYDRATES.[1]

VEGETABLES[2]				
5 per cent.		10 per cent.	15 per cent.	20 per cent.
1 per cent to 3 per cent.	3 per cent to 5 per cent.			
Lettuce	Tomatoes	String beans	Green peas	Potatoes
Cucumbers	Brussels sprouts	Turnip	Artichokes	Shell beans
Spinach	Water cress	Kohl-rabi	Parsnips	Baked beans
Asparagus	Sea kale	Squash	Lima beans (very young)	Green corn
Rhubarb	Okra	Beets		Boiled rice
Endive	Cauliflower	Carrots		Boiled macaroni
Marrow	Egg plant	Onions		
Sorrel	Cabbage	Green peas (very young)		
Sauerkraut	Radishes	Pumpkin		
Beet greens	Leeks			
Dandelion greens	String beans (very young)			
Swiss chard	Broccoli			
Celery	French artichokes			
Mushrooms				
FRUITS.				
Grapefruit				
Ripe olives (20 per cent fat)		Watermelon	Currants	Plums
		Strawberries	Apricots	Bananas
		Lemons	Pears	Prunes
		Cranberries	Apples	
		Peaches	Huckleberries	
		Pineapple	Blueberries	
		Blackberries	Cherries	
		Gooseberries	Raspberries	
		Oranges		

A deduction should be made in the percentage of carbohydrate in the vegetables of the 5 and 10 per cent groups because a part of the carbohydrate is in the form of cellulose, and this is not assimilable. Then too, there are pentosans and, though these through bacterial decomposition in the intestinal tract may yield calories, they do not act as carbohydrate. For this reason 3 per

[1] Percentage values for foods in this table will be found included in the comprehensive Table 333, p. 924.

[2] Reckon *average* carbohydrate in 5 per cent vegetables as 3 per cent and 10 per cent vegetables as 6 per cent.

cent and 6 per cent represent more accurately the content of available carbohydrate in the 5 per cent and 10 per cent vegetables. This being the case, it is convenient and fairly accurate to consider 30 grams, or 1 ounce of 5 per cent vegetables, to contain 1 gram carbohydrate and the same quantity of 10 per cent vegetables 2 grams of carbohydrate. The vegetables in the 15 per cent and 20 per cent groups should be reckoned at their full value.

Many of the vegetables under the 5 per cent group contain very little carbohydrate; for instance, lettuce contains 2.9 per cent, spinach 3.2 per cent. The vegetables are arranged in each group in sequence according to their content of carbohydrate.

Indeed, one will not be very wrong if he considers the total carbohydrate of the 5 per cent vegetables which a diabetic patient will eat as 10 to 20 grams in the twenty-four hours. As an actual fact, 300 grams of a mixture of 5 and 10 per cent vegetables served to a diabetic patient at the New England Deaconess Hospital were found by analyses at the Nutrition Laboratory to contain 10 grams carbohydrate.

1. *Thrice-cooked Vegetables.*—Vegetables lose carbohydrate in the cooking, and this loss is favored (1) by changing the water in which they are prepared two or three times, and (2) by preparing the vegetables in finely divided form so that the water can have easy access to the whole mass. Such vegetables were used extensively in the days of undernutrition prior to the discovery of insulin. Von Noorden[1] pointed out that 100 grams of raw spinach contained 2.97 grams carbohydrate, but cooked spinach only 0.85 grams. Similarly, 100 grams of ripe peaches contained 9.5 grams carbohydrate, but when boiled and the water changed, only 1.8 grams. Allen[2] has utilized this method of removing carbohydrate from vegetables and thus allows patients to have bulk in their diet. He terms vegetables so prepared "thrice-cooked vegetables." "Under these conditions the vegetables may be boiled through three waters, throwing away all the water. Nearly all starch is thus removed. The most severe cases generally take these thrice-cooked vegetables gladly and without glycosuria."

The carbohydrate content of "thrice-cooked" or "washed" vegetables has been studied by Wardall.[3]

2. *Lettuce and Cabbage.*—Lettuce and cabbage are the most useful 5 per cent vegetables. The so-called iceberg lettuce is a boon to diabetics, because it keeps so long. In our Northern states it is of the greatest help in the winter time. Presumably

[1] Von Noorden: Loc. cit., p. 122.
[2] Allen: Boston Med. and Surg. Jour., 1915, **173**, 241.
[3] Wardall: Jour. Am. Med. Assn., 1917, **69**, 1859.

it contains less vitamin D than loose-leaf lettuce, because the inner leaves are less exposed to the sun.[1]

Bulletin No. 28, Office of Experiment Stations, U. S. Department of Agriculture, gives 2.9 per cent as the average percentage of carbohydrate in lettuce and 5.6 per cent for cabbage. By its bulk lettuce satisfies appetite and is far more agreeable than the insipid washed vegetables. In fact it has replaced these entirely at the New England Deaconess Hospital. When large quantities of a single vegetable are employed, one must not depend on the group analysis. Cabbage is the poor man's 5 per cent vegetable. It can be eaten daily for months, raw and cooked, without repugnance. Its composition is so constant that the amount tolerated can readily be determined. Case No. 866 was sugar-free at the hospital with difficulty and in the course of eight months the lowest blood sugar was 0.13 per cent. When he went to sea on a lumber schooner and lived almost exclusively on cabbage for his vegetable, he returned after one month not only without glycosuria but with a blood sugar of 0.1 per cent. In the spring of 1922, he went to sea again, returning to the hospital in October without glycosuria and with a blood sugar of 0.12 per cent. Whether there is any peculiar virtue in cabbage other than the above I am unaware, but a physician in New York extols the useful effects of cabbage water in diabetes. Could there be glukokinin in it? Cabbage is always obtainable and thus no diabetic has an excuse for breaking diet because he cannot secure vegetables.

3. *Potatoes.*—The variation in the percentage of carbohydrate in potatoes before and after cooking is negligible, save with potato chips, in which it more than doubles. The loss of protein is slight, but if soaked in cold water before boiling the loss of protein is 25 per cent and of mineral matter 38 per cent. If the potatoes are not soaked, but dropped at once into boiling water the loss is much decreased and if the potatoes are boiled with the skins on the loss is very slight. Emphasis should be laid upon the comparatively small amount of carbohydrate in potato in comparison with its bulk and in comparison with the percentage of carbohydrate in bread. A considerable number of my milder cases of diabetes, by giving up bread and bread preparations entirely, have been able to eat potatoes freely. In prescribing potatoes for diabetic patients it is desirable to designate baked potatoes, for these can be eaten with the skins if pains are taken to have them carefully cleaned with a scrubbing brush in the kitchen. This is advantageous in two ways: The skins are quite an addition to the meager diet of the diabetic, and, furthermore, they counteract constipation.

[1] Jour. Am. Med. Assn., 1927, **89**, 794.

Unfortunately potatoes are not of uniform size, and it is against human nature to expect a diabetic to take a small one.

4. *Nuts.*—Nuts containing 15 and 20 per cent carbohydrate are probably far less objectionable than most other foods with a similar carbohydrate content. This is due to the fact that in such nuts as almonds a larger part of the carbohydrate is in the form of pentosan, galactan, or other hemicelluloses some of which probably do not readily form glucose. (See p. 499.)

The usefulness of nuts in the diabetic dietary would furnish an interesting problem for investigation. The danger of nuts to the diabetic rests not in the content of carbohydrate, but rather in their high percentage of protein and fat. Ignorant diabetics often eat nuts as freely as they would 5 per cent vegetables and wonder why they develop glycosuria and acidosis. Case No. 1930, quite mild when her treatment was inaugurated, went home, ate nuts about as freely as some 5 per cent vegetables, escaped diabetic coma, but only through severe undernutrition from which later a special nurse and insulin rescued her. Carrasco Formiguera[1] had an almost identical experience. The initial downward course of my case followed the excessive use of nuts. Her story is worthy of record, particularly because she is still alive despite continual disregard to a greater or less extent of her diet.

The protein of nuts is valuable and Morgan and Heinz[2] found the protein of almond meal to have a biological value superior to that of wheat gluten.

Sherman cites the digestion experiments of Jaffe upon California fruitarians whose diet consists of fruits and nuts and concludes that "apparently the fruits and nut diet was as readily and almost as completely digested as would be expected of ordinary mixed diet." Sherman further states that fruitarians, both adults and children, maintain a well-nourished condition on diets of fruits and nuts which are moderate in total food value and low in protein content, and considers this strong evidence that the nutrients are well digested and efficiently utilized in metabolism.

It is well known, through the work of Osborne, that the vegetable proteins are not all equally efficient in supplying the nitrogen requirement of normal growth and development for the reason that some lack essential amino-acids. Probably this is true of nut proteins but these have not been so extensively studied. The protein of the Brazil nut has been demonstrated to be completely adequate for normal growth and development of young animals. The vegetable and animal fats are supposed to be equally well

[1] Carrasco Formiguera: Footnote, Joslin: Tratamiento de la Diabetes Sacarina, Montaner y Simon, Barcelona, 1925, p. 452.

[2] Morgan and Heinz: Jour. Am. Med. Assn., 1919, **72**, 730.

digested, but they differ in their vitamins which are more conspicuous in fats of animal origin.

5. *Fruit.*—Fruit is most desirable for a diabetic patient if his tolerance will allow him to take it. The taste is agreeable, it serves instead of a dessert, and so relieves the patient of the embarrassment of sitting idly at the table when others are eating. The best varieties of fruit for diabetic patients are grapefruit (7 per cent), strawberries (7.4 per cent), and oranges (11.6 per cent).[1] These fruits are safer than apples (14.2 per cent) for the patient, because they contain 5 to 10 per cent less carbohydrate and are more satisfying. Furthermore, it is less easy thoughtlessly to eat an orange than an apple and thus break dietetic restrictions. To a diabetic an apple is devoid of skin, seeds and core. A small apple contains 1 tablespoonful of sugar, a moderate-sized apple 2 tablespoonfuls and a large apple 3 tablespoonfuls. Even the 20 per cent carbohydrate fruit, banana, contains scarcely more carbohydrate than a small apple, because it weighs only about 100 grams. A small apple weighs 120 grams. Unfortunately, steaming an apple removes little of the carbohydrate which it contains.

Equivalent weights of various fruits which contain approximately 10 grams of carbohydrate are given in Table 194.

TABLE 194.—EQUIVALENTS OF 10 GRAMS CARBOHYDRATE IN VARIOUS FRUITS.

Orange pulp	100
Grapefruit pulp	200
Strawberries	150
Blackberries	100
Raspberries	75
Peaches	75
Blueberries	65
Banana	50

6. *Grapefruit, Oranges, Lemons.*—The quantity of carbohydrate in a very small orange is not far from 10 grams. My children counted for me the number of compartments in 48 oranges, and found these to vary between nine and eleven in 43 instances, but in 3 there were 12 and in 2 were 13 compartments. Consequently, one will not be far wrong to consider that 1 compartment of a small orange contains 1 gram carbohydrate.[2] The same statement will likewise apply to a small-sized grapefruit. It is interesting to note how constantly inconsistent the variations are in the amount

[1] For practical purposes I teach patients to reckon grapefruit 5 per cent, oranges 10 per cent, apples 15 per cent, and bananas 20 per cent carbohydrate.

[2] According to a recent authority there were 16 oranges with 10 sections, 9 oranges with 11, and 1 orange with 12. Two lemons counted contained 10 sections each, and 1 grapefruit, 11 sections. Irving Bailey, aged eight years.

of edible portions in small, medium, and large oranges as prepared for patients by a nurse. Grapefruit vary more, but it is not difficult to select one of moderate size or to take less of a large one. Table 195, shows these variations. Gross appearance and the weight of the edible portion do not correspond.

TABLE 195.—WEIGHTS OF GRAPEFRUIT, ORANGES AND BANANAS COMPARED WITH EDIBLE PORTIONS AS DETERMINED BY A NURSE.

Grapefruit.				Orange.			Banana.		
	Whole, grams.	Edible portion, grams.	%		Whole, grams.	Edible portion, grams.	%	Whole, grams.	Edible portion grams.	%
Small	347	145	42	Medium	260	118	46	149	92	62
Large	677	320	47	Large	275	116	42	149	91	61
				Small	252	113	45	121	74	61
Florida				Medium	253	101	40	125	79	63
				Large	308	141	46	136	84	62
				Small	260	108	42	119	74	62
California				Medium	278	121	44	160	96	60
				Large	282	129	46	119	73	61
							—	145	89	61
						Average	44	167	101	61
								158	97	61
								153	94	61
								—	—	—
							Average	141	87	61

The observations recorded in Table 195, prompted me to pursue the matter further, for it was evident that inaccuracies must creep into the dietetic calculations in this way. In Tables 196 and 197 are shown analyses made for me by Edward M. Frankel, Ph.D., on aqueous extracts of oranges and grapefruit after cautions were taken to remove the bulk of the protein and cellulose with lead acetate. The results, therefore, represent the amounts of water-soluble carbohydrate calculated as glucose after hydrolysis. No account is taken of the insoluble material on the assumption that such carbohydrate not soluble in water is of the hemicellulose type, which has been shown not to be utilized by the human body.

Frankel has added data on the acidity of the fruit calculated as citric acid, because it has been pointed out by Greenwald[1] that this substance is converted quantitatively by the diabetic organism into glucose.

The quantity of levulose in oranges is discussed on p. 353.

The edible portion of a grapefruit or orange as prepared by a nurse is about 45 per cent of the total weight, as shown in Table 195, but upon more accurate analysis about 77 per cent, as shown in Table 196. Trust the diabetic, if left to himself, to extract all the edible portion from all fruits. Half a grapefruit would contain from 12 to 23 grams of carbohydrate and a whole orange from 10 to 20 grams.

[1] Greenwald: Jour. Biol. Chem., 1914, **17**, 115.

TABLE 196.—ANALYSES OF ORANGES.

Made by Edward M. Frankel, Ph.D., New Haven, Conn.

Sold as	Size.	Gross weight, grams.	Edible portion, grams.	Edible portion, %	Grams of sugar as glucose.	Percentage of edible portion.	Total acidity as citric acid, grams.	Percentage of edible portion.
Florida	Small	188	152	81	12.0	7.9	1.5	1.0
"	Small	169	143	85	12.3	8.6	...	...
"	Medium	214	172	80	12.4	7.2	1.2	0.7
"	Medium	215	179	83	15.7	8.8	...	...
"	Large	290	222	80	19.6	8.4	1.3	0.6
"	Large	357	282	79	19.7	7.0	...	...
"	Large	310	243	78	20.4	8.4	...	...
California	Small	189	149	79	10.9	7.3	...	...
"	Small	178	149	84	10.9	7.3	...	...
"	Medium	250	188	75	17.5	9.3	2.2	1.2
"	Medium	236	170	72	16.2	9.5	1.6	0.9
"	Medium	270	203	75	17.2	8.5	...	...
"	Medium	264	193	73	15.4	8.0	...	...
"	Large	287	220	77	16.5	7.5	1.4	0.6
"	Large	322	219	68	19.3	8.8	1.3	0.6

TABLE 197.—ANALYSES OF GRAPEFRUIT.

Made by Edward M. Frankel, Ph.D., New Haven, Conn.

Sold as	Size.	Gross weight, grams.	Edible portion, grams.	Edible portion, %	Grams of sugar as glucose.	Percentage of edible portion.	Total acidity as citric acid, grams.	Percentage of edible portion.
Porto Rico	Small	401	301	75	24.0	8.0	2.4	0.8
"	Small	428	318	74	26.7	8.4	2.3	0.7
California	Medium	581	449	77	31.8	7.1	6.5	1.4
"	Medium	550	394	72	23.8	6.0	6.4	1.6
"	Large	676	515	76	34.8	6.8	5.6	1.1
"	Large	773	606	78	46.6	7.7	6.7	1.1
Florida	Small	538	409	76	25.0	6.1	4.2	1.0
"	Medium	712	539	76	34.2	6.3	5.0	0.9
"	Medium	724	585	81	44.8	7.7	6.2	1.1
"	Large[1]	834	624	75	40.3	6.5	5.4	0.9

Similar analyses for lemons are shown in Table 198.

TABLE 198.—ANALYSES OF LEMONS.

Sold as	Gross weight, grams.	Edible portion, grams.	Edible portion, %	Grams of sugar as glucose.	Percentage of edible portion.	Total acidity as citric acid, grams.	Percentage of edible portion.
California . .	92	50	54	0.576	1.15	3.10	6.20
California . .	90	42	47	0.518	1.20	2.83	6.75
Messina . . .	87	60	69	0.459	0.77	3.82	6.35

[1] Greener than the others

7. *Bananas.* — Bananas are useful for diabetic patients not because the content of carbohydrate is low, for in reality it is equivalent to that in potato, 20 per cent, but because of their comparative uniformity in size. It is infinitely safer for a patient to be told that he can have a banana of moderate size than an ounce of bread, though each would contain the same amount of carbohydrate. For the same reason they are safer than potatoes. Anything which introduces a moderate degree of definiteness into the diabetic diet is advantageous. In general the riper a banana, and for that matter any vegetable or fruit, the more the starch in it has changed to sugar, and also the more carbohydrate it contains. Since unripened fruits with their lower carbohydrate content can be made palatable by cooking, a way is afforded for diabetic patients to use them. I notice this expedient is adopted by Petrén.

8. *Ripe Olives.*—Ripe olives make a pleasing change in the diet. They contain 4 per cent carbohydrate in contrast to green olives, which contain 1.8 per cent. Furthermore, ripe olives are more easily digested. Five ripe or 10 green olives contain 1 gram carbohydrate and a ripe olive contains a gram and a green olive half a gram of fat. The quantity of protein in 10 olives is about 1 gram.

9. *Distilled Vinegar.* — Distilled vinegar contains no protein, fat, or sugar because it is made from a dilute alcoholic distillate. Cider, wine, malt and sugar vinegars are made of fermented juices, infusions or solutions, *not distilled,* and may contain small amounts of sugar. For analyses of vinegar, see p. 938.

10. *Milk.* — The carbohydrate in milk is in the form of lactose and can be reckoned at 5 per cent or 1.5 grams per 30 cc, or 1 ounce. It is the same in skimmed milk and whey; but cream and koumyss contain about 3 per cent, or 1 gram carbohydrate to the ounce. Buttermilk contains essentially the same quantity of carbohydrate and protein as milk, but only a trifling amount of fat. Fermented milk may contain 3 per cent sugar. I could not understand for years why doctors so frequently gave it to their patients but the reason is plain. It represents undernutrition and the physician who prescribed skimmed milk or buttermilk for his mild diabetic patient was employing a modern therapeutic agent.

One quart of milk contains about 600 calories, of skimmed milk[1] 300 calories, of cream with 20 per cent butter fat 2000 calories, and of 40 per cent cream 3700 calories. Milk contains so many desirable food elements that it is always desirable to insert some of it as milk or cream into the diet.

11. *Oatmeal.* — Oatmeal is two-thirds carbohydrate. In calculations one should always be guided by the dry weight, because

[1] So-called "skimmed milk" upon one occasion by analysis contained 4 per cent butter fat.

the different preparations vary greatly in bulk and weight when cooked. It would be of great advantage to diabetics if uncooked oatmeal could be bought in 1 ounce packages, so that the diabetic could secure constant portions. It is by far the most desirable cereal for the diabetic. A saucerful of cooked oatmeal contains about carbohydrate 20 grams, protein 5 grams, fat 2 grams. (See Table 211, p. 570.) A discussion of the oatmeal treatment of diabetes appears on p. 611.

12. *Bread.*—The carbohydrate in white wheat bread amounts to about 53 per cent. If the bread is toasted, enough water is lost to raise the percentage of carbohydrate in the toast to about 60 per cent. If the bread is made without sugar and with water instead of milk the carbohydrate content is lowered and may amount only to 45 per cent. Coarse breads if made without sweetening or milk would contain slightly less carbohydrate. It is undesirable to give bread to diabetic patients unless their tolerance is very high, because they can take so little without causing glycosuria that the bread is simply an aggravation. An error in weight of 1 ounce of a 5 per cent vegetable amounts to 1 gram carbohydrate, of potato to 6 grams, but of bread to 18 grams. Crackers and Zwieback contain still less water than toast, and in consequence the percentage of carbohydrate is raised to the neighborhood of 70 per cent. Bread can be prescribed with considerable accuracy by volume instead of by weight. For a description of a bread block, see p. 570.

Diabetic breads are discussed on p. 913.

So much do I hesitate to give bread to a diabetic for fear he will overstep the limits that I advise a standard biscuit or cracker like an Uneeda biscuit, two of which contain about 10 grams carbohydrate, 1 gram of protein and 1 gram of fat, or a Shredded Wheat biscuit, 23 grams carbohydrate, 3 grams protein, the equivalent of which is 6 Triscuits. In general one can estimate the carbohydrate in crackers as 70 per cent.

Bread is a great temptation. Total abstinence in respect to bread for the diabetic is as desirable as total abstinence in respect to alcohol is for human kind.

3. **Protein.**—The quantity of protein required by diabetic patients varies with the age, weight, and activity of the individual as well as with the condition of the kidneys. It is a safe rule at the beginning of treatment to attempt to increase the protein gradually up to the same quantity as that required by a normal individual.

Until the Chittenden low protein diet is proved to be entirely satisfactory for healthy individuals over a long period of years it is best not to have recourse to it for long periods in the treatment of diabetes. Temporarily small quantities may be given, but

safety lies not far from 1 gram protein for each kilogram body weight for adults, while for children considerably more is required. In the arrangement of the diets of severe diabetics it is now seldom necessary to lower the protein below 1 gram per kilogram body weight. Without the help of insulin frequently the protein was reduced to $\frac{2}{3}$ gram and Petrén lowered it often to $\frac{1}{3}$ gram and even less. With low-protein intake the relative quantity of fat can be increased. (See p. 603.) Protein stimulates the metabolism more than any other kind of food, favors acidosis both experimentally and clinically and can lead to the formation of 58 grams of glucose for every 100 grams metabolized. Reference has already been made to the excessive quantities of protein ingested by diabetic patients when living upon an unprescribed diet (see p. 289) and will be made to the similarly large quantities of protein metabolized both by patients in the course of acid intoxication (see p. 782) and rarely during the course of fasting when inanition is extreme (Case No. 1011, p. 290).

It has been claimed that vegetable proteins give rise to less carbohydrate in the diabetic organism than do animal proteins. As a matter of fact, carbohydrate may be formed out of any protein.

Janney[1] studied the formation of glucose from protein in fasting, phlorizinized dogs and found no difference existed between animal and vegetable proteins and that the glucose yielded in metabolism varied directly with the amount of glucogenetic amino-acids contained in each individual protein. Thus the wheat protein gliadin which contains 43.7 per cent of the highly glucogenetic glutamic acid yields 80 per cent of glucose in metabolism. Indeed gliadin yields the largest amount of glucose of all proteins hitherto examined and casein and ovalbumin the least. The quantity of glucose yielded by various proteins is shown in Table 199.

TABLE 199.—GLUCOSE YIELDS OF INGESTED PROTEINS (JANNEY).

Casein, per cent.	Ovalbumin, per cent.	Serum, per cent.	Gelatin, per cent.	Fibrin, per cent.	Edestin (hemp protein), per cent.	Gliadin (wheat protein), per cent.	Zein (corn protein), per cent.
48	54	55	65	53	65	80	53

The amount of sugar formed from protein, apart from the glucose-yielding amino-acids is negligible. No great variation existed in the amount of glucose produced from muscle obtained from various species of animals, including man. The percentage obtainable was 58, corresponding to a glucose-nitrogen ratio of 3.4 to 1. (See p. 298.)

Attention should be paid to this glucose formation from protein, but as yet I have not adopted the plan of calculating diets upon

[1] Janney: Arch. Int. Med., 1916, **18**, 584.

the supposed glucose-producing values of all three food elements. Various clinicians in the past have advised their patients to estimate the glucose value in the total diet, but it is doubtful if they will continue to do so in the light of the recent theories of carbohydrate metabolism. The carbohydrate derived from protein should be added to the carbohydrate given as such in the diet in estimating the diabetic's power to burn carbohydrate.

Diabetic breads and also patent diabetic foods may contain a small quantity of carbohydrate, yet the protein in them is high and capable of furnishing a large amount of glucose. The result is that such commercial products may actually produce as much glucose in a diabetic as does ordinary bread. However, one must not be wholly governed by analytical conditions, as Janney has pointed out, for although vegetable and animal protein yield glucose according to their content of amino-acids, it is quite possible that the vegetable proteins will be less well digested owing to the form in which they are eaten, and thus less protein is assimilated, and in consequence less glucose formed.

The restricted allowance of carbohydrate with an unrestricted allowance of protein and fat must be held responsible for many untimely diabetic deaths. In fact the more the doctor curtailed the carbohydrate, the more he yielded to the appetite of his patient by increasing protein and fat and then both physician and patient wondered why glycosuria persisted. Indeed, it was not until von Mering and Minkowski with their depancreatized dogs and Lusk with his phlorizinized dogs established a dextrose-nitrogen ratio in total diabetes that the profession fully appreciated the carbohydrate-forming qualities of protein. Even if both the theory and the accuracy of the dextrose-nitrogen ratio are supplanted, they have been of the greatest service both scientifically and practically in the every-day treatment of patients.

(*a*) **Meat and Fish.**—The chemical composition of meat and fish is simplified by the fact that except in liver and shell-fish, carbohydrate is absent. Fortunately in liver the quantity of carbohydrate is almost negligible, for the popularity of this food, and consequently its consumption, has recently increased as a result of the Minot and Murphy treatment of pernicious anemia.[1]

The chief difficulty in computations of the nutritive value of meat and fish is due to the varying content of fat. Thus, the edible portion of chicken may contain on the average only 2.5 per cent of fat, whereas lean ham may contain 14 per cent of fat, fat ham as much as 50 per cent, and smoked bacon 65 per cent, though lean smoked bacon 42 per cent. It is obvious, therefore, that with-

[1] Minot and Murphy: Jour. Am. Med. Assn., 1926, **87**, 470.

out accurate analyses of the fat in meat, only an approximate idea can be had of its caloric value. I pity patients who labor with decimals for an obviously false accuracy.

Fish differs from meat chiefly in the small quantity of fat. Even salmon, which contains more fat than most other fish, showed in its analysis only 12.8 per cent fat, shad 9.5 per cent, and herring and mackerel 7.1 per cent. In general, other kinds of fish show 6 per cent or less of fat. Halibut steak, for example, contains 5.2 per cent, and cod 0.4 per cent. Preserved fish, however, is quite rich in fat; thus sardines contain 19.7 per cent. In substituting fish for meat, my patients are taught to add from ½ to 1 teaspoonful of olive oil to the diet for each 30 grams of fish.

The quantity of protein in meat also varies considerably and usually falls as the percentage of fat rises. Tripe is an exception. In 100 grams the protein amounts to 17 per cent and the fat is but 9 per cent. A value of 20 per cent for protein in uncooked lean meat represents about the average, and this is increased to 25 per cent or more when the meat is cooked. The quantity of protein in fish is very slightly less than that in meat. Shell-fish make agreeable additions to the diet: (1) They are desirable because they are palatable; (2) they are bulky foods and so are satisfying; (3) they furnish a separate course at a meal. Half a dozen oysters or clams are quite sufficient. The edible portion of a medium-sized oyster on the shell weighs on the average half an ounce, and half a dozen oysters would amount to 90 to 100 grams. The six would contain about 6 grams protein, 1 gram fat, and 4 grams carbohydrate—the equivalent of 50 calories. Half a dozen clams on the shell (edible portion) weigh 35 grams and contain 0.7 gram carbohydrate, 3 grams protein, and a negligible quantity of fat.

(*b*) **Broths.**—Broths were so extensively used upon fasting days in the treatment of diabetes that their composition deserves notice. In the Composition of American Food Materials, Bull. 28, U. S. Dept. of Agriculture, the average of three analyses of bouillon shows it to contain protein 2.2 per cent, fat 0.1 per cent, carbohydrate 0.2 per cent. This is based on the supposition that all the nitrogen is present in the form of protein, which all understand is not actually the case. It is apparent that patients taking 1 quart of bouillon or broth in a day must get considerable nitrogenous material. Frequently bouillon cubes[1] are used by patients. These consist chiefly of common salt; the amount of meat extract present ranges from 8 to 28 per cent; and the third important ingredient is plant or vegetable extract, which constitutes from 3 to 30 per cent.

[1] Bouillon Cubes, Bull. No. 27, U. S. Dept. of Agric., November 5, 1913.

In a research with Riche upon the metabolism of amino-acids, Lusk[1] investigated the nutritive value of Liebig's Extract of Beef. His metabolism experiments upon fasting dogs in the calorimeter led to the conclusion that "Liebig's Extract is without influence upon the metabolism in spite of the glandular activity it is known to induce."

The large quantity of salt in broths is of importance. Analyses of various broths in use in hospitals in Boston have been made by Mr. A. H. Smith. These are given in Table 200, and to these data other analyses of various broths examined at the Connecticut Agricultural Experiment Station have been added.

The table shows that the quantity of salt in the broths is quite considerable and that it varies markedly in the different broths. One quart of broth at one hospital, for example, contained approximately 20 grams of salt, while at another, less than 1 gram. This furnishes one reason why edema may occur during the course of diabetic treatment. The quantity of salt in broths should certainly not exceed 0.5 per cent, and if there is any tendency to edema, all salt should be eliminated.

The percentage of fat in the broth as shown by the ether extract is almost invariably slight and all the broths were free from carbohydrate.

The variation of the total nitrogen in the broths is marked and is the most important feature brought out by these analyses. It will be seen that in broth D-2 over 10 grams of nitrogen were present to the liter, and that the protein-nitrogen in this broth amounted to 61 per cent of the total. If the broths were strained, as they usually are before serving to patients, the removal of the sediment would lower the protein and make the analyses more uniform. In general it is a safe statement to make that nearly three-quarters of the total nitrogen in broths is made up of protein- and amino-nitrogen. Such a large quantity of protein demands cognizance and must be allowed for in any dietetic computations.

In general, therefore, thin, clear meat broths, agreeably seasoned and lightly salted, can be considered desirable for diabetic patients. If the broths that are concentrated and form a jelly when cold are served without complete removal of the fat and the sediment, they are unsuitable unless account is taken of their nutritive value. Undoubtedly such broths have repeatedly prolonged the periods required to make patients sugar-free.

Protein for diabetics should be given in the form of Class A proteins according to Banting, Campbell and Fletcher.[2] These Class A proteins—meat, eggs, fish, milk—are desirable instead of broths

[1] Lusk and Riche: Jour. Biol. Chem., 1912, **13**, 155.

[2] Banting, Campbell and Fletcher: Jour. Metab. Research, 1922, **2**, 547.

TABLE 200.—ANALYSES OF BROTHS. MR. A. H. SMITH, NEW HAVEN, CONN.

Hospital.	Total solids, per cent.	Ash, per cent.	Chlorine as NaCl, per cent.	Ether extract, per cent.	Carbohydrates.	Total nitrogen, per cent.	Protein nitrogen, per cent of total.	Extractive nitrogen, per cent of total.	Amino nitrogen, per cent of total.	Remarks.
A-1	2.45	0.42	0.07	0.26	No reduction test	0.26	39.3	45.7	15.0	A beef broth, unsalted; very turbid, but settling quickly to a water-clear broth; some fat; with salt this would be very palatable.
B-1	4.39	2.38	2.02	0.27	No reduction test	0.25	34.1	38.1	27.8	A light yellow, slightly turbid chicken broth; salted and very palatable.
C-1	9.85	0.10	0.03	4.53	No reduction test	0.12	12.7	52.0	35.2	A light yellow clear broth, considerable yellow fat; it tasted flat and a trifle bitter; was much too fat and it lacked flavor.
C-2	8.76	0.38	....	0.63	No reduction test	0.54	84.3	14.9[1]	....	This was a thick, white, jelly; there was no salt in it, but it was palatable; very characteristic taste of mutton; small amount of fat.
C-3	1.49	0.41	0.22	0.07	No reduction test	0.16	43.9	35.7	18.8	This was a clear, light yellow broth, palatable though unsalted; had no definite taste.
D-1	7.54	0.99	0.77	0.12	No reduction test	0.86	83.7	9.1	7.2	When cold this broth was a brown jelly; flavored with spices and onion; very little salt; carried a small amount of fat well; tasted fairly good.
D-2	12.53	3.14	1.73	0.12	No reduction test	1.09	61.0	23.5	15.5	When cold this broth was a dark brown jelly with small amount of fat; it was salted and was very palatable; was very concentrated.
D-3	7.73	1.24	1.10	0.13	No reduction test	0.91	88.0	6.9	5.6	When cold this broth was a light brown, thin jelly with sediment in it; it seemed to contain vegetable extracts; unsalted or slightly salted and most palatable.
Station No.										
13342	2.10	0.28	0.05	0.04	None	0.23	....	....	....	Mutton bone.
13343	1.42	0.36	0.03	0.04	None	0.23	....	....	....	Veal bone.
13344	1.32	0.30	0.05	0.04	None	0.20	....	....	....	Beef bone.
13345	0.92	0.32	0.03	0.03	None	0.15	....	....	....	Beef bone.
13346	0.90	0.18	0.03	0.04	None	0.16	....	....	....	Mutton bone.
13347	1.85	0.30	0.05	0.02	None	0.28	....	....	....	Veal bone.
13348	0.69	0.19	0.03	0.04	None	0.10	....	....	....	Chicken.
13349	1.60	0.48	0.06	0.03	None	0.24	....	....	....	Clams chopped.
13391	1.93	0.30	0.07	0.04	None	0.20	....	....	....	Clams unchopped.

[1] The sum of extractive and amino-nitrogen.

which contain amino-acids and thus use up insulin without, at the same time, serving for tissue replacement.

(*c*) **Increased Utilization of Carbohydrate in Absence of Protein.**—The effect of a low protein diet upon the assimilation of carbohydrate was first strikingly brought out by Klemperer,[1] who showed that even dextrose would be assimilated to a considerable degree by a severe diabetic patient provided the protein in the diet was low. Clinicians of the older school beginning with Cantani, appreciated the importance of restricting the quantity of protein, though Bouchardat, and still earlier Prout, Walter and Rollo saw the dangers of overfeeding. But it is only within the last few years, when the theory of avoiding acidosis by balancing the ketogenic-antiketogenic values of the diet and Petrén's theory of a nitrogenous threshold of metabolism in diabetics above which acidosis occurred were promulgated that the profession appreciated the usefulness of low protein in the diet. Both theories may be wrong, but they have kept diabetics alive.

Far less protein is given the diabetic today than ever before. This is possible with the help of insulin allowing more calories, but we should not forget that such masters of diabetic treatment as Cantani and Naunyn fed much more.

Naunyn, for example, frequently mentions 125 grams protein (20 grams nitrogen) (500 grams cooked = 625 grams uncooked meat) in the dietaries of his patients, though I am inclined to believe he usually employed a somewhat smaller amount. The tolerance of the diabetic for protein, should be determined just the same as is the tolerance for carbohydrate; it should be determined in the presence of carbohydrate and fat as well. Protein is indispensable to a diabetic, and his tolerance for carbohydrate and fat must be subservient to it.

(*d*) **Dextrose-nitrogen Ratio.**—The quantity of dextrose which can be formed from the protein molecule has already been discussed on p. 296. In dietetic computations I think it safest to consider the maximum quantity of sugar in the urine which can be attributed to the protein in the diet as 58.4 per cent, which is Lusk's dextrose-nitrogen ratio. (3.65 grams dextrose: 1 gram nitrogen, equivalent to 6.25 grams protein.) For convenience in clinical computations the value 60 per cent may be employed. Lusk points out that the quantities of sugar in the urine in excess of the ratio of 3.65 grams dextrose for 1 gram nitrogen, are an indication that the patient is taking carbohydrate and so far all my data support this view. The theoretical maximum of carbohydrate which can be formed from protein is 83 per cent. A ratio of 3.65:1 in a severe

[1] Klemperer: Die Therap. der Gegenwart, 1911, **52**, 447.

diabetic is not necessarily of fatal omen.[1] Minkowski found that 2.65 grams of dextrose appeared in the urines of his depancreatized dogs for each gram of nitrogen, thus giving a D:N ratio of 2.65:1.

(*e*) **The Carbohydrate Balance.**—The carbohydrate balance represents the difference between the total quantity of carbohydrate as such ingested in the diet and the sugar excreted in the urine during the same period. When the quantity of carbohydrate in the diet is greater than the quantity of sugar in the urine the patient is said to have a positive carbohydrate balance. When the carbohydrate in the diet is less than the quantity of sugar in the urine the carbohydrate balance is said to be minus or negative. Under the latter circumstances it is evident that the sugar in the urine is derived either from sugar stored in the body or is being formed out of protein or fat. If it simply represents stored-up sugar, within a few days the negative carbohydrate balance will promptly change to zero and perhaps eventually to a positive balance. Case No. 8, in Table 201, will illustrate this, but Case No. 2095, shows it in more modern form. (See Table 202).

TABLE 201.—THE CHANGE IN THE CARBOHYDRATE BALANCE FROM NEGATIVE TO POSITIVE. CASE NO. 8. AGE AT ONSET, SIXTY YEARS. NORMAL EXPECTATION OF LIFE, FOURTEEN YEARS AND TEN MONTHS. THE PATIENT LIVED FOURTEEN YEARS. TREATMENT ACCORDING TO NAUNYN.

Date, 1899.	Diacetic acid, grams.	Sugar in urine, grams.	Carbohydrate intake.	Carbohydrate balance.	Weight, pounds.	Remarks.
June 28	0	61	?	?	161	Diabetes discovered.
30	0	65	0	−65		
July 1	0	13	10	− 3		
2	0	0	10	+10		
1900						
Jan. 1	..	4	45	+41	174	
1909						
Oct. 12	++	19	54	+35	..	Carbuncle.
17	+	0	76	+76		
21	0	0	70	+70	146	
1911						
May 18	0	42	65	+23	..	Pneumonia.
1912						
Sept. 11	0	10	30	+20	143	
1913						
April 20	..	21	?	..	140[1]	Hemiplegia.
June 17	..	2.4%	?	..	..	Pneumonia; died.

[1] March 23.

This moderate case of diabetes, Case No. 8, first came under observation June 28, 1899, and for the first twenty-four hours during which the urine was collected the intake of carbohydrate was not known. Upon the following day no carbohydrate at all was administered, but sugar had existed for so considerable a period in the body

[1] Lusk: Arch. Int. Med., 1909, 3, 1.

that time was necessary for its excretion. The minus carbohydrate balance of 65 grams, therefore, was simply due to retained sugar in the body. This is plainly shown because upon the following day, when 10 grams carbohydrate were allowed, the sugar in the urine decreased to 13 grams, constituting a minus carbohydrate balance of 3 grams; but a day later upon the same diet the urinary sugar completely disappeared and the carbohydrate balance was plus 10 grams. Six months later the tolerance for carbohydrate had risen to 41 grams. It rose somewhat during the subsequent years, persisted during a carbuncle, fell with an attack of pneumonia, then again fell, and in 1913, the patient died of a second attack of pneumonia three months after a cerebral hemorrhage in the fourteenth year of the disease. I do not believe this patient could have tolerated for fourteen years as low a carbohydrate intake as that advocated by Newburgh and Marsh, namely 40 grams, but she might have been better off if her protein had been restricted. However, she lived out her full expectation of life after the onset of diabetes and constitutes my standard case of the efficacy of the Naunyn diet. For Professor Naunyn's advice and for the unusual kindness of Professor Magnus-Levy, then in his clinic, I have always been most grateful.

TABLE 202.—CHANGES IN CARBOHYDRATE AND GLUCOSE BALANCES. CASE NO. 2095. AGE AT ONSET, TWENTY-SEVEN YEARS, DEC. 1920.

Date.	Urinary sugar		Diet in grams.			Carbohydrate balance.	Glucose balance.	Weight, lbs.	Blood sugar.	Insulin, units.	Remarks.
	%	gm.	C.	P.	F.						
1921											
Feb. 21	9.0	54	53	25	0	−1	+14	131			
22	3.7	37	99	57	0	+62	+95	132	0.20		
25	0	0	16	6	4	+16	+20	131			
28	0	0	61	33	9	+61	+81	132	0.08		
Mar. 7	0	0	131	67	22	+131	+172	131			
14	0	0	205	74	52	+205	+253	130	0.08		
1922											
Feb. 7	0	0	175	74	85	+175	+227	132	0.11		
Apr. 26	0.5	8	88	37	43	+ 80	+113	115	0.17		Temperature 102°, jaundice in March
May 19	0	0	140	60	68	+140	+182	115	0.11		
Sept. 13	0	0	175	75	85	+175	+227	122	0.18		
1923											
Mar. 14	0	0	148	64	72	+148	+194	124	0.12	2	
21	0	0	147	73	121	+147	+209	126	0.18	2	
28	0	0	171	77	133	+171	+230	124	..	3	
2	0	0	171	77	133	+171	+230	125	0.08	3	
Apr. 6	0	0	171	77	141	+171	+231	126	..	3	

Case No. 2095, a minister, married three years, aged twenty-seven years, developed symptoms of diabetes in December, 1920, and came for treatment February 21, 1921, seven weeks later. He followed the scheduled regimen employed at that time, the negative carbohydrate balance changed to positive and with a

high-carbohydrate, low-fat diet he remained sugar-free and held his weight one year. He then returned to see if insulin would put him back into the pulpit. It did and at the same time it put him into mine, for his case preaches that (1) 9 per cent of sugar is consistent with mild diabetes when treatment, based upon a high-carbohydrate, moderate-protein and low-fat diet, is begun early; that (2) tolerance can be maintained when the diet is always faithfully followed as Allen and Sherrill have claimed, with (*a*) preservation of weight; (*b*) absence of glycosuria; (*c*) a normal percentage of blood sugar; (*d*) a recuperative power with 3 units of insulin that within a few weeks allowed a gain in strength, mental vigor, and weight which has persisted to date, Jan. 10, 1928. His diet is now carbohydrate 184 grams, protein 72 grams, fat 148 grams; the weight is 146 pounds, insulin (the gift of the Eli Lilly Company for over four years) 20 units, and he has an active parish.

On the other hand, a minus carbohydrate balance which is persistent is indicative of severe diabetes with the formation of sugar from protein or fat. The severity of the diabetes in such a case is also shown by the fact that when a minus carbohydrate balance is permanently present, acidosis is extreme. (See Case No. 344, p. 747.) It will be seen that the carbohydrate balance was minus on June 28, and on July 4, 6, 10 and later remained at quite a uniform figure, although the carbohydrate intake was varied to a considerable degree, but increased along with the severity of the diabetes. During the year represented by these days, the quantity of nitrogen was not very far from 16 grams, and with allowance for fecal nitrogen might be taken as 18 grams, representing the metabolism of approximately 112 grams protein. From this enough sugar could be formed to account for the minus carbohydrate balance if 60 grams of sugar are derived from 100 grams protein in accordance with Lusk's D:N ratio of 3.65 : 1. Unlike the temporary minus balance in Case No. 8, it will be seen that the minus carbohydrate balance in Case No. 344, was persistent and in consequence the acidosis was extreme. The remarkable change in the carbohydrate balance toward the end of life took place after the patient had developed diffuse tuberculosis and was about to die. Attention is called especially to the disappearance of acidosis at this time. It is referred to in the discussion of Allen's theories of diabetes, under Treatment, and again in the Section upon Tuberculosis. (See p. 741.)

The cases above cited are illustrations of changes in the carbohydrate balance over considerable periods of time. They indicate at a glance that, when the diet is being rapidly altered, the carbohydrate balance is not a true index of the carbohydrate utilized and should not be regarded as such. A true carbohydrate balance demands a constant diet with the patient in nitrogen equilibrium

as well. Here again as in making tests of the basal metabolism or with glucose and test meals to determine the presence or absence of diabetes, the patient should be on a uniform diet for several days.

(*f*) **The Glucose Balance.**—The term "glucose balance" is employed frequently instead of "carbohydrate balance," and the "total glucose" of the diet is usually employed in reckoning the glucose equivalent of insulin. But what is the glucose equivalent of the diet? Here in the United States we obtain it by multiplying the carbohydrate by 100, the protein by 58, and the fat by 10. In Europe it is estimated otherwise by Rubner, Falta,[1] and by Priesel and Wagner.[2] They multiply the carbohydrate by 100 and the protein by 80, and disregard the fat. Indeed the latter two authors are very emphatic that the fat need not be reckoned even in regulating insulin dosage and evidently consider those of us who are against large doses of fat as taking a backward step in diabetic treatment. In a more recent article I note they have computed the glucose in the diet upon the American basis.[3] It is therefore worthy of note that Burn and Marks[4] have found that when a liver taken from a cat or a dog fed on a fat diet is perfused with blood from the same species there is a production of reducing sugar at a rate of from 2 to 4 mg. per gram of liver per hour and further, that a small formation of glycogen is also demonstrable. They proved that the sugar did not come from lactic acid or protein. Wierzuchowski[5] has also found an increased production of ketone bodies after feeding a phlorizinized dog olive oil. Evidently some glucose had been oxidized by the animal.

With so much uncertainty as to the source of the total glucose I believe we clinicians would best treat our cases in terms of carbohydrate until the experts reconcile their ideas. I am all the more led to this by the article of Lawrence,[6] who shows how almost essential it is for some carbohydrate to come from fat in the course of exercise. Indeed the physiological wind appears to have veered toward the transformation of fat into carbohydrate. The term "glucose balance" also is not wholly satisfactory aside from the doubt as to the accuracy of the percentages, because it implies that all the protein and fat consumed are immediately oxidized and the carbohydrate which can be formed out of them has at once entered into the metabolism. Shaffer and Wilder are correct in utilizing the urinary nitrogen as a guide to the actual amount of protein entering into the metabolism. It is quite a question, however,

[1] Falta: Wien. klin. Wchnschr., 1925, **38**, 577.
[2] Priesel and Wagner: Loc. cit., p. 695.
[3] Priesel and Wagner: Klin. Wchnschr., 1927, **6**, 1225.
[4] Burn and Marks: Jour. Phys., 1926, **61**, 497.
[5] Wierzuchowski: Jour. Biol. Chem., 1927, **73**, 417.
[6] Lawrence: Quart. Jour. Med., 1926, **20**, 69.

whether this will suffice, and I, for one, am skeptical whether the carbohydrate, fat, and protein of the diet, even basing the latter on nitrogen excretion, accurately represent the actual metabolism of these three substances. If knowledge of the carbohydrate, protein, and fat burned is desired, recourse must be had to the respiratory metabolism aided by the nitrogen excretion and even here it is only the uninitiated who will pin all their faith on the respiratory quotient as the crucial factor in such determinations.

Finally these carbohydrate and glucose balances merely show at best what is taking place but not the potential balances which, only too often, we overlook to the detriment of the patient.

The glucose balance is shown in Table 202 along with the carbohydrate balance. I inserted a column for the words "Glucose Balance" on my hospital charts in 1922 but I did not employ it and later omitted it.

To the total glucose and the glucose balance of the diet Woodyatt[1] attached great weight. His classic paper should be read, because it represents a progressive step in the dietetic treatment of diabetes, even though present ideas do not confirm it. Also the searching but friendly criticism of it by Allen[2] is worth perusal.

4. **Fat.**—(*a*) **The Value of Fat to the Diabetic.**—Fat forms the bulk of the diabetic patient's diet. Even with the most modern ideas on treatment the statement holds. Whereas in the normal diet it furnishes less than one-third of the total calories, that diabetic diet is exceptional which is not made up one-half of fat, and there are few diabetic diets in which fat does not represent two-thirds.

It is surprising how readily in the past double and even treble the quantity of fat ingested by normal individuals was borne by the stomach of the diabetic patient. It is, however, unwise to push the administration of fat too energetically for fear of causing a dislike for it or even indigestion. I once prevented a diabetic boy from enjoying and deriving benefit from sardines, with their accompanying oil, by allowing him to eat the first time as many as he liked. He promptly ate a boxful and the disgust Case No. 4 then acquired for sardines was never overcome. Perhaps this is one reason why I still avoid high ketogenic-antiketogenic ratios. Frequently I see patients who have taken large quantities of fat with obvious benefit for long periods. Case No. 8 (p. 106) must have taken 150 grams of fat daily for fourteen years and died at the age of seventy-three years. The quantity of carbohydrate in her diet for the greater part of the time was below 75 grams. The fat could hardly be said to have done injury in this case, for the patient outlived most of her family and as has been said, her own life

[1] Woodyatt: Arch. Int. Med., 1921, **28**, 125.
[2] Allen: Jour. Metab. Res., 1923, **3**, 61.

expectancy. Case No. 564, Table 203, age at onset sixteen years, ate 170 grams daily—too much, I acknowledge. His case is interesting, because in 1919 he was three and a half months in getting sugar-free and for a large part of the time showed acidosis. After four years of diabetes he passed his preliminary examination for Harvard. A brief abstract of his case is given below to show that, even formerly, patients sometimes did surprisingly well. He lived within a month of ten years although only sixteen years of age at onset. Notice the persistence of acidosis while he was taking sodium bicarbonate.

TABLE 203.—CASE NO. 564. THE COURSE OF SEVERE DIABETES IN A BOY OF SIXTEEN YEARS. TREATMENT BEGUN IN DECEMBER, 1912.

Date.	Urine.				Carbohydrate in diet, grams.	Sodium bicarbonate, grams.	Naked weight, pounds.
	Volume, c.c.	Diacetic acid.	Total NH_3, grams.	Total sugar (polar.), grams.			
1912							
Dec. 17–18	5430	+++	...	230	160	16	99
18–19	5100	sl. +	5.2	130	160	16	99
19–20	4710	++	...	180	135	16	100
20–21	4710	++	...	190	125	16	99
21–22	4050	++++	...	115	125	16	100
22–23	3840	++	...	119	115	16	100
23–24	4020	+++	...	137	75	16	99
1913							
Jan. 1– 2	4140	++	...	89	50	20	101
2– 3	4440	+++	...	115	50	20	100
3– 4	3420	+++	...	75	50	20	101
4– 5	3120	++	...	37	15	20	103
5– 6	4200	+	...	143	165	20	104
6– 7	2100	++++	...	13	15		106
9–10	2700	++++	3.8	49	40		102
Mar. 31							
April 1	945	....	1.1	0			
7– 8	1240	sl. +	...	0			113
1914							
Jan. 5	2000	0	...	0			
1915							
April 26	1800	0	1.0	0	50		134 (dressed)
1916							
Sept. 23 [1]	700	..	0.7	0			129 (dressed)
Oct. 18–19	1600	+	...	6			
Dec. 20–21	800	0	...	0			134 (dressed)
1917							
Jan. 25–26	1000	+	1.0	0	45		
1920							
May 11[2]	2600	0	...	0	55		104
1922							
Nov. 16	Died. Perforation of gastric ulcer. Autopsy.						

[1] May 1, 1915, blood sugar, 0.13 per cent; Sept. 23, 1916, blood sugar, 0.13 per cent.
[2] May 11, 1920, blood sugar, 0.1 per cent.

Case No. 564, came under observation November 30, 1912, at the age of sixteen, three weeks after his onset, which occurred without previous symptoms after an important football game. Volume of urine 8 quarts during the day. The marked acidosis at that time led me to make very gradual changes in the diet and the sugar in the urine decreased from presumably more than 500 grams a day before entrance to the hospital to 230 grams on the first day after entrance, December 17–18, 1912. The patient was discharged, with 42 grams of sugar in the urine on February 13–14, 1913. Under the close care of his physician and a trained diabetic nurse he became sugar-free March 31, 1913, and remained sugar-free, with the rarest exceptions, until his death by perforation of a gastric ulcer on November 16, 1922. It was not by accident he lived so long, because his physicians were F. G. Brigham, B. H. Ragle, and Bertnard Smith. One other of my standard cases, a child, Rexane, Case No. 894, also died like this young man within a few days of the date set for beginning insulin. Her diabetes began at the age of 1.3 years and she was 10.2 years old when at Christmas coma developed. The Eskimos live largely upon fat. Their duration of life can hardly be known with accuracy, and many of the men die as a result of their hazardous seafaring occupations. The duration of life of the Eskimo women should furnish an interesting study.

How much fat should a diabetic patient eat? Plainly, from what has been and will be recorded in the next section, this does not depend upon the capacity of his digestion. The safest answer would be as little as possible above the normal ration of 50 to 100 grams. It all depends upon whether the fat is completely oxidized. If the endogenous insulin is deficient and fat in consequence breaks down, yielding fatty acids which are not burned, harm results.

Unquestionably the quantity will vary from time to time, and it may increase with years without detriment to the patient. Nevertheless, I am always glad to see a diet with carbohydrate-fat ratio under 1 to 1.5, and dread to see one with a ratio above 1 to 2.

Fat is most agreeably taken as cream, and cream which contains 20 per cent butter fat is usually better borne than a richer cream. It is seldom advisable to allow more than half a pint (240 cc.) of cream, although patients prefer to increase the quantity of cream at the expense of other forms of fat in the diet. Rather than increase the quantity of cream increase its richness in fat. There is no other form of food from which a diabetic patient can derive more pleasure for its caloric value and yet with less harm to himself than from cream. Half a pint of 20 per cent cream contains approximately 50 grams of fat, and yet the quantity of carbohydrate in cream of this richness is but little over 8 grams, and may be estimated in clinical work as 8 grams or 1 gram to the ounce of cream.

Occasionally, patients bear butter better than cream, and, as a rule, fresh unsalted butter is preferred. Thirty grams of butter contain 25 grams of fat, and this is a welcome addition to the diet. Intarvin is of about the same strength, 85 per cent fat, but actually less, because it is a higher fatty acid. Oleo or butterine contains no sugar and has about the same percentage of fat as butter and the cost is approximately one-half that of first-class butter. Lard, being nearly 100 per cent fat can be used to advantage more than it now is in the diabetic's diet. Crisco, also nearly 100 per cent fat, is often more welcome than lard, because of its lack of flavor. Oil is an ideal diabetic food, because it is a pure fat. Oil is so desirable for a diabetic that I hesitate to have a patient take more than 15 grams (1 tablespoonful) lest he weary of it. If oil is disliked upon vegetables it can be taken in small quantities after meals as a medicine.

Italian patients naturally bear olive oil unusually well. An Italian diabetic patient under my care at the Boston City Hospital with typhoid fever not only passed through the disease uneventfully upon oatmeal gruel and olive oil, but incidentally became sugar-free and developed no acidosis. Olive oil forms an excellent lunch for diabetic patients, and is useful upon retiring to combat insomnia. It is the diabetic patient's cough medicine; it relieves the symptoms of his hyperacid stomach. Peanut, corn or cotton-seed oil may be substituted if expense is a factor. Cod-liver oil is very readily taken by children and of much value, and I nearly always give it.

(*b*) **The Danger of Fat to the Diabetic.**—Fat is the chief source of the dreaded acidosis, though to this in lesser degree the amino-acids of the protein molecule with even numbers of carbon atoms contribute as well. Fat, therefore, at one time may save the life of the diabetic, but at another period may destroy it.

One of the most potent agencies in the prevention of acidosis is the withdrawal of fat from the diet. The absence of acidosis in totally depancreatized animals and in a human case of pancreatic insufficiency like that of Spriggs and Leigh[1] is to be explained by the non-absorption of the fat given. Fat dogs are more susceptible to acidosis than thin dogs.

One cannot treat diabetes successfully without increasing the quantity of fat, but the extent of increase depends somewhat upon the attitude of the clinician. Fortunately, however, there are certain definite criteria. It is unreasonable to give less than in health or more than the patient can take without developing acidosis. Probably an amount sufficient to bring the weight up to

[1] Spriggs and Leigh: Jour. Am. Med. Assn., 1915, **65**, 1952.

10 per cent below normal is adequate. Excess of fat may lead to arteriosclerosis.

Allen has again made us all his debtors by a series of experiments upon diabetic dogs which show the insidious way in which fat is harmful in the manner in which it has been customarily employed in the treatment of diabetes. "Fat unbalanced by adequate quantities of other foods is a poison."[1] And Shaffer, Woodyatt, Newburgh and Marsh, Petrén, Wilder, Campbell, Strouse, Ladd and Palmer all contributed formulæ to show the adequate quantities of other foods. Newburgh and Marsh and Petrén courageously demonstrated that patients did not die in the hospital while living upon a high-fat, but low-carbohydrate and very low-protein diet, even before the explanation therefor was perfectly plain. Previously, however, Arloing of Lyons and later Maignon had employed a regimen very rich in fat and poor in protein and carbohydrate. Shaffer[2] has assiduously studied the ketogenic and antiketogenic properties of foods and has shown that 2 molecules of aceto-acetic acid, representing 2 molecules of a higher fatty acid, are offset by 1 molecule of glucose and to this Wilder[3] agrees and that acidosis occurs when this ratio is exceeded. Woodyatt[4] places the ratio as 1 molecule fatty acid to 1 molecule of glucose, which ratio Hubbard and Wright[5] adopt. This is based on the supposition earlier adopted by Shaffer that 1 molecule of a higher fatty acid is offset by 1 molecule of glucose. However Mason's[6] fat subject living for seventy consecutive days on a molecular ratio above 2:1 oxidized the same without ketosis.

Various formulas have been devised by which to calculate the maximum amount of fat which a diabetic patient can take with a given tolerance for carbohydrate. All agree that the protein should be kept low, certainly not over 1 gram per kilogram body weight and permanently not below 0.66 gram per kilogram. Shaffer and Wilder each base the quantity of protein in their formulæ upon the nitrogenous metabolism as determined by the urinary nitrogen excretion. Likewise all would concede that the patient should be in nitrogenous as well as in caloric equilibrium.

Shaffer's formula is as follows:

$$\frac{(\text{Calories of Basal Metab.} \times 120\,\%) - (\text{Grams Urinary Nitrogen} \times 100)}{50} = G \times 2.$$

Given: basal metabolism 1000 calories : urinary nitrogen 8

[1] Allen: Am. Jour. Med. Sci., 1917, **153**, 313.
[2] Shaffer: Jour. Biol. Chem., 1922, **50**, 26.
[3] Wilder: Jour. Am. Med. Assn., 1922, **78**, 1878.
[4] Woodyatt: Arch. Int. Med., 1921, **28**, 125.
[5] Hubbard and Wright: Jour. Biol. Chem., 1922, **50**, 361. Hubbard and Nicholson: Ibid., 1922, **53**, 209.
[6] Mason: Jour. Clin. Invest., 1927, **4**, 93.

grams. Thus, if the basal metabolism is 1000 calories and 200 calories are added for hospital activity, we have 1200 calories from which must be subtracted the 8 grams of urinary nitrogen × 100 = 800, leaving 400 to be divided by 50, or 8, a quotient representing the lowest quantity of glucose in grams which could burn the amount of ketone molecules represented in the protein and fat of the equation. Since the glucose must be burned continuously and in all parts of the body, Shaffer multiplies the result by 2, for a safe margin, making 16 grams glucose.

The glucose calories would be, therefore, carbohydrate	16 grams × 4	= 64
The protein calories would be 8×6.25 = protein	50 grams × 4	= 200
The fat calories would be $\frac{1200 - 264}{9}$ = fat	104 grams × 9	= 939
		1200

Wilder uses two formulæ:

$$C = 0.024\ M - 0.41\ P \qquad \text{Formula 1}$$
$$F = 4\ C + 1.4\ P \qquad \text{Formula 2}$$

"In these formulæ, F is the number of grams of fat, C the number of grams of carbohydrate, P the number of grams of protein allowable, and M the total caloric requirement. The calculation is further simplified by the nomographic chart."

The protein can be taken at 0.66 gram per kilogram body weight and, as the diabetic metabolism is so much below standard, a standard metabolism will allow enough calories for moderate activity. Charts for rapid calculations of basal metabolism and optimal diets have been devised. These are described in Wilder's article previously cited.

Woodyatt, assuming a ratio of 1.5 grams fatty acid to 1 gram glucose, gives three formulæ for the estimation of the fat for the quantity of glucose tolerated. The glucose in the diet is estimated by formula (1):

$$(1),\ G = C + 0.58\ P + 0.1\ F$$

The fatty acids are estimated by formula (2):

$$(2),\ FA = 0.46\ P + 0.9\ F.$$

Assuming that when the ratio $\frac{FA}{G}$ exceeds 1.5 ketonuria develops, the maximum quantity of fat is shown in formula (3):

$$\frac{0.46\ P + 0.9\ F}{C + 0.58\ P + 0.1\ F} = 1.5\ i.\ e.\ F = 2\ C + 0.54\ P \text{ or simply}$$

$$(3),\ F = 2C + \frac{P}{2}$$

Conclusions Regarding Fat—Carbohydrate Ratios and Formulæ.—(1) It is rarely necessary to give the maximum quantity of fat, which the carbohydrate allows without acidosis, to any diabetic and for practical purposes one can say wholly unnecessary with insulin at our disposal. (2) If the urine is sugar-free, one need not worry about acidosis if the fat is twice the carbohydrate, or even thrice the carbohydrate provided the protein is but 1 gram per kilogram of the patient's body weight, and if the protein is reduced to 0.66 gram per kilogram and the calories not over 30 per kilogram the fat can be four times and probably five times the carbohydrate with safety. A still lower protein would allow a still higher fat-carbohydrate proportion, but this is best avoided. Rather than give more than 3 grams fat for 1 gram carbohydrate, the doctor had best use insulin to raise the carbohydrate tolerance. Fat in any form is absorbed by the diabetic patient very well, but probably in more cases than supposed it has escaped absorption due to a deficiency in the external secretion of the pancreas as Chester Jones[1] has demonstrated. It also escapes absorption in those rare cases of diabetes with general pancreatic involvement.

One such case (No. 670) was seen by me a few days before coma. In this instance diabetes occurred after partial loss of the gland from acute pancreatitis. The case is reported in detail by Jurist.[2]

Fat, however, is not well absorbed by the dog made diabetic by the removal of the pancreas. This fact explains one of the difficulties experienced in producing acidosis in dogs. When Allen succeeded in making a dog with severe diabetes gain or even hold his weight by forced feeding of fat, increasing acidosis occurred.[3] Depancreatized dogs treated with insulin also show defective fat metabolism which must be protected by administration of trypsin in some form in order to prolong life beyond eight months.

(*c*) **The Increased Assimilability of Carbohydrate in Absence of Fat.**[4]—Notwithstanding it was the belief in this country until very recently that sugar was not formed from fat, the addition of fat to a diet upon which a severe diabetic patient was sugar-free was observed to be followed by the appearance of sugar in the urine, and the converse was equally true. Allen[5] with insulin and Leclercq[6] without insulin have demonstrated this clearly. Formerly it seemed as if the fat molecules displaced the sugar molcules from their attachments in the body and set them free for excretion. Today we

[1] Jones, *et al.*: Arch. Int. Med., 1925, **35**, 315.
[2] Jurist: Am. Jour. Med. Sci., 1909, **138**, 180.
[3] Allen: Am. Jour. Med. Sci., 1917, **153**, 313.
[4] Sansum discusses this subject in considerable detail. Sansum, *et al.*: Jour. Am. Med. Assn., 1926, **86**, 178; Colorado Med., 1927, **24**, 307.
[5] Allen: Loc. cit., p. 196.
[6] Leclercq: Loc. cit., p. 467.

explain the phenomenon by the premature breakdown of the fat molecule yielding ketone bodies on the way to the formation of carbohydrate.

The remarkable power by which the individual can gradually become accustomed to a fat-protein diet is well shown by many diabetic patients. Thus, Case No. 344 took 372 grams of fat on an oatmeal day September 15–15, 1910. The acidosis on this day was extreme, as shown by the excretion of 27.6 grams β-oxybutyric acid. Formerly many diabetic patients took 100 grams fat in the form of cream in addition to that in bacon, butter, eggs and fat meat. Von Noorden's oatmeal cure called for 200 to 300 grams butter, but one is led to ask if it was not the simultaneous ingestion of the large quantity of carbohydrate or the low quantity of protein, (Petrén), which prevented this taking the patient's life. Very recently Weeks, Renner, Allen and Wishart[1] in studies upon the effects of fasting and diets in epilepsy observed a remarkable hyperglycemia which developed in every case on a high-fat diet, but not with any of the other diets. This has been confirmed by Odin,[2] noted also in depancreatized dogs as a consequence of which the insulin must be increased.

(*d*) **Synthetic Fat, Ketosis, Odd Carbon Atom Fat, Intarvin.**—From fat a diabetic develops acidosis and dies, but not from every fat, thanks to Max Kahn and Ralph H. McKee of Columbia University. The harmful fat is that with the even number of carbon atoms, but as the common edible fats in the animal and vegetable kingdoms, such as stearic acid ($C_{18}H_{36}O_2$), palmitic acid ($C_{16}H_{32}O_2$), and oleic acid ($C_{18}H_{34}O_2$), are all even number carbon atom fats and as the diabetic must have fat he has had no recourse, but to live upon them and take his chances. The story of the discovery of an odd number carbon-atom fat follows:

Knoop[3] demonstrated that fatty acids in the course of their oxidation in the body lost two carbon atoms at a time from the fat acid chain. Dakin[4] confirmed and added to the Knoop theory by showing that in the katabolism of fats under normal conditions there is a rapid oxidation of the fat acid radical, such as $C_{18}H_{36}O_2$, to butyric acid, $C_4H_8O_2$, and that this is in turn also rapidly oxidized to CO_2 and H_2O provided there is simultaneous oxidation of a sufficient amount of carbohydrate. In diabetics the mechanism is different. As usual the fats are broken down to the butyric acid stage but here, instead of continued oxidation, the butyric acid $C_4H_8O_2$ is decomposed first into β-oxybutyric acid ($CH_3CHOH.$-

[1] Weeks, Renner, Allen, and Wishart.: Jour. Metab. Res., 1923, **3**, 317.
[2] Odin: Acta Med. Scand., 1927, Supp. 18.
[3] Knoop: Hofmeister Beiträge, 1905, **6**, 150.
[4] Dakin: Jour. Biol. Chem., 1909, **6**, 203.

CH_2COOH) and then to diacetic acid (CH_3COCH_2COOH). This final transformation is what led to Rosenfeld's oft quoted remark that fats burn only in the fire of carbohydrate.

Embden clarified the situation when he found that only those fat acids of even number of carbon atoms yield diacetic acid when transfused through the liver of a dog. Presumably this earlier work led Ringer[1] to conceive the idea that since oxybutyric acid was derived from only those fatty acids with an even number of carbon atoms one should seek for a fat with an uneven number of carbon atoms which a diabetic could assimilate without danger of acid poisoning. He argued that if such fats could be made to burn in the body, acidosis might be avoided because the β-oxybutyric acid could not be formed. Ringer, however, was unsuccessful in his attempts to prepare the odd number carbon atom fat. Janeway and Mosenthal also saw similar possibilities, but it was left to Max Kahn to carry to completion the manufacture of such a fat.

The fat used for the manufacture of intarvin, this new fat, was stearic acid and out of this was produced magaric acid $C_{16}H_{33}COOH$. This is easily purified, then united with glycerol to form a neutral fat. The substance is of a white creamy color, odorless and tasteless, melting at 38° C, neutral in reaction. When cold and granulated it is quite palatable.

By means of this fat Max Kahn has been able to bring about the disappearance of acidosis with a group of diabetics. In one case 150 grams of fat were given daily. Also in a normal individual in whom acidosis was artificially produced by fasting, its disappearance was accomplished by the use of this synthetic fat. Unfortunately acidosis of the ketone type disappears but it is replaced by another type of acidosis described by Lundin.[2] Thus after all one cannot advantageously utilize this ingenious discovery. In a subsequent paper Kahn[3] takes issue with Lundin's conclusions.

5. **Alcohol.**—In no disease would the employment of alcohol appear to be more useful or more justifiable, but I do not give it, because of (1) the pathetic cases, few I will acknowledge, of protracted alcoholic neuritis which I have seen among diabetics, (2) the danger of a patient with a chronic disease contracting a habit, (3) the deliberate and voluntary omission of alcohol by two of my patients as their health improved with insulin, and (4) my personal disapproval of the use of alcohol. Alcohol furnishes an agreeable form of food in a diet which is often disagreeable, and the quantity of nutriment which it contains is by no means negligible. Alcohol is the only food material which is free from the special characteristics

[1] Ringer: Jour. Biol. Chem., 1913, **14**, 48.
[2] Lundin: Jour. Metab. Res., 1923, **4**, 151.
[3] Kahn: Jour. Metab. Res., 1925–1926, **7–8**, 81.

of carbohydrate, protein, and fat and as it is of nutritive value might be of special advantage to diabetics. Alcohol is not convertible directly into glucose or fatty acids: *i. e.*, neither ketogenic nor antiketogenic. There is no evidence that alcohol is etiologically harmful save from the production of obesity. With but one patient have I a record that he gave up alcohol, increased sweets, and developed diabetes. As to its action in protecting protein Mosenthal and Harrop[1] conclude that "the addition of an equal number of calories of protein, fat or alcohol to a low caloric carbohydrate-free diet in cases of diabetes mellitus results in the assimilation of considerable amounts of nitrogen when the protein is used, a favorable nitrogen balance in only occasional instances with fat, and no change in the nitrogen equilibrium when alcohol is given." Higgins, Peabody, and Fitz[2] from tests upon themselves when upon a carbohydrate-free diet found that alcohol did not stop the progress of the acidosis or show any antiketogenic action. Coincident with its administration there was further increase in the oxygen consumption and in the disagreeable subjective symptoms.

Few of my cases have taken alcohol and still fewer take it now than in years gone by. In former days with our crude notions about diet 15 to 30 cc. of alcohol were often useful, when the patients were given excessive quantities of fat. Though Allen originally suggested its use in fasting at the beginning of treatment, he discarded it so soon that I doubt if a dozen of my patients received it under such circumstances. Diabetic patients require no alcohol and as yet I have not found it necessary or desirable to prescribe it, and this statement applies to my assistants as well. Thirty cc. of alcohol are to be found in approximately 60 cc. of whisky, brandy, rum, or gin, or 300 cc. of most of the sugar-free wines. Thirty cc. of alcohol are equivalent to (30 × 7) 210 calories. Few of my patients ever took as much alcohol as this, but half the quantity will replace about 5 per cent of the total diet, and allows the omission of $\frac{(105)}{9}$ 12 grams of fat. This does not appear of great moment, but it would amount to 2100 calories in twenty days. Alcohol may be administered in various forms which are free from sugar. These are specified in the diet tables on p. 941.

The effect of alcohol must be more thoroughly studied with the calorimeter. Allen and DuBois[3] found its ingestion was occasionally followed by respiratory quotients higher than would theoretically be expected.

Allen and Wishart's[4] studies of the effect of alcohol upon two

[1] Mosenthal and Harrop: Arch. Int. Med., 1918, **22**, 750.
[2] Higgins, Peabody, and Fitz: Jour. Med. Research, 1916, **34**, 263.
[3] Allen and DuBois: Arch. Int. Med., 1916, **17**, 1010.
[4] Allen and Wishart: Jour. Metab. Research, 1922, **1**, 304.

diabetics "support the prevailing belief that ethyl alcohol is not converted into sugar in the body. At the same time, they are interpreted as signifying that the addition of calories in the form of alcohol in excess of the patient's caloric tolerance produces a return of glycosuria and other diabetic symptoms.

"The experiments also corroborate the prevailing view that alcohol is not converted into acetone in the body. No antiketogenic action was demonstrable; on the contrary a slight production of acetone seemed to be caused when alcohol was given in considerable quantities. 'Luxus' diets formed by the addition of alcohol or a mixture of fat and alcohol to a standard diet gave rise to very much less acidosis both chemically and clinically than similarly excessive diets built up by the addition of fat alone. The former therapeutic use of alcohol is thus justified, with respect to the lessened danger of acidosis when part of the fat of a high caloric diet is substituted by alcohol. The experiments do not establish such a fact for undernutrition diets, or warrant attempts to prevent combustion of fat by administration of alcohol. On the contrary, the conversion of an undernutrition diet into a 'luxus' diet by addition of alcohol may result in an actual increase of acetone. . . .

"The experiments with alcohol, if fully confirmed, are of crucial importance in supporting the undernutrition treatment They add to the existing evidence that the assimilative power of the diabetic organism is limited not only in respect to carbohydrate (preformed or potential) but also in respect to total calories as such. . . . In confirmation of the view that the harmfulness of excessive fat in diabetes does not consist merely in its possible conversion into either sugar or acetone but preëminently in the overload of the total metabolism, it is found that alcohol, which is clearly recognized as not convertible into sugar or acetone in the body, produces a return of glycosuria and other symptoms when added to the diabetic diet in quantities exceeding the caloric tolerance."

Leclercq[1] likewise demonstrated on two patients with severe diabetes the production of hyperglycemia in consequence of adding excessive calories to the diet in the form of either fat or alcohol. It is readily conceivable that replacing a certain amount of fat might lower glycosuria and acidosis, and Fuller[2] found this true in most cases of mild and moderate diabetes. "This effect is most pronounced when the alcohol is substituted for the caloric equivalent of fat, but is also frequently manifest, when the alcohol

[1] Leclercq: Jour. Metab. Research, 1922, **1**, 308.
[2] Fuller: Jour. Metab. Research, 1922, **1**, 609.

is given as an addition to the previous diet. These effects are usually lacking in diabetic cases of great severity."

6. **Liquids.**—It is rarely necessary to restrict the liquids at the beginning of treatment in diabetes. The diminution of the carbohydrate in the diet usually leads to a corresponding diminution in the thirst and quantity of urine. I hesitate to restrict liquids in severe diabetes for fear too little liquid will be available for the body with which to eliminate the acids that may have been formed. On the other hand in the course of treatment, if the patient is upon an undernutrition diet, he may take liquids too freely in the form of broths, cocoa, tea, and coffee to make up for lack of food.

The metabolism increases 3 per cent according to Benedict and Carpenter[1] when large quantities of liquids are drunk. The increase has amounted to 16 per cent. Liquids also impose a demand upon the metabolism if they are taken cold. The quantity of heat required of the body to raise the temperature of a glass of ice-water to body temperature is not negligible. Patients on the verge of coma often upset the digestion by drinking large quantities of liquids rapidly. This is avoided by allowing only half a glass of liquid at a time, though the patient is instructed to take that every half hour. Ice-water should be discouraged.

Polyuria persists in certain cases of diabetes. Usually a cause can be found in some peculiarity of diet such as an excess of salt. This happened with Case No. 1196 who continually voided large quantities of urine. Upon investigation it was found that he ingested 20 or more grams of salt, bouillon cubes in variable number, or 21 half-grain saccharin tablets a day. Rabinowitch has noted it in insulin-treated cases whose glucose threshold has risen.

The free administration of liquids at the approach of coma is, next to insulin, the most important factor in rescuing the patient. At such a time the liquids should be introduced by mouth, by rectum, and as a rule subcutaneously, but one must not forget that insulin works less well in the presence of edema. (See p. 633.)

Graphic charts of the liquids ingested and excreted are often seen on hospital rounds. These are very crude affairs. In recording the intake, even if everything that flows is regarded as intake, there are amusing inconsistencies. While an egg, in an egg-nog is liquid, it escapes being recorded if boiled to the point of coagulation; cream is liquid, ice cream solid; vegetables and fruits are solid, though they contain 85 per cent, more or less, of water; potatoes are 75.5 per cent water and meat 77 per cent. The retained water of an enema is forgotten. Errors also creep into the estimation of the quantity of liquids excreted. The water in the

[1] Benedict and Carpenter: Carnegie Inst., Washington, Pub. No. 261, p. 247

feces is seldom estimated, the excretion of water by the skin is most variable, depending largely on the amount of exercise, the excretion by the lungs is entirely neglected and this amounts to about 300 cc., Dr. Carpenter tells me. Finally, as Du Bois pointed out to members of the Interurban Club, in the combustion of each 60 grams of sugar there are 5 cc. of water formed, of 100 grams of protein 41 cc. of water, of 100 grams of beef fat 107 cc. of water.

7. **Sodium Chloride.**—Salt is of great service to the diabetic patient. If it is withdrawn from the diet the weight falls, due to excretion of water, and the skin and tissues of the patient become obviously dry. In the early days of the fasting treatment patients often lost much weight because water alone was allowed. For example, I learned of one case who lost 13 pounds in four days in this manner. Conversely, when broths are freely given during fasting it is not uncommon, particularly in the presence of acidosis, to see a patient gain weight, and invariably such patients feel better than those who lose.

Butter may contain a large amount of salt. Analyses of 695 samples of butter reported in Bulletin 149, Bureau of Animal Industry U. S. Department of Agriculture, show an average of 2.51 per cent salt in finished butter.

Salt is very freely used by diabetic patients. I do not remember having ever seen a diabetic patient who took too little salt of his own volition. One of my fasting cases was accustomed to shake it into his hand to eat. Patients will often salt their broths, although they contain considerable salt. An analysis of the duplicate portion of the broth which Case No. 765 drank in three days showed it to contain salt 10.7 grams. In the early days of treatment I remember a boy, Case No. 707, who once carried a saltcellar to the midst of a garden planted with tomatoes and regaled himself with 40 in an afternoon.

TABLE 204.—EXCESSIVE INTAKE OF SODIUM CHLORIDE BY A DIABETIC BOY.

Date.	Urine.					Diet.			
	Vol., cc.	NaCl, grams.	Diacetic acid.	Nitrogen, grams.	Sugar, grams.	Carbohydrate, grams.	Protein, grams.	Fat, grams.	Calories.
1916									
Feb. 14–15	1920	40.3	0	10.9	0	61	72	106	1486
18–19	2880	44.8	0	12.4	0	101	103	143	2103
20–21	1800	44.8	0	12.4	0	101	103	143	2103
			SALT IN DIET RESTRICTED.						
22–23	2010	15.0	..	11.8	0	122	107	143	2199
23–24	1290	15.0	..	11.8	0	131	97	144	2208
24–25	1050	15.0	..	11.8	0	119	95	144	2152

Case No. 982, a young man with onset of diabetes at the age of twenty, excreted 40.3 grams of sodium chloride on February 15, 1916, and a few days later the aliquoted urine of two days contained 89.6 grams. Upon inquiry I learned from his nurse that in addition to the ordinary amount of salt in the food as it was prepared the young man filled a salt-cellar each morning and emptied it before night. Table 204.

The quantity of sodium chloride in 30 grams of cooked bacon at one hospital amounted to 3.3 grams and at another hospital to 7.3 grams.

An oatmeal cure is accompanied by the use of much salt. In the preparation of the standard 240 grams dry oatmeal a cook would employ about 10 grams salt. This may be of importance in the explanation of the edema which often accompanies the oatmeal cure.

Vegetable foods are rich in potassium and, as any farmer's child knows who salts the cattle Sunday mornings, are deficient in sodium. It is not strange that with our free use of vegetables the diabetic patients, like cattle, crave salt. But there is still another reason, because when an excess of potassium is eaten, it is quickly discharged and along with the potassium goes sodium as well. A meat diet requires little salt.

Attention may be called to the low excretion of salt in coma. In one case (No. 1053) two days before death the quantity of salt was 1.28 grams, and in the twenty-four hours preceding death amounted to but 0.44 gram. Magnus-Levy's[1] series of cases of severe acidosis showed a low-salt excretion particularly in those which were fatal. It is possible that under such conditions renal insufficiency may enter in, but more probably the sodium ions are retained to offset the acidosis.[2]

Sodium ions in combination with carbonate and lactic acid ions increase the sugar in the blood in contrast to calcium ions which cause hypoglycemia when given in the form of chloride or lactate.[3]

[1] Magnus-Levy: Die Oxy-Buttersäure, Leipzig, F. C. W. Vogel, 1899.
[2] Peters, Bulger, Eiseman, and Lee: Jour. Clin. Invest., 1925, **2**, 167.
[3] Labbé *et al.*: Arch. d. Mal. d. l'Appart. Digestif., 1927, **17**, 601.

SECTION VII.

ONSET, DIAGNOSIS, PREVENTION, CLASSIFICATION, PROGNOSIS, SYMPTOMATOLOGY.

A. ONSET.

The date of onset of diabetes is usually indefinite. My assistants and I have zealously investigated this point with 500 successive cases, verifying the conclusions of one another. Our previous opinions were confirmed, because the time of onset could not be located within any two months' period by 76.6 per cent of the patients and so was classed as "indefinite." The onset appeared to be within an interval of two months to one week, a "gradual onset, in 17.2 per cent, came on with a "rapid" onset during a period of six days in 4.8 per cent, and in 1.4 per cent of the number was quite definitely placed as having developed in the course of twenty-four hours and therefore was a "sudden" onset.

Table 205.—Types of Onset of Diabetes. 500 Cases.

	No. of cases.	Per cent.
Indefinite (2 months to years)	383	76.6
Gradual (1 to 8 weeks)	86	17.2
Rapid (1 to 7 days)	24	4.8
Sudden (24 hours)	7	1.4

The reason for statements in the literature that diabetes is often of sudden onset may be due to imperfect histories, based more upon impressions or death certificates, but for such a purpose both are unreliable. The diabetic patient a generation ago lived so short a time and his career was so tragic, particularly in children, that it was very natural to record the onset as "acute" and the end as "acutely fatal." It may be said that "acutely fatal" diabetes is a diabetic ghost which, like another of its kind, "complete diabetes," has vanished from medical nomenclature. One has only to seek acute cases of diabetes to be convinced of the truth of the above statements.

The latency of diabetes is illustrated by its development in a parent, or even a grandparent, Case No. 4242, after it has appeared

in a child, and in obesity in which one can observe the disease in its stage of incubation. In cases in which it came on almost as an apoplectic stroke the circumstances were varied.

The examples of acute onset which stand out in my memory are Case No. 7, the man who was injured by a bull, Case No. 10, the Boston bank clerk whose diabetes came on during an important mission while turning a corner in New York City, Case No. 5786, the boy who fell through the ice and was rescued by his dog, and yet I could not take oath that these patients were free from sugar even a few days before the assigned date.

It will be worth while to endeavor to learn more accurately the type of onset of diabetes. It will furnish assistance in a search for the etiology and will raise queries in the minds of the pathologists; it will surely indicate the character of the methods which must be adopted for prevention; it may be of value in classification and prognosis.

The symptoms of the latent period, corresponding to the prodromal period in an infectious disease, in contrast to the symptoms of the clinical period at onset, are instructively discussed by Marañon.[1] He emphasizes that this latent period should be utilized for preventive treatment. In addition to the factors mentioned above, such as obesity and heredity, and he has obtained a history of diabetes in parents, grandparents, uncles and aunts in 260, 31 per cent, of 825 cases, he includes hypertension and itching of the skin as of much importance.

Irrespective of the type of onset whether fulminating or slow, so soon as the diagnosis is made the profession has come to regard the active stage of the disease, the progressive stage, completed and to feel that all the damage has been done. This is contrary to common sense and analogy. Even in hemiplegia the first few hours of the illness show rapid changes taking place about the embolus or the hemorrhage and in an acute infectious disease there is no sharp line between pathological degeneration and regeneration. During the beginning stage of diabetes the patient should be considered as in a labile condition and we should hold ourselves expectant to observe whether the disease is to become mild, moderate, or severe. Quite likely it receives its stamp of severity at its very inception and is severe or mild largely as the diet and the doctor decree. If a diabetes of moderate severity of long standing can be made to become severe by improper treatment, such as sudden restriction of carbohydrate and excessive administration of protein and fat, how much more easily may the diabetes in its nascent stage suffer injury.

[1] Marañon: Loc. cit., p. 6.

B. DIAGNOSIS.

If a patient has sugar in the urine, consider the diagnosis to be diabetes until the contrary is proved. Difficulties in diagnosis are usually but for a day, because persistence of the glycosuria while upon a liberal diet with percentages of sugar in the blood above 0.14 fasting or above 0.16 after a meal indicate diabetes. There is little difficulty in establishing the diagnosis if the urine is examined after a meal; the trouble comes in neglecting to examine the urine. It is easy to agree with Prof. Roger H. Dennett[1] of New York when he writes: "In my opinion there are not a few children who die in diabetic coma in whom the diagnosis has never been made."

The only way in which an early diagnosis of diabetes will ever be made is to search for it. Tests of the blood give us early hints of the presence of the disease, but the practical method is to make frequent examinations of the twenty-four-hour quantity of urine or single specimens one hour after meals.

"Diabetes does not develop over night."[2] If the disease is detected early it is far more susceptible to diet. It is easier to diagnose than tuberculosis. How considerable was the interval between the date of the onset and the beginning of treatment can be inferred by the average loss of weight of 30 pounds that occurred during this period in 600 of my cases. One of the reasons for this delay in diagnosis is the neglect of frequent or routine urinary examinations. Thus in 100 successive cases of diabetes first seen during 1927 in which the patients were especially questioned with this in view, it was found that in 63 instances there had never been a urinary examination before the disease was discovered, and in 15 instances the interval since the previous examination was three or more years. Since the onset of diabetes is most frequent at fifty years of age in women and fifty-one years of age in men, and since it is almost invariably preceded by obesity in adults, any adult over forty years of age who is above normal weight should have a monthly examination of the urine for sugar. Doctors should insist upon this phase of preventive medicine. Eight months are said to intervene between the onset of symptoms of cancer and the first visit to the doctor. Think of the lives which could be saved if in cancer there was a Benedict test by which the diagnosis might be earlier established! An early diagnosis is of inestimable value in the treatment of diabetes; we have the means of diagnosis and yet it is not employed. Therefore, it is necessary to establish the custom of making urinary examinations more systematically. Everyone should have the urine examined on his or her birthday. Start the custom with the

[1] Dennett: New York State Jour. Med., 1926, **26**, 43.
[2] John: Ohio State Med. Jour., 1921, **17**, 826.

children and it will persist to old age. How easily new cases of diabetes can be brought to light, the subjoined incident will disclose:

March 30, 1920, there came to my office a woman with diabetes. She was given the usual examination with suggestions for treatment, and as it was impracticable for her to enter the hospital, she was taught on the spot to examine her urine. She went home and shortly after contracted pneumonia and died. But in the intervening days amid her household cares she found time and took enough interest to examine the urines of ten others in her boarding house, and in so doing discovered the presence of diabetes in a boy. She gave him sound advice and sent him to his own physician, who also subsequently died and eventually the boy came to me, telling this story. On the day she learned the Benedict test and made these ten urinary examinations for her friends, Louisa Drumm, Case No. 1796, was seventy-nine years and four months old.

The physician should take pride in the prevention of diabetes in his practice. Obese patients should be frankly told that they are candidates for diabetes. The physician should consider it as important to prevent his patients acquiring diabetes as he feels it incumbent on himself to vaccinate them against smallpox or typhoid fever, or to protect them from exposure to tuberculosis.

The results of life insurance examinations (see p. 137) show how useful such examinations are, and it is a hopeful sign that the insurance companies are offering to examine gratis at frequent intervals the urines of their policy holders. It is gratifying that in the last few years, according to my statistics, the doctors have been getting ahead of the insurance companies, as shown by the decrease in percentage of my new cases discovered by the latter. The custom of health examinations by the family doctor may have quite a little to do with this change. No physician should see a patient without examining the urine at least every six months, and no physician should discharge a patient after a contagious disease without examining the urine. The urine should be tested before departure from a hospital as well as at entrance. Responsibility for urinary examinations rests not alone upon the family physician, it is the duty of all specialists either to examine the urines of their patients or to assure themselves that such examinations have been recently made, and the time is not far distant when this course will be adopted by progressive dentists as well.

A routine fasting blood sugar estimation for every patient is insisted upon by John[1] just as the Wassermann test is routinely applied.

Recognizing the hereditary and familial tendency, relatives of a

[1] John: Texas State Jour. Med., 1923, **18**, 512.

diabetic patient should always be under the doctor's supervision with urinary examinations at more frequent intervals, particularly when conditions arise which favor the development of diabetes.

C. PREVENTION.

There are entirely too many diabetic patients in the country. To avoid accessions to this group preventive measures must be employed. At present the increase in the incidence is most rapid in the changeable period of middle life. In my series the most frequent year of onset for women is fifty years, for men fifty-one years. It is much more frequent in Jews. Consequently efforts for prevention should be concentrated upon women, and especially Jewish women. As today obesity is the most common etiological factor one must insist that these susceptible individuals do not get fat, particularly if there is also present an hereditary tendency to diabetes.

The slow onset of diabetes is favorable for prevention. There is good reason to believe that the outbreak can be postponed or even prevented. In children diabetes comes on more rapidly, but among children this halting onset is occasionally seen and a considerable interval occurs before the disease becomes permanent. Case No. 129 showed sugar in the urine in 1901, at the age of three years. "at a time when she appeared out of condition. Examining frequently after that I failed to find it and did not look for it again until in February, 1905, when she appeared like a full-fledged case of diabetes." Death occurred in coma in July, 1907.

Case No. 235 showed 1.3 per cent of sugar in the urine January 3, 1901, at the age of twenty-six years, one month after an attack of severe catarrhal jaundice. The glycosuria disappeared at once on restriction of diet and did not return after resumption of a liberal diet containing sugar. December, 1904, right pyelonephritis, urine sugar-free; January 3, 1905, sugar appeared with a moderate amount of acetone, but no diacetic acid, and the patient became sugar-free with a strict diet and, until July, 1906, was able to eat freely of toast, oatmeal, potato, rice or oranges without glycosuria. Death in coma May 4, 1910.

Case No. 1008 showed sugar in the urine on repeated occasions at the age of forty years, was carefully treated for sixty days and later no sugar was found, but it reappeared when the patient was fifty-one, and he came under my observation three years later, with severe diabetes.

Patients with an hereditary tendency to diabetes should be instructed (1) to control, by their body weight, the total quantity of food eaten; and (2) to take carbohydrate almost exclusively in the form of starch rather than sugar, and never to indulge in unusual

quantities of carbohydrate, such as candy, maple sugar, or sweet fruits; and (3) not to make the great mistake of considering the diet alone of importance. Mental relaxation and physical exercise should be promoted. If we are to bring about a decrease of diabetes in the community it will be with measures such as these. Every agency which promotes health and physical development tends to prevent an outbreak of the diabetic tendency. "It is easier to keep well than to get well." (Greeley.)

It would be most unfortunate for two individuals each hereditarily burdened with diabetes to wed, though by care in environmental conditions the consequences of heredity might be averted and the tendency decrease in the third generation.[1]

Who would say that the onset of diabetes in George M., Case No. 2151, aged twenty years, could not have been prevented? His grandfather and father had diabetes. His weight was 29 per cent above standard for his age, and he reports eating two whole pies a day and a whole bottle of cream on his pudding on Sunday. Now, he has cataract though the diabetes is mild.

Overweight predisposes to diabetes and I certainly know it, yet I have recently had under my care again, but this time with diabetes and hemiplegia, Case No. 5823, whom I treated unsuccessfully for obesity 20 years ago. The individual, overweight, is at least twice, and at some ages forty times, as liable to the disease. For the prevention of more than one-half of the cases of diabetes in this country, no radical undernutrition is necessary; the individual is simply asked to maintain the weight of his average fellow man. (See Tables 67 and 68, p. 157.) It is desirable to spread the information that those live longest who above the age of thirty-five years are 5 to 10 per cent below the average normal weight. Patients should be cautioned against gaining weight particularly after infectious diseases, pregnancy, the climacteric, and following changes from an active to a sedentary mode of life. Although emphasis is usually laid upon the appearance of sugar in the urine with a patient losing weight, it cannot be too strongly emphasized that it is a common occurrence for sugar to appear in the urine when a patient is gaining weight. The first hint of diabetes occurred in Case No. 1207 when she weighed 142 pounds in 1895, but the disease did not become established in full force until 1912, when her weight was 248 pounds. In 1917, her weight was 200 pounds, and in 1921, she was "in the very best of health."

Diabetics who had never been obese according to medico-actuarial weight standards were found by Root and Miles[2] to have been 10 per cent overweight when compared with Dreyer's standard.

In the presence of a wasting disease diabetes is almost unknown.

[1] Pribram: Ztschr. f. klin. Med., 1914, **81**, 120.
[2] Root and Miles: Jour. Metab. Res., 1922, **2**, 173.

With the advent of tuberculosis and cancer it may almost disappear. This is the foundation of the treatment suggested by Dr. Allen, who substituted for the wasting diseases the symptom, emaciation, without the disease. If the principle of low nutrition is effective in treatment, how much more will it be effective in prevention.

1. **Infectious Diseases.**—The development of diabetes following infectious diseases is not common. During infections a diabetic loses tolerance, and it is reasonable to conclude that patients are more susceptible to diabetes at such periods, but such cases are rare. Mumps has been suspected of being a disease in which diabetes would easily develop. As a matter of fact, diabetes after mumps is extraordinarily unusual. Priscilla White proved this for the children (see p. 172). Cases of diabetes following infectious disease, however, are so startling when they do occur and at times, though by no means always (see the case of Schmitz, p. 146), are apt to be so severe that the physician should always examine the urines of patients during an infectious disease, during convalescence and without fail before discharging the patient. This is doubly important because a nephritis might be disclosed even though diabetes were not. The usefulness of urinary examinations will become increasingly apparent just as soon as busy physicians get the habit of testing the urine for albumin and sugar in the patient's home with as little formality as they make a test of the blood-pressure.

2. **Pregnancy.**—During pregnancy sugar is apt to occur in the urine. The subject will be discussed more in detail on p. 861. It is mentioned here simply to emphasize the point that mild cases of glycosuria which go untreated in pregnancy may later in the same or in subsequent pregnancies become aggravated cases of diabetes. Perhaps some, and I suspect many, of the cases of diabetes in pregnancy may prove to be similar to cases of renal glycosuria.

3. **Gall Stones.**—Gall stones are about 50 per cent more common among diabetics over twenty-five years of age than among a similar group in the community at large. As gall stones are proverbially more frequent among women it is of especial interest that females are now showing a higher incidence of diabetes than men. Gall stones often precede diabetes and may precipitate it by direct extension of infection to the head of the pancreas. This seems likely, because there the islands of Langerhans are few and the gall stone type of diabetes is mild. But the association of gall stones and diabetes is more far-reaching. Have they not a common origin? Do they not represent results of antecedent, perverted fat metabolism? Diabetes has long been known to be due to a disturbance of carbohydrate metabolism. It is only recently that the teachings of Pflüger, Geelmüyden, Allen, and many others concerning the disturbances of protein and especially fat metabolism in diabetes have been confirmed by experiments in the laboratory and in the clinic.

It is sound doctrine to advise the removal of gall stones to avert diabetes, but one is nearer the heart of the diabetic and gall stone problem in devising methods which will halt or better prevent this perversion of fat metabolism.

The gall-bladder contained calculi at autopsy in 50 of 211 cases of diabetes who were twenty-five years of age or older. For unpublished data I am indebted to many of my friends and am able to include 49 cases from the Deaconess Hospital. Speculation concerning the frequency of gall stones in diabetic patients has little excuse when it is a simple matter to gather facts from 2000 reliable diabetic autopsies. The author hopes Table 206 will be quickly amplified. It would be a great mistake, however, to add to the series cases which were not known to be authentic or any cases save from a consecutive series of diabetic autopsies.

TABLE 206.—THE FREQUENCY OF GALL STONES IN DIABETIC PATIENTS TWENTY-FIVE YEARS OF AGE OR OLDER AS PROVED BY AUTOPSY.

Clinic.	Dates.	No. of autopsies.	Gall stones present.	
			Cases.	Per cent
Boston City Hospital . . .	. . .	29	6[1]	21
Deaconess Hospital	. . .	49	15	31
Massachusetts General Hospital	1902–1927	69	12	19[2]
Peter Bent Brigham Hospital .	. . .	64	17	27

The type of gall stones may be an argument for the common origin of gall stones. Hazel Hunt is studying this feature. If she finds that the percentage of cholesterol stones in diabetics is notably greater than in non-diabetics, the point is proved.

Based upon clinical histories, surgical operations, and autopsies a table has been constructed to illustrate the time of onset of symptoms of gall stones and diabetes, the duration of the diabetes, and the age at operation. 199 cases were found in 4589 cases of true diabetes. (See Table 207.) The average age at diagnosis of the gall stones in 189 cases was 47.7 years and of the diabetes in 199 cases was 51.3 years, thus showing a definite but not marked precedence of gall stones. A common etiology could be inferred from such data.

The mildness of the gall stone variety of diabetes is proverbial and explanations therefor have been already given. The gall-stone diabetics and the children with a hereditary history of diabetes were the groups of cases which gave me hope for improvement in diabetic treatment, because these two types of diabetes seemed apart from the rest. The average duration of life of the 35 fatal gall stone cases was 7.7 years and already has reached 7.6 years for those still alive. Despite this definite surgical complication these diabetics lived a greater length of time than other diabetics of

[1] One additional case showed marked chronic cholecystitis.
[2] Nineteen cases, 30 per cent, showed abnormalities of the gall-bladder.

similar age. Forty of the patients were males, 159 females, thus again emphasizing the need for the prevention of diabetes in females. (See Table 51, p. 140.) It would appear that if one is to have diabetes the gall-stone variety is to be preferred.

Of 36 cases of so-called alimentary glycosuria seen by Eustis,[1] 15 showed definite gall stone disease. Six of these later presented symptoms of definite diabetes.

Eighty per cent of patients with symptoms of cholelithiasis showed hyperglycemia, though not of sufficient degree to produce glycosuria according to Rabinowitch.[2] Statistically from biometrical studies with Althea Frith he found that at the Montreal General Hospital "nine times as many patients with disease of the gall-bladder and its passages had diabetes as would be expected if the influencing factors were completely independent. . . . The incidence of diabetes was greater in cholecystitis than in cholelithiasis and that in acute pancreatitis the incidence was forty times greater than chance would allow." With cholecystograms Tedstrom *et al.*[3] showed that 44 per cent of 70 diabetic patients past the age of forty years had abnormalities in the gall-bladder. The percentage in males was 24 and in females 49. It is also of interest that Barber[4] observed a lowering of the tolerance for carbohydrate as demonstrated by hyperglycemia in cholecystitis experimentally produced in animals. Ophüls[5] found pancreatic lesions associated with gall stones at 14 of 214 autopsies in which gall stones were present. The lesions consisted of focal necroses, chronic pancreatitis, and acute hemorrhagic pancreatitis.

The influence of gall stones in the development of diabetes was strikingly shown in Case No. 954, described on p. 167.

Several cases of diabetes associated with gall stones have done remarkably well when the inflammation about the gall stones has subsided. They suggest that surgical intervention might be advantageously employed in other selected cases. Case No. 18, age at onset of diabetes thirty-five years, first seen by me in August, 1900, at the age of thirty-nine years, for years showed no symptoms of her previously diagnosed diabetes; formerly she had had symptoms of gall stones, which disappeared. I felt so sure that her mild diabetes must be explained by gall stones, that in 1916, although symptomless, these were demonstrated by Percy Brown by Roentgen-ray. Three years later in 1919 attacks of biliary colic occurred and, despite a blood-pressure of 200 systolic and 110 diastolic, the patient was operated upon and gall stones found. She died of chronic nephritis in 1922.

[1] Eustis: New Orleans Med. and Surg. Jour., 1923, **75**, 449.
[2] Rabinowitch: Canadian Med. Assn. Jour., 1924, **14**, 296.
[3] Tedstrom, *et al.*: Jour. Am. Med. Assn., 1926, **87**, 1603.
[4] Barber: Jour. Am. Med. Assn., 1926, **87**, 1635.
[5] Ophüls: Stanford Univ. Pub., 1926, **1**, 301.

Case No. 309 went through a period of involuntary fasting in 1914 and suffered loss of weight which was extreme because of digestive symptoms. Sugar disappeared, tolerance trebled, and Roentgen-ray showed gall stones. She remained alive until 1927, thirty years after onset of diabetes, when she died of gangrene when 3000 miles away.

One of the most remarkable cases is that of Case No. 845. She noticed polyuria and sent her urine to a chemist for examination. He reported 6.58 per cent sugar in 1915. Her history showed previous attacks of inflammation in the gall-bladder region, and in 1913 she was operated upon and gall stones found. There has been no recurrence of the gall-bladder trouble. Her diabetes has re-remained so mild that she goes for months without more than a trace of sugar in the urine and usually with none, and is in fair health today, 1928, although cholesterol deposits show in areas from which they are less easily removed. Her life expectancy at the onset of her diabetes was fourteen years. She has now lived twelve years. Had not her carbohydrate tolerance been as high, cholesterol might have earlier closed her career. Perhaps the development of diabetes saved her life by reducing her weight from 170 to 115 pounds.

Still another case, Case No. 310, is striking. This patient developed diabetes at the age of seventeen years, gall stones were definitely diagnosed at the age of twenty-one years, and the duration of her diabetes was twenty-one years. Unfortunately, as described on p. 373, she died at sea of coma in 1910.

Finally, Case No. 3137, since her diabetes began four and a half years ago at the age of forty-five years, has successfully withstood typhoid fever, coma, and an operation for gall stones. She appeared in my office in January, 1928, sugar-free; after taking insulin 4.5 years she has lived without it for nine weeks and will probably continue to do as well.

TABLE 207.—GALL STONES AND DIABETES.

Cases.	True diabetics in 1000.	True diabetics over twenty years of age.	Gall stones.		Average age.	
			No. of cases.	Per cent.	Diagnosis gall stones.	Onset diabetes.
1–1000	906	783	28	3.6	45.3[1]	49.0
1001–2000	865	746	29	3.9	45.7[2]	44.4
2001–3000	839	708	39	5.5	46.3[3]	49.6
3001–4000	843	753	39	5.2	50.4	54.8
4001–5000	809	716	41	5.7	48.3	52.5
5001–5400	327	297	23	7.7	49.9	55.0
Total	**4589**	**4003**	**199**	**5.0**	**47.7**	**51.3**

[1] 26 cases. [2] 27 cases. [3] 33 cases.

In reference to the duration of the diabetes and the incidence of gall stones I have seen no tabulations, but Dr. Shields Warren has compiled the Deaconess Hospital data for patients over twenty-five years of age and writes as follows:

"Of those cases with duration of disease 0 to 5 years, 27 in number, 6 showed gall stones and 7 showed inflammation of the gall-bladder either alone or in combination with the stones. A total of 11 cases in this duration showed evidence of gall-bladder disease.

"Of 10 cases with diabetes from six to ten years' duration, 4 showed gall stones and 3 showed evidence of inflammatory lesions about the gall-bladder. A total of 5 cases showed either stones or evidence of inflammation of the gall-bladder in this age group.

"Of the 7 cases whose diabetes had lasted from eleven to fifteen years, 2 showed stones and 1 additional case showed evidence of cholecystitis, making a total of 3 showing evidence of gall-bladder disease.

"There were 2 cases whose disease lasted from sixteen to twenty years, 1 of these showed gall stones, the other did not."

Dr. Allen has quoted a whole series of interesting cases relating to diseases of the pancreas and liver in which sugar disappeared.

The desirability of surgical intervention in diabetes with gall stones is unquestioned, but no more important than the removal of gall stones in non-diabetics. Even the subsidence of symptoms of gall-bladder infection reacts quickly upon the diabetic, and the reverse is as unfortunately true. These facts make one all the more ready to advise operation.

My advice to non-diabetic patients with gall stones is to be operated upon not only because of the danger of repeated attacks of gall stones and of the danger of a subsequent carcinoma, but also because of the danger of the development of diabetes. To diabetic patients my advice is to have the gall stones removed when the conditions of time, place, surgeon, and physician are all propitious. Surgeons who operate for gall stones in a non-diabetic may prevent diabetes, although unaware of the good they have done.

4. **Gall-bladder.**—Among the early writers to attempt to point out statistically the connection between disease of the gall-bladder and diabetes were Lichty and Woods.[1] The association was not proved and even their cases of apparent cure seem doubtful because of intercurrent disease in the cases themselves or because of lack of duration since the attack. This latter point has been brought out also by Cammidge[2] in his comment on a case recently reported by Shapland[3] in which removal of a stone filled gall-bladder resulted in

[1] Lichty and Woods: Am. Jour. Med. Sci., 1924, **167**, 1.
[2] Cammidge: Lancet, 1927, i, 846.
[3] Shapland: Ibid.

remarkable improvement in the diabetic condition. However, the impetus afforded to the discussion by Lichty and Woods has been of real service.

How intimately the functions of the gall-bladder and pancreas are related is shown by Whitaker,[1] who has demonstrated that the expulsive action of the gall-bladder invariably depends upon the digestion and absorption of proteins or fats, especially the latter. The work of Jones, Castle, Mulholland, and Bailey[2] has shown that the external secretion of the pancreas suffers in diabetes as does the internal secretion.

Infectious jaundice was followed by glycosuria in the 3 cases of Frissell and Hajek[3] and 1 of the cases eventually proved to be true diabetes.

Among 68 unselected cases of diabetes at the Massachusetts General and New England Deaconess Hospitals, Jones *et al.* found one with a known history of acute pancreatitis requiring surgical intervention, a second one was known to have chronic pancreatitis following a long period of gall-bladder attacks, and two others were probable cases of chronic pancreatitis.

Pancreatic enzyme activity was diminished in nearly one-half of their cases. Bile pigment elimination in the duodenal contents was abnormally high in about three-fourths of the cases. In nearly one-third of the cases there were associated enzyme and pigment abnormalities. The greatest alterations in enzyme activity were noted in the lipolytic and proteolytic ferments. They interpret these phenomena as probably due to associated anatomical and functional changes in the acinar tissue of the pancreas and believe such alterations in pancreatic or liver function may well contribute to the symptomatology of diabetes. It is suggested that the diminution of enzyme activity may result in disturbances due to improper digestion of fat and protein.

Efficient insulin therapy with its associated increase in food intake and improvement of tissue function seemed to be associated with a reduction in pancreatic and hepatic abnormalities.

Acidosis produced a marked disturbance of pancreatic enzyme activity and liver function. The improvement in pancreatic and hepatic function, as measured by changes in the enzyme activity and bile pigment alimentation, following recovery from acidosis, is very striking and illustrates the degree to which acidosis affects all bodily functions.

Cholelithiasis, as diagnosed by examination of the duodenal sediment, occurred in 19 per cent of their cases in their series. In

[1] Whitaker: Am. Jour. Phys., 1926, **78**, 411.
[2] Jones, Castle, Mulholland, and Bailey: Arch. Int. Med., 1925, **35**, 315.
[3] Frissell and Hajek: Arch. Int. Med., 1924, **33**, 230.

addition several other patients had histories or operative findings consistent with the diagnosis of gall stones. They believed that the existing figures for the incidence of gall stones in diabetes were far too low. This led me to compile the data in Table 206 and to beg for its enlargement.

In adults cholelithiasis is probably one of the most important etiological factors in diabetes mellitus, yet one should remember that gall-stones are frequent in the general population, Kaufmann[1] having reported their presence in 10.9 per cent of 16,025 autopsies at Basle.

D. CLASSIFICATION FOR TREATMENT.

A classification of true diabetic cases based upon the assimilation of carbohydrate will always be found helpful in their treatment. It is customary to divide cases of diabetes into three types: mild, moderately severe, and severe. Such a classification, however, can never be arbitrary because cases which at first appear to belong to the severest type of the disease may run a favorable course and cases showing at the outset only a small quantity of sugar may prove to be quite intractable. For this reason Naunyn did not pretend to be able to distinguish accurately between types. Furthermore, up to the present time it has nearly always been considered that diabetes was a progressive disease, and that each patient, if he lived long enough, was destined to pass through the three stages. Time is showing that this unfortunate conception of the malady must be given up. In illustration of the above, Case No. 344 belonged to the type of mild diabetes for nearly four years, but gradually the character of the disease changed, and ultimately reached its greatest severity in this patient; tuberculosis then intervened, acidosis disappeared, and he died, four years after the onset, of tuberculosis rather than of coma. The diabetes had resumed its mild character. Case No. 8 responded so well to treatment as to justify being classed as mild in type, and even at the end of fourteen years was only moderately severe, death ensuing without acidosis but as a result of arteriosclerotic complications. Case No. 552 appeared to belong to the severe type of diabetes, but after prolonged treatment improved sufficiently to reach the borderline of the moderately severe group. Diabetes in children is usually looked upon as severe, but a distinct fraction of these cases prove to be mild. The mere presence of 9 per cent of sugar in the urine when the patient is upon an unrestricted diet is no proof of severity. (See Case No. 2962, p. 86.) Of the last 100 cases seen in 1915, 12 were considered as severe cases, 52 moderate and the remaining

[1] Kaufmann: Spezielle pathologische Anatomie, Berlin, 1922, p. 771.

36 cases mild, but of the last 100 cases prior to March 1, 1917, the statistics were 8 severe, 47 moderately severe, and 45 mild. In 1923, of 100 consecutive cases, 2 were considered severe, 21 moderately severe, and 77 mild. In 1927, the tabulation of 100 cases is 2 severe, 8 moderate and 90 mild.

Most diabetics are mild and the percentage of mild cases to the total number of diabetics has been constantly increasing.

In the first three editions of this book the classification of diabetes was based upon the supposition that severe cases of diabetes have a tolerance from 0 to 10 grams carbohydrate, moderately severe cases have a tolerance from 10 to 50 grams of carbohydrate, and that the remaining cases are mild. In making the classification in 1927 this rule was followed, but so many cases were taking insulin that it was necessary to adjust for the carbohydrate in the diet and the insulin injected. This was done on the basis that 1 unit represents 1 gram carbohydrate. No one realizes better than the writer how unsatisfactory such a method is, because the value of the first unit given is worth many times in carbohydrate that of the last unit. Glucose from protein and fat was disregarded and the value of a unit of insulin taken at 1 gram instead of 1.5 gram for this reason.

Units of insulin are not satisfactory for purposes of classification for the reason cited in the preceding paragraph and also because of the constantly changing value of the unit with diet, exercise, acidosis, infection, and glucose threshold in the blood. Then, too, the varying weights of the patients present difficulties, because although it is easy to place a patient upon carbohydrate 1 gram, protein 1 gram, fat 2 grams per kilogram body weight, these values would be absurd as a standard basis for young children. One might employ this method with individuals whose weight is 50 kilograms or more and then if no insulin is needed the case can be regarded as mild, if less than 25 units are required to prevent glycosuria, the case can be called moderate, and cases requiring 25 or more units can be called severe. By this standard about 5 per cent of my cases taking insulin would be classified as severe. I am restudying the classification of my patients and hope to report upon it soon.

The presence, absence or intensity of acidosis affords an unsatisfactory basis for classification. Even the mildest case of diabetes by restriction of carbohydrate and increase in the amount of fat can be made to develop an acidosis which will be mild, moderate, or severe in degree.

Heiberg[1] rightly criticizes methods of classification. He proposes that first of all the weight of the patient shall be kept in equilibrium,

[1] Heiberg: Mediz. Welt., 1927, 1, 1.

the fasting blood sugar normal and then the calories necessary to attain these results per kilogram body weight will serve as a standard.

The respiratory quotient in the series of 113 cases by Benedict and myself proved to be 0.73 for the severe and 0.77 for the moderately severe as well as the mild. But the respiratory quotient depends in such large measure on the diet as to render it an undesirable method by which to differentiate cases of diabetes even if it were practicable. Then, too, the rise in the quotient which has been observed with fasting diabetics confuses the picture.

Any of the above classifications of diabetes denotes the state of the disease at the moment, but gives no information concerning the response of the patient to treatment. Consequently a working classification with this in mind has been adopted at the New England Deaconess Hospital. For the purpose of treatment it is not of so much interest to be told that a patient is a severe or a mild diabetic as it is to be informed whether he is doing very well (A), fairly well (B), not very well (C), or is in a dangerous condition (D). To arrive at such a decision is not difficult with a knowledge at hand of the urine (sugar, diacetic acid, albumin), the diet (carbohydrate, protein, fat) the weight, pulse and blood-pressure. For convenience, upon the slip which gives these data the letters A, B, C, D are printed. Somehow when you yourself deliberately or someone else deliberately scores your patient (D) it makes more of an impression upon the mind than simply to gather from the accumulated reports that he is not doing well. This working classification has proved very helpful. It should save some lives.

According to Escudero[1] diabetes is produced by a derangement of metabolism of carbohydrate and occurs in two clinical forms, one with glycosuria and the other without. To the latter he gives the term "hidden diabetes," which is manifested by hyperglycemia without glycosuria with a tolerance for more than 2 grams of carbohydrate per kilogram body weight. To the latter type belong three clinical forms associated with (1) obesity, (2) hypertension without cardiac hypertrophy, and (3) some such cutaneous disease as eczema, furunculosis, or pruritus. The normal blood-sugar content after twelve hours fasting should not exceed 0.1 per cent, and a transitory glycemia is indicated when this reaches 0.12 per cent, and diabetes when the percentage is above this figure. To discover hidden diabetes Escudero depends upon a glucose tolerance test comparing the results obtained immediately after twelve hours fasting and at three hours after the test with that obtained after living upon a diet for ten days consisting of carbohydrate 2 grams,

[1] Escudero: Traitement du Diabète, Paris, Malaine, 1925, p. 13.

protein 1 gram, per kilogram body weight, with fat enough for maintenance. Patients with actual diabetes thus become disclosed and the latent cases without glycosuria become apparent because the fasting blood sugar at the end of the ten days rises above the normal level or the subsequent hypoglycemia at the end of three hours is not only absent but a slight hyperglycemia becomes manifest. I confess I fear to trust the diagnosis of diabetes or the demonstration of latent diabetes to such slight difference in blood-sugar tests.

1. **Classification of Supposed Diabetics.**—With the help of my student friends, Mr. Alexander Marble and Mr. Richard Middleton of the fourth year class of the Harvard Medical School, I spent the summer evenings of 1926 in personally recording the classification of each one of the diabetics I have seen since 1898. Classification of the supposed diabetic is still puzzling and in fact is quite as difficult as it was years ago. Despite the aid of tests for blood sugar one runs across a great many patients who have lived so long that the disease appears "burned out." About the only remains of it one finds are the calcified arteries which represent the ashes. An infection will make these latent cases apparent. Then, too, there is another group who evidently have never been severe, very likely were educated in the tenets of the Allen School, originally were fasted for a day or two, and have held to a Spartan régime ever since. These patients usually have a urine which is sugar-free and before a meal the blood sugar is almost normal, and not a few of them show a normal blood sugar following a meal. One hesitates to give a liberal carbohydrate meal, much less a glucose tolerance test, to these "faithful" merely to gratify a classification whim. Then there is the group of patients in whom the disease was diagnosed very, very early, by reliable physicians, was probably unmistakably present, yet actual proof of it is now wanting. A vivacious Miss, Case No. 1484, whose glycosuria was 1.7 per cent in my own laboratory when I first saw her in 1919 but later decreased to the merest trace with diet, came to my office recently. When her diabetes was detected in 1917 by the late Doctor Koplik, he kept her out of school for a year and the sugar fell to a mere trace. For the following years she was on a rigid diet, but now before lunch the blood sugar is 0.1 per cent, and one hour after a characteristic boarding school girl's lunch of a chicken salad sandwich, hot chocolate, ice cream with fudge marshmallow, it rose to but 0.12 per cent. Is she, was she a diabetic or a renal glycosuric? These baffling situations arise in selecting the group of true diabetics. After all is said and done, can it be that in the past we have builded better than we knew? Is it not possible that diabetes may "burn out" in the young, as well as in the old, if we allow the element of time to work?

TABLE 208.—CLASSIFICATION OF 5000 SUPPOSED DIABETICS.

	True diabetes.				Potential diabetes.				Renal glycosuria.				Unclassified.			
	Number.	Dead.	Alive.	Untraced.	Number.	Dead.	Alive.	Untraced.	Number.	Dead.	Alive.	Untraced.	Number.	Dead.	Alive.	Untraced.
1 to 1000	906	716	164	26	13	1	12	0	0	0	0	0	81	31	41	9
1001 to 2000	865	510	313	42	11	0	10	1	5	1	3	1	119	14	90	15
2001 to 3000	839	245	520	74	27	2	24	1	16	2	13	1	117[1]	7	94	16
3001 to 4000	843	157	608	78	42	0	37	5	8	1	6	1	107	5	89	13
4001 to 5000	809	74	677	58	47	0	47	0	13	0	13	0	131	5	117	6
Total	4262	1702	2282	278	140	3	130	7	42	4	35	3	555	62	431	5

[1] One diabetes insipidus.

(*a*) **True Diabetics.**—Time and death are great classifiers, and Table 208 shows this very plainly. The first 1000 supposed diabetics coming for treatment contained 906 true diabetics, but this number has decreased in succeeding thousands so that in the fifth at this writing the true diabetics number 809. As time goes on undoubtedly there will be transfers to the true diabetic group from the other groups, particularly the "unclassified" group. I do not think the group of true diabetics will ever grow as large in the fifth thousand as it was in the first, because it is my impression—and I think the medical directors of insurance companies hold the same opinion—that more doubtful diabetics are coming to light now than ever before. Rarely a case will be transferred from the diabetic group to one of the other groups, but I shall certainly be very cautious before I allow a child to qualify as a diabetic of ten years' duration unless he or she fulfils all the requirements. This table shows that of the true diabetics in the first 5000, more than two-thirds are alive, and if the 1000 recent cases are added, the living percentage will be still higher.

The tracing of diabetics for end-results is enticing even if it is as expensive as most sports. So far 93 per cent of the first 5000 cases have been traced. Of the first 395 children all have been traced, and indeed, this is true of the 435 children in my series of 6120 diabetics up to July 1, 1927.

By a true diabetic I mean, in the first place, a patient who shows a considerable glycosuria with a percentage of sugar in the blood of 0.17 per cent or more. In the older cases evidence of considerable sugar in the urine, which was obviously related to diet, justifies the diagnosis, especially when taken in connection with the further history of the case. A normal fasting blood sugar, but with proof of considerable sugar in the urine varying with the diet, would establish a diabetic's identity, and so would a history of a moderate glycosuria if the fasting blood sugar was 0.14 per cent or above. In any series of 1000 cases one is struck by the number of patients who gave a history of recent onset, yet with repeated questioning symptoms are disclosed which would indicate that the disease had begun in a mild degree years before, and only recently flared up on account of an infection. Just as the beginning of the disease in this group is easily overlooked, so the end of the disease is overlooked in the "burnt out" cases, because the complications or intercurrent diseases, such as cancer, are so much more important and consequently displace diabetes on the death certificate.

(*b*) **Potential Diabetics.**—A potential diabetic is a patient with glycosuria closely related to the diet, who easily becomes sugar-free with slight restrictions and whose blood sugar is below 0.14 per cent fasting and never reaches 0.17 per cent after a meal. This group

is constant in the tabulation for the first and second thousand patients, doubles, trebles, and quadruples for succeeding thousands. In connection with the 395 examples of true diabetes in children some 68 other supposed diabetics were referred to me, and of these 14 were placed in the group of potential diabetics. Thus far, in but one instance has there been evidence that a case once carefully classified as a potential diabetic later became a true diabetic. Possibly Case No. 129 as well should be added.

I doubt if this constancy of classification will hold for adults. With the children it is important, because such facts are a comfort to the family and the physician.

The potential diabetics among my first 5000 cases number 140, and of these but 3 have died and but 7 are untraced. It would appear as if a diagnosis of potential diabetes predisposed that individual to health, and that he was a good risk for an insurance company. Faber[1] has not observed any case of benign glycosuria, which later became true diabetes after the definite determination of a benign glycosuria and Malmros takes a similar position.[2] However one must be cautious and remember that time alone can prove a potential diabetic benign. This view is shared by Malmros. See also Holst.[3]

(*c*) **Renal Glycosurics.**—Twenty years ago renal glycosurics were rare and I did not recognize one as such in my first 1000 cases which ended in the year 1916. Doubtless a certain number were overlooked. In the second thousand they are represented by 5 cases and in succeeding thousands the number rises as high as 16. The total number for the 5000 is 42 cases, of whom 4 are dead and 3 remain untraced. One of the 4 cases who died succumbed to an automobile accident while coasting, and the other 3 to cardiac disease, cirrhosis of the liver,[4] and a gall-bladder operation.

The characteristics of a renal glycosuric are now generally recognized to be (1) a permanent glycosuria (2) which is largely unrelated to diet, (3) a normal blood sugar, (4) freedom from diabetic symptoms, (5) a duration extending over a period of years.

(*d*) **Unclassified Diabetics.**—Unclassified diabetics in my classification include all those cases of glycosuria not easily caught in the preceding nets, but especially those cases not previously classified, which are associated with organic disease, for example, of the gall-bladder, thyroid, and kidney, cancer of the pancreas and often pregnancy. These latter cases appear to be of varied type and therefore one must not be content to consider them lightly but endeavor to determine whether their glycosuria is that of true

[1] Faber: Jour. Clin. Invest., 1926, **3**, 203.
[2] Malmros: Acta Med. Scand., 1925, **62**, 294.
[3] Holst: Acta Med. Scand., 1926, **63**, 47.
[4] This case was later excluded. See p. 900.

diabetes, potential diabetes, renal glycosuria, or merely unclassified. One is struck by the increase of the unclassified group in successive thousands. Thus in the first thousand there were 81, in the second, 119 cases, but in the last and most recent thousand where time has not had a chance to show its hand the number is 131. These 555 unclassified cases make a very important group for study. They are a dangerous group. One never rests easy with an unclassified diabetic. Such a diagnosis worries the doctor, annoys the patient and exasperates insurance agents.

E. PROGNOSIS.

Postpone a prognosis. Cases often appear severe when first seen, but upon further acquaintance it is found that this is due to some temporary and alleviable circumstance, such as the presence of acidosis brought on by an infection or the sudden institution of a fat-protein diet or simply lack of knowledge in the use of diet and insulin. One cannot too strongly emphasize the mild character of most cases of diabetes.

The prognosis depends first of all upon the general condition of the patient entirely apart from the existence of the diabetes; second, upon his disposition and *savoir faire;* third, upon the disease; and fourth, upon your zeal, doctor, to secure for him the best treatment modern medicine affords.

Complications are important, and among these arteriosclerosis is so preëminently a cause of death in diabetes that it controls the prognosis rather than the disease itself. Carbuncles are so serious that only recently has the prognosis of a diabetic with a carbuncle changed from every other case being fatal to every fourth. See p. 782. Other infections, whether general or local, increase the gravity of the diabetes, and so does pregnancy.

Carelessness and coma have ended the life of many a diabetic and, of course, will continue to do so. Therefore, for careless cases cut the life expectancy in half.

The past is not a guide. Malmros'[1] statistics published in 1925, although compiled with exceeding care, are out of place today. For each one of my diabetic children who has lived a decade a hundred adults have done the same. At present (July, 1927) in my group there are 16 children who have already had the disease nine years or longer, 8 for eight years, and 14 for seven years, and the remainder for the years shown in Table 292. Hitherto but 8 of the children attained a duration of ten years. If children can live so much longer, as the table proves and their appearance implies, the prognosis for adults is better, too. It is useless to predict for the

[1] Malmros: Acta Med. Scand., 1925, **62**, 294.

child, but one can be confident that the treatment of diabetes will improve. For adults one cannot expect the average diabetic to live out the full life expectancy of health, but this is possible for many diabetics, and for the diabetic who has been much overweight one can anticipate that he will even exceed it. Do not rest a prognosis upon the quantity of sugar in the urine, the percentage of sugar or fat in the blood, or even the acidosis. These are evanescent. Fifty-three of the patients showed extremes in all these directions when in coma, and although 7 died within one month, there remain 41 alive at periods ranging from four months to four years. However, it must be acknowledged that by and large the higher the glycosuria and the sugar and fat in the blood in cases under careful treatment, the more grave the prognosis, but even here the element of time, with the opportunity it affords for regeneration, may change the outlook.

The presence of obesity, a favorable heredity, an early diagnosis, or the history of benign diabetes of several years' duration with gain rather than loss in tolerance, the retention of body weight, are good prognostic signs, but a placid, cheerful, brave, and honest disposition, inherent or acquired, is fully as important.

The diabetic dies of his complications and not of his disease.

One gets a hint for prognosis from the histories of the patients. They are constantly relating that at the onset of the disease polyuria and polydipsia were severe, and likewise many of these patients declare that they have never undergone careful dietetic treatment and that their dieting was most desultory; they claim that after three, four, or five years the symptoms of polyuria and polydipsia have greatly decreased, or they may even deny their existence at all. In general from patients' stories one is obliged to say that the longer diabetes lasts the less severe it becomes.

In 1924[1] it encouraged me greatly to be able to say that diabetics formerly died at the age of forty-one years and were now living to the age of fifty-two years. But even two years later the statement from the 60 fatal cases during the year ending July 1, 1926, showed that the average age at death was fifty-nine years, and the average age at death of the 43 fatal cases in the 1926–1927 group was 60.9 years. Diabetics are not immortal, although one would think immortality was expected of them by statisticians.

F. SYMPTOMS.

The fear that the mere enumeration of the symptoms of diabetes might lead a doctor or a possible diabetic to feel secure without an examination of the urine is responsible for their omission in previous editions. Whereas the disease may develop in a symptomless

[1] Joslin: Jour. Am. Med. Assn., 1924, **83**, 727.

manner or with non-distinctive symptoms,[1] this is not the rule, although it is significant that recently taken histories reveal a higher percentage of symptomless cases than those of a few years ago. As a rule, however, most symptoms have increased, and this is notable particularly of polyphagia and those symptoms and signs which relate to the skin. The increasing improvement in the medical care of the individual in 1926 over that of 1920 is reflected by the rise in number of persons whose urine had been examined previous to the date of diagnosis of diabetes. In 1920 there were only 18 such, but by 1926 there were 34 per 100 cases.

TABLE 209.—PRESENTING SYMPTOMS OF 200 CONSECUTIVE CASES OF TRUE DIABETES FIRST SEEN IN 1920 AND 1926.

Presenting symptoms.	1920 (100 cases), No. cases.	1926 (100 cases), No. cases.	Total (200 cases), No. cases.	Per cent
Loss of weight	23	19	42	21.0
Loss of strength	46	73	119	59.5
Polyuria	74	69	143	71.5
Polydipsia	65	62	127	63.5
Polyphagia	25	55	80	40.0
Pruritus, skin, and gangrene	12	42	54	27.0
Pains in extremities	17	17	34	17.0
No symptoms	9	12	21	10.5

Loss of strength in the recent series of 1926 is the chief presenting symptom, being present in three-fourths (73 per cent) of the cases, and polyuria was not far behind it (69 per cent). A history of polydipsia was obtained in two-thirds (62 per cent) of the patients and polyphagia in a trifle over one-half (55 per cent). In 1920 symptoms referable to the skin were undoubtedly more numerous than my records imply, but attention of all has been directed much more to them of late. Pains in the extremities have never been common, only 17 per cent of the patients complaining, although all have been asked leading questions regarding pains in general and in particular about pains in the legs. Even with diabetes of prolonged duration pains in various parts of the body can be explained from physical causes, such as arthritis as proved by Roentgen-ray examinations or by arteriosclerosis and not by diabetes. Neuritis is supposed to be common in diabetics, but a renewed investigation of the histories with Dr. Marble's help confirms the impressions of Dr. Root, Dr. White, and myself, and our neurological consultants that it is exceptionally rare in patients in Boston. (See p. 734).

It is of interest that symptoms disappear during the course of treatment in much the same order as the records show they first became manifest with these exceptions: that the polyuria, polydipsia, and polyphagia may vanish overnight in contrast to the

[1] John: Texas State Jour. Med., 1923, **18**, 512.

complaint of loss of strength which requires a longer period; all these phenomena can easily be accounted for by the diet which reduces the output of sugar. The moderate restriction of diet during the first few days of treatment prevents the prompt disappearance of loss of strength, which in the end is almost invariably banished. Reference to polyuria is made on pages 416 to 417. Polydipsia is a symptom which patients often date back for almost their entire lifetime and is so definite that one cannot escape a thought of its connection with some disturbance of pituitary function. Polyphagia is very often denied by the patient, and only persistence in questioning shows it to have been present. I fear sometimes it is recorded as an active symptom as a matter of routine because it is the third of the "polys." Polyphagia may persist when the patient is sugar-free and Hédon records its presence in his dog, although well-fed. (See p. 25.)

Loss of weight, contrary to expectation, was observed by the patient in only about one-fifth to one-fourth of the cases. Of course, this is a sign rather than a symptom, but it is encouraging to note that this is less evident now than formerly because it speaks for an earlier diagnosis of the disease.

It is also encouraging that the number of patients without any symptoms, namely, 12 per cent, is a trifle larger than seven years ago.

Impotence is rarely a complaint. It very likely could be more often elicited, but has been neglected purposely in the anamnesis, because with general improvement under treatment it may disappear, or if not, the less the attention of the patient is directed to it the better.

In closing this section may I warn once more against depending upon symptoms for diagnosis. Even 47 per cent of the young men examined for the draft had a military defect of sufficient importance to note at the time of the physical examination. Neither such defects nor diabetes will be found without search.

In a series of 224 patients of Marañon[1] symptoms were far less common. Polyuria and polydipsia were noted in 59 cases; loss of weight in 47 cases; pruritus in 25 cases; "rheumatic" pains in 16 cases; asthenia in 14 cases; boils or other lesions of the skin in 9 cases. Other signs and symptoms such as hunger, impotence, etc., were fewer.

[1] Marañon: Jour. Am. Med. Assn., 1926, **87**, 1953. See also Abhand. aus d. Grenzgebiet. d. Inn. Sekretion, Novak and Co., Budapest., 1927, Heft 5.

SECTION VIII.

TREATMENT.

A. GENERAL DISCUSSION.

The dietetic treatment of diabetes is extraordinarily simple and yet so engrossing that unless the physician takes care he will fall into schematic ways and forget that it is the patient who comes for treatment and not the diabetes. Each is a case unto itself. The etiology of the disease in each instance should be carefully investigated and faulty habits corrected. It will be found that the symptoms which annoy the patient bear little relation to diabetes, and these should be appropriately treated. This is particularly true in the diabetes of middle life and old age, which is so often accompanied by complications. This broad view of the case should be maintained throughout the course of treatment, and whenever unsatisfactory results are obtained the whole situation should be investigated anew to determine the cause. It is always a safe axiom to look upon diabetes as a good disease which has bad companions. When treatment goes awry, blame them and not her. More than once I have discovered the existence of advanced tuberculosis which had previously escaped attention.

Patients with diabetes often come to the physician in a state which is endurable. It is the function of the physician to improve upon this state. Only too frequently in the past treatment has done the patient more harm than good, but the fault lies not in the principles of treatment, but rather in their application. The physician who undertakes to treat the patient with diabetes whose condition is comfortable resembles the surgeon, who, operating for an interval appendix, assumes a responsibility far greater than when acute symptoms make such an operation imperative.

In illustration of this point I would cite the following instance: Case No. 473, aged forty-eight years, buried her diabetic child at the age of fifteen years. During November, 1911, she began to lose weight, and though 2 quarts of urine were voided, no sugar was found in two *morning* specimens of urine. On December 5, 1911, a little sugar was discovered. January 24, 1912, she consulted

a "specialist." The quantity of urine was then 6 quarts, the percentage of sugar 7 per cent, making the total quantity of sugar for the day nearly a pound.

The "specialist" *radically restricted the carbohydrate in the diet* and three days later, in consultation with her family physician, I found her in coma. This is one of the cases which led me to consider the first year following the detection of the disease to be the diabetic's danger zone. It is one of the cases which formerly would have gone down in the literature as "acute diabetes." How needless a death! A high percentage of sugar is usually a favorable sign in that it is seldom accompanied by acidosis and is evidence that the patient has not been living on a low-carbohydrate high-protein fat diet.

The responsibility for the management of the diet of a diabetic patient should always rest upon one individual. As a rule that individual is the patient, but at times another member of the household. Children who are above the age of ten years should be taught to plan their own diet. They readily learn to do this and in so doing make their elders blush. In fact it is more important for diabetic children to learn what and how much to eat than all the knowledge which their schools afford, for upon this information their life depends. A child at five years should be familiar with the Benedict test and what a positive test means for him. Perhaps it is because this personal responsibility is so deeply felt in the management of little children that the treatment of diabetes in them proceeds so uniformly and always produces results so much better than are expected. Conversely, the failure of diabetic patients to do well in the open wards of large hospitals has been due not so much to the alleged dishonesty of the patient as to the division of responsibility among several nurses. Errors in the diet or in the collection of the urine must be promptly traced to their source.

The treatment of a patient with diabetes lasts through life. Treatment must, therefore, be adjusted to this condition and should be so arranged that it can be continued for years without harm. This is doubly important today because diabetics live so long. The more concrete one's directions to a diabetic, the more likely they are to be followed; likewise, the easier it is for the doctor to discover the severity of the case and later to see why this diet has worked well and that diet worked poorly. It is well-nigh impossible to correct the diet unless the patient is following some definite plan, eating a certain daily total of carbohydrate, protein, and fat. The great advance in treatment came when the patient realized for himself exactly what error in his régime made him worse. It is impossible for the patient to play his part and to follow the plan unless it is simple.

The reasons for the treatment prescribed should be made real to the patient from the very start. It should be visibly demonstrated to him that the quantity of sugar which he is excreting amounts to a pound, more or less, in twenty-four hours, and that this waste of food accounts for his loss of strength and weight, his unusual appetite, thirst, frequency of urination, and his liability to complications. With rearrangement of diet and with the aid of insulin he should be shown that the sugar in the urine decreases. The quantity of sugar and starch in common foods which he is to eat or not to eat, but will see constantly before him, should be taught. He should learn that a large apple weighs 300 grams (10 ounces) and contains 45 grams, 3 tablespoonfuls of sugar, that a moderate-sized apple contains 2 tablespoonfuls, and that a small apple weighs about 100 grams, almost ¼ pound, and contains 1 tablespoonful of sugar, the same amount as does a medium-sized orange. It is worth while to set forth the dangers of bread by comparing the 18 grams carbohydrate in 30 grams (1 ounce) with the same amount which is contained in 540 grams of 5 per cent vegetables or even 900 grams of lettuce. It takes but a moment to point out that in a Uneeda biscuit are 5 grams of carbohydrate and in 1 shredded wheat biscuit 23 grams, that an egg has 6 grams of protein and 6 grams of fat. The patient may not learn all the food values, but he must be taught the kind of food he is to eat, its weight, or its size. If he knows but one 5 per cent vegetable, let him live upon that until he learns another. In hospitals there should be daily lessons. The patient is at school to learn how to save his life. Time should be taken at the beginning of treatment to describe thoroughly to the patient the plan of procedure and the necessity of his being under close observation until the urine is sugar-free and until he understands how to keep it so. The diabetic patient should be made to realize that he has a lesson to learn and that the earlier he learns it the sooner he can be discharged.

Insulin makes even more necessary the education of the diabetic. It is his accident insurance policy, and he cannot learn its use too early. If he does not need it permanently, so much the better. His favorable acquaintance with it may save his life or that of some other diabetic in an emergency. Insulin introduces him to medical science and creates respect for medical research. An understanding of the properties of insulin will make clear the value of exercise, the danger of an infection, the properties of the different components of the diet. Office visits are sufficient for the treatment and education of the patient, but they are time-consuming and it is hard to instill the spirit of the game into a patient when alone. The urine should be examined at the visit, preferably a twenty-four-hour specimen, and in addition a specimen corresponding to each

blood-sugar test. In diabetes one cannot be in too close touch with the actual condition of the patient at the moment. If the reports can be given to the patient while he waits, their value for purposes of treatment is doubled. Precise directions can then be given at once, errors in treatment adjusted, correspondence eliminated, and time saved. Orders should be written down in the patient's notebook just as carefully as they are in the hospital's order book. This notebook should contain a list of the diet and insulin in tabular form with reports of tests of urine and the body weight. So soon as carelessness in this regard is condoned, indifference to other advice follows.

Urinary tests were not taught formerly, because doctors could not keep the urines sugar-free. Today the situation is altered and any modern patient knows that without urinary examinations a diabetic cannot secure the best results. Patients weary of testing the urine, but only under very exceptional circumstances should they be allowed to omit making the test. A daily negative Benedict reaction gives confidence and, on the other hand, in the presence of danger, it is never wise to follow the habits of the ostrich.

Bearing in mind all that has been said about treatment of the individual irrespective of the diabetes, the intimate treatment of the case is based primarily on urinary examinations and on the estimations of the blood sugar. Since Gray's studies and the advent of insulin, the usefulness of the examination of several single specimens of urine in a single day has become apparent. These lessen the necessity for many a blood-sugar test. The latter, however, are almost essential and without them the patient may be exposed to the dangers of hypoglycemia from insulin reactions and in elderly people when the blood sugar is less responsive to treatment the carbohydrate may be kept needlessly and harmfully low. The new and simple methods for blood-sugar tests will surely lead to their universal adoption. As yet there are few patients who can do these for themselves, but nurses much concerned with diabetic treatment feel lost unless they are skilled in their use.

Undernutrition widened the horizon for the diabetic, but insulin has given him back his world of work and joy. Without undernutrition a large share of the wonders attributed to insulin would not have been forthcoming. One can well stand aghast at the thought of the deaths which would result from the greatly increased insulin diets had not the prevention and treatment of coma become matters of routine. The simplicity of undernutrition shows its worth and the increasing duration of life of diabetics since its introduction, is largely, though by no means wholly, to be explained by it. But it must not be forgotten that the first years of diabetes following the discovery of the disease are the diabetic's danger zone.

Yet diabetes is an out-and-out chronic disease, and the greatest mortality from it should occur not in the first years following its discovery but in later years. The first years of a diabetic's life should be his safest and deaths in the early years should be regarded as preventable accidents. More than three-fourths of the deaths the first year are due to coma. When acidosis exists in a patient, he must be in daily communication with his doctor. In general the higher the blood sugar above normal, the more frequent must be the visits.

1. **Diabetic Creed.**—For my own practical guidance in 1923 I adopted a diabetic creed, but, like the best of the creeds, it has undergone alterations and I am sure will soon require more.

I believe at the beginning of this year, 1928:

1. That *diabetes mellitus* should be considered so probable in any person who has 0.1 per cent or more of sugar in the urine that he should be watched for life.

2. That *normal weight* or less should be insisted upon in each diabetic, suspected diabetic, or relative of a diabetic, but that therapeutic loss of weight should be extremely gradual.

3. That *mildness* of the diabetes should be assumed, a long life be expected, and the patient be treated accordingly. Hence, the nearer the proportions of carbohydrate, protein, and fat in the diabetic diet conform to those of the normal diet, always seeking to avoid glycosuria and hyperglycemia, the better it will be for the patient, even at the sacrifice of weight, though not of strength. A carbohydrate tolerance, unutilized, retrogrades.

4. That *reversal of the diet*, namely high-fat and low-carbohydrate, assumes the contrary, severity of the diabetes, and is dangerous both in principle and in practice and unless accompanied by a minimum protein intake frequently ends in coma.

5. That *undernutrition* (*a*) prevents diabetes and (*b*) is the foundation-stone of diabetic treatment, but if hunger can be avoided a smaller number of patients will yield to temptation, break treatment, and in consequence die of coma.

6. That *extreme inanition* with loss of body protein is not worth while *simply to render the blood sugar normal.*

7. That diabetes of itself is not fatal, but that death ensues from other diseases or complications; that *coma* is an accident usually inexcusable and is more easily prevented in 99 cases than treated in 1, and, therefore, diabetics when ill from any cause should (1) go to bed, (2) keep warm, (3) take a glass of hot water, tea, broth, orange juice, or oatmeal water gruel every hour, (4) empty the bowels with an enema, (5) call a doctor, who, if he finds acidosis the dominant factor, will give insulin and caffeine, may wash out the stomach and inject subcutaneously a solution of salt. A diabetic

under treatment with insulin should not omit it unless sugar-free and under medical supervision.

8. That the diabetic should be regarded as unusually susceptible to arteriosclerosis and should be treated with this in view. The carbohydrate in the diet should not long remain under 100 grams and foods high in cholesterol should be restricted. *Gangrene* and the complications therefrom can usually be avoided by treatment with posture and by washing the feet daily and by reporting the discovery of any lesion to the physician.

9. That any patient with a tolerance of less than 100 grams of carbohydrate should (*a*) test his own urine for sugar, (*b*) keep sugar-free, and (*c*) take home food scales and use them until he can keep sugar-free without them.

10. That the *immediate aim* of practice should be to simplify treatment and to encourage physicians to develop in their *own* communities homes and clinics to which they may refer their patients for a diabetic education in case their own time and facilities are inadequate.

11. That *firm persistence* in a strict diabetic diet (*a*) finds ample justification in the patients kept alive by it to profit by insulin; and (*b*) is essential to safety and success in the use of insulin. Insulin utilizes rather than replaces the advances in diabetic treatment hitherto achieved.

2. **Technique of Dietetic Treatment.**—To render the urine of the diabetic patient sugar-free at the beginning of treatment is one of the simplest tasks which confronts the physician. Formerly this was considered to be an achievement, but now it is considered simply a matter of routine. But it is not without its danger. Two decades ago, when carbohydrate was the only food element carefully regulated for the diabetic, this alone was curtailed, and to make up for its loss the patient was urged to devour, not merely eat, protein and fat *ad libitum*. Thereby the ketogenic-antiketogenic balance was upset, acidosis appeared, the patient was then set down as a severe case, the carbohydrate in consequence still more curtailed and as a result the really severe case either died suddenly soon after entrance to the hospital or just barely escaped with his life. The moderately severe diabetics automatically were transformed into severe; many even of the mild type progressed into the moderate group and never regained their mild character with its high tolerance for carbohydrate, partly because they were not given the opportunity and partly because disuse and the high-protein-fat diet destroyed it. The doctor who treated his diabetics the most had the severest cases for patients and thought his practice unique. I was then almost afraid to send a patient into the hospital, believing it safer to allow him to eat his accustomed diet at home, gradually

reducing the carbohydrate to a moderate degree. In this way the severe cases escaped immediate death and the moderately severe and the mild lived with comparative comfort. Considering all the fat and protein the patients were urged to eat, it is a wonder so many survived. There were so many cases of "acute diabetes" that the average duration of life for all diabetics was about three years.

Undernutrition then entered upon the stage in 1914, introduced by Guelpa and Allen, though earlier recognized by Weintraud, Naunyn and in this country intuitively perceived by Hodgson. The results were remarkable. Patients became sugar-free who were never sugar-free before, hospital stay was shortened and the number of severe cases was materially reduced, coma was far less frequent, and the average length of life of my diabetics rose to 4.8 years. However, diabetic accidents still occasionally occurred and unstable diabetics, the old, the long-standing, the very fat, and the diabetics with high metabolism such as those suffering from goiter or from dietary excesses, did not react well to abrupt fasting. The ketogenic-antiketogenic balance was here upset by endogenous rather than by exogenous factors and the exceptional case developed coma, albeit in the days of undernutrition far less than with the previous overnutrition. It was at this stage that the old practice of gradually changing the diet proved to be of service and I found safety in omitting fats, combining thereby at commencement of treatment the advantage of undernutrition with a lessening of the formation of ketone bodies, and also by diminishing the carbohydrate and protein until the results of undernutrition so much improved the tolerance that enough of the carbohydrate was burned to prevent acidosis. With this regimen hospital deaths from coma during treatment were abolished and the entrance of new patients into the hospital was not a cause for alarm.

The practical importance of endogenous metabolism for the diabetic as well as for Benedict's fasting normal man was the note then sounded by Newburgh and Marsh, and explained in detail by Woodyatt. Utilizing a diet of undernutrition, which perhaps they scarcely appreciated at first, and a protein ration far below bodily requirements Newburgh and Marsh demonstrated that with 15 grams of carbohydrate, 10 grams of protein, and 89 grams of fat, acidosis did not develop. They pointed out that it was no more harmful to furnish the diabetic exogenous fat for consumption than to compel him to subsist upon his own. Other advantages and disadvantages of their program will be discussed later. (See p. 603.) It will suffice for present needs to say that as a result of their teachings I returned to my diets a portion of the fat taken away. This was all the more gladly done because the result of the

metabolism tests at the Carnegie Laboratory upon normals and diabetics in undernutrition had vividly shown that the value of a pound of body weight which the patients lost so freely was equivalent to 1500 calories. Likewise a lower protein ration was utilized, about 1 gram per kilogram body weight, though not as low as that of Newburgh and Marsh or that of Petrén. (See p. 607.)

The need of balanced diets began to be gradually recognized. Shaffer and Woodyatt started the current in this direction, and Woodyatt's formula by which the ketone forming elements of the diet could be estimated and balanced against the antiketone elements was the first to gain general adoption. In a word, his formula $\left(F = 2C + \frac{P}{2}\right)$ indicated that the fat in the diet should not be more than twice the carbohydrate plus half the protein. (See p. 524.) Woodyatt emphasized the necessity of estimating the total glucose in the diet, counting for each gram of carbohydrate 1 gram of glucose, for each gram of protein 0.58 gram glucose (which for convenience one may safely reckon at 0.6), and for each gram of fat 0.1 gram glucose. From the total glucose of the diet thus computed the sugar in the urine can be subtracted to get the glucose balance. For the other formulæ of Woodyatt and Shaffer, see pp. 523 to 524.

Irrespective of belief or non-belief in the D:N ratio or a greater formation of carbohydrate from fat than the 10 per cent derived from glycerol, Woodyatt's and the subsequent formulæ gave a safe working basis for dietetic treatment and so did the demonstration by Petrén that when the protein metabolism was reduced to that represented by 3 to 5 grams of urinary nitrogen the acidosis was nearly always absent despite or, as he believed, because of 200 or more grams of fat in the diet. When the protein metabolism is low, acidosis is rare, and likewise irrespective of the theory of a protein threshold above which acidosis hovers, the therapeutic lesson is applicable.

The dietetic treatment of diabetes today rests upon a surer foundation than ever before. There are still different systems, but undernutrition is utilized in one stage or another in all, and all diets are planned to be adjusted so properly that the ketone-forming elements shall be so related to the antiketone-forming elements that acidosis shall not result. As a rule so much carbohydrate can be burned by the patient that this state does not arise and with insulin can be averted. Indeed, this will rarely if ever take place if the protein in the diet is held at 1 gram per kilogram body weight and the grams of fat at not more than three times the grams of carbohydrate with the calories at 30 per kilogram body weight. If the patient is not sugar-free upon this schedule, the protein should

be reduced to $\frac{2}{3}$ gram per kilogram body weight. The grams of fat can then be raised with a fair degree of safety to four times the grams of utilized carbohydrate. Formerly if the patient did not remain sugar-free with this combination, undernutrition was the only recourse until dietetic theories were revolutionized by insulin. And now, even with insulin, the best results are obtainable only when the tenets of the above program are followed to the letter.

B. THE AUTHOR'S PLAN OF TREATMENT.

The treatment of diabetes is simple and becomes spectacular only when bizarre methods are employed or complications arise. One asks the patient to eat less food, particularly less sugar and starch, and simultaneously prescribes a few units of insulin to offset the loss of his own. Until the urine becomes free from sugar the total diet is curtailed and the insulin raised. The protein is always maintained at a moderate level or reduced one-third or even more in the presence of acidosis. The fat is increased to make up for the calories eliminated as carbohydrate, but the total food value of the diet is held 10 per cent below the normal level unless sugar-free and losing weight. Ultimately the carbohydrate should be about 100 grams, the protein 60 grams, and the fat 125 grams for the average individual whose naked weight is 60 kilograms. Meanwhile insulin may need reduction or increase and 5 or 10 or 15 units will be injected once, twice, or three times a day. With time adjustments of diet and insulin may be made and the faithful patient can look forward to an increase in his carbohydrate.

The onset of diabetes is slow and it is rational to correct the disturbed metabolic balance of the body slowly, too, always with the purpose in mind to restore pancreatic function rather than to dispel diabetic symptoms.

The impaired function of the pancreas should be kept in view at the very beginning of treatment. The islands should be spared by restriction of carbohydrate and the acinar tissue by reduction of protein and fat. The pathologists have taught us and clinicians have proved that the external juice as well as the internal secretion is defective and treatment should be aimed to meet both conditions. Empirically such treatment has worked well and now it is scientifically justified.

The urine is to be made sugar-free and the blood sugar normal: (1) because normal values are obviously the best; (2) because a high blood sugar is a stimulus for insulin secretion and the impaired island tissue should be spared overwork; (3) because the removal of the glycosuria proves utilization of the diet. A fourth reason is customarily given: namely, that a high percentage of sugar in the

blood implies the same in the tissues and that this conduces to lack of tissue repair and resistance to infection, causes degenerative phenomena in arteries and nerves, leads to weakness, weariness, and impotence. Concerning this fourth reason I have some doubt. The sugar in the tissues is not especially high in diabetes (p. 195), wounds heal well in the presence of a high blood sugar (p. 577), and there is little reason to suspect that a high blood sugar causes arteriosclerosis (p. 684). I prefer to say that the blood sugar should be normal because the blood sugar is an index of the disease and if normal it is assurance that the whole disease is being treated well. A normal percentage of sugar in the blood in diabetes as a rule, but not invariably, indicates a blood normal in other respects as well.

The technique of inaugurating the diet is aided by the use of adjustable standard diets. Most clinics have their own, but in all there has been a tendency toward simplification with frequent alterations which indicate progress. My own standard diets have been reduced in number from 18 to 12 and now with the aid of insulin even those designed for the third, fourth, and fifth days of treatment are rarely necessary. The diets for the first three days are termed Test Diets and the remainder Maintenance Diets. The components of the diet are given in detail in easily obtainable and digestible articles and their values can readily be reckoned from a diet card with which the patient is supplied. (See Tables 189, 193.)

Even should a trace or a few tenths per cent of sugar remain in the urine, this usually disappears during the days of undernutrition of the early Maintenance Diets. So striking have been the results obtained with these diets that I have been impressed as never before with the inherent mildness of diabetes, even in the presence of high percentages of sugar. Indeed, the early untreated case who shows 9 per cent of sugar is about the most amenable to treatment. The refractory cases are the long-standing ones with low percentages of glycosuria upon moderate diets.

The diet of the patient for the first day he begins treatment is not a matter of indifference. Decision rests upon his previous diet or the quantity of sugar which he is known to void in the twenty-four hours. Usually the patient first coming for treatment is placed upon Test Diet 1. This allows temporary undernutrition, because the calories are 931, one-half those required by a 60 kilogram man, the carbohydrate is 100 grams, which is a two-thirds reduction from the standard ration at desk employment, and protein 35 grams. Test Diet 1, therefore, combines undernutrition with a reduced carbohydrate and fat; it is a safe diet even with acidosis and within twenty-four hours allows an estimate of the future course of the patient. With it insulin may be given to the amount of 3 to 5 units before a meal, or even more insulin may be given,

if its action is adjusted by the results of examination of all urinary specimens.

TABLE 210.—TEST AND MAINTENANCE DIETS.

		Total diet.				Carbohydrate (C).						Protein and fat (PF).				
		Carbohydrate.	Protein.	Fat.	Calories.	5 per cent vegetables.	Orange.	Oatmeal.	Shredded wheat.	Uneeda.	Potato	Egg.	Cream 20 per cent fat.	Bacon.	Butter.	Meat.
TEST	T.D.1	101	35	43	931	300	300	..	1	2	120	3	120	..	..	..
	T.D.2	66	24	37	693	300	300	..	½	2	..	2	120	..	..	..
	T.D.3	34	15	30	466	300	200	..	..	..	..	1	120	..	..	..
MAINTENANCE	C4+PF4	42	29	52	752	600	200	..	..	..	..	2	60	30	15	..
	C5+PF5	52	32	66	930	600	200	15	..	..	..	2	60	30	30	..
	C6+PF6	64	44	83	1179	600	200	30	..	..	..	2	120	30	30	30
	C7+PF7	74	52	88	1296	600	300	30	..	..	..	2	120	30	30	60
	C8+PF8	84	61	94	1426	600	300	30	..	2	..	2	120	30	30	90
	C9+PF9	98	65	106	1606	600	300	30	½	2	..	2	180	30	30	90
	C10+PF10	109	66	119	1771	600	300	30	1	2	..	2	180	30	45	90
	C11+PF11	135	80	135	2075	600	300	30	1	2	120	2	240	30	45	120
	C12+PF12	159	84	135	2187	600	300	30	1	2	240	2	240	30	45	120

The effect of diet and insulin is controlled by the urine which at first is best examined in four periods, morning (M), afternoon (A), evening (E), night (N). Estimations of the blood are made upon entrance, fasting before breakfast the next morning, and subsequently as indicated an hour after a meal, fasting, and always in the late forenoon before discharge from close observation. I rarely give the patient an opportunity to continue his former diet to serve as a baseline at the beginning of treatment unless he is already under treatment, because experience shows that he will not do this, but actually modifies it according to his own ideas as to what he thinks best for himself to eat. As a rule he radically restricts his diet in carbohydrate and frequently as a result will develop acidosis. Consequently in practice it will be found wiser to err on the safe side by giving the patient on the first day too much rather than too little carbohydrate. I feel it most important to begin with the carbohydrate high and avoid the baneful effect of a low-carbohydrate diet. Aside from the possibility of the development of acidosis, which is slight, there is the possibility of giving the patient less carbohydrate than his real tolerance would allow and thus his tolerance will fall through disuse.

Upon the second day of being sugar-free or nearly so, as shown by the trend of the analyses of the urine for different periods, the diet is changed to a Maintenance Diet with similar quantity of carbohydrate, but protein and fat appropriate to the age, weight, and occupation of the patient. Insulin is reduced and, if the urine is

still sugar-free and blood-sugar test favorable, the carbohydrate may be raised by increases of 10 to 25 grams daily to a quantity somewhat below that which shows lack of carbohydrate utilization.

If sugar persists upon the second day, the carbohydrate is dedecreased by choosing a Maintenance Diet such as C_7PF_7, which contains carbohydrate 74 grams, protein 52 grams, and fat 88 grams. Insulin would be raised to units 5–5–5 (5 units three times a day), because most likely the patient received less on his first day in the hospital, as he may have entered after breakfast.

Upon the third day if glycosuria is considerable and calories still below 30 per kilogram body weight, the insulin would be raised to 10–5–5 or 10–5–10 or even 10–10–10 and the fat increased by changing the cream from its value of 120 cc. in the C_7PF_7 diet to 180 cc. or 240 cc., the latter quantity ($\frac{1}{2}$ pint) being convenient and generally obtainable by diabetics.

Upon the fourth day, if sugar-free, protein can be brought to 1 gram per kilogram body weight by seeking a Maintenance Diet with more protein, such as C_7PF_8 in which the meat is raised from 60 to 90 grams. The noon insulin may be omitted. Subsequently fat can be raised by addition of butter, oil, or cream, and the fat value of the latter can be doubled, which is rarely indicated, by changing to cream with 40 per cent fat content.

If glycosuria persists, insulin is usually increased and in addition the diet is changed to C_6, which contains about 60 (actually 64) grams carbohydrate as indicated by its digit, the digits of the grams of carbohydrate in the Maintenance Diet being so arranged as to correspond to the C number of the diet. Rarely the patient is placed upon C_5. If not sugar-free with that or with C_6, it is often an indication that an infection or some such complication as hyperthyroidism is present. Cases of considerable severity may require more insulin 15–15–15, or 25–0–20, even 30–0–15, or 25–10–15–10.

Effort is made by adjustment of diet and insulin to bring the carbohydrate to 100 grams, the protein to 1 to 1.5 grams per kilogram, and the fat sufficient to provide 30 calories per kilogram body weight. He will be a rare diabetic who cannot assimilate such a diet with 45 units of insulin. If such a case is found, the protein can be decreased to $\frac{2}{3}$ gram per kilogram and if necessary insulin raised. I seldom see such a case.

Above a diet represented by C_{10} one should seldom go unless very confident that the patient has an adequate tolerance for carbohydate. The reason for this is that when one reaches 100 grams of carbohydrate in the diet, additions in carbohydrate must consist of foods containing high percentages of carbohydrate, and errors, innocently and easily, may creep into the patient's dietetic regimen. Thus a patient cannot readily eat more than 100 grams of carbo-

hydrate in the form of 5, 10 and 15 per cent vegetables, oatmeal, grapefruit, strawberries, and orange. Above this level his carbohydrate must begin to be taken in the form of a banana, which to be sure is very useful, because a single banana contains about 20 grams of carbohydrate, in potato which is far less easily measured, or in bread which is almost invariably dangerous and therefore does not appear in the diet schedule at all.

If one wishes to get along with less insulin, more undernutrition and a lower quantity of carbohydrate may be employed, as C_6PF_6, C_5PF_5, or even C_4PF_4. Such diets would be temporary or for an occasional day. One shrinks from forcing a patient to draw too much on his body tissue. However, I cannot escape the conviction that the diabetic who is forced to draw upon his own body tissues for protein and fat will involuntarily reduce his demands upon these to a lower figure, than when they are furnished in food. Ladd and Palmer have stated that in their studies endogenous fat was less likely to give rise to acidosis than exogenous fat.

The endeavor to develop to the fullest extent the diabetic's power to utilize carbohydrate is the principle underlying the gradation of the Maintenance Diets. In practice it has been found that if undernutrition was maintained to a greater or lesser extent for a few days the quantity of carbohydrate which could be utilized steadily grew. Diabetics are not so bad as painted. They have far more tolerance for carbohydrate than is often supposed. One must give them a chance to demonstrate what they can do, and unless some such scheme is adopted, it is difficult to find out. To follow the schedule of Test and Maintenance Diets in every case would be absurd because of variations in age, weight, and occupation of the patient. It is a very simple matter, however, to modify these. The only aim of the schedule is to simplify orders for the nurse in the hospital, treatment for the doctor in his practice and at the same time to enable patients to become sugar-free, and to acquire the allotment of carbohydrate which their disease deserves with protein and fat sufficient for maintenance.

Weighing the food is almost easier than approximating it in the treatment of a diabetic and demands almost less intelligence on the patient's part. However, occasionally it is desirable to use food equivalents. Those necessary for the utilization of the Test and Maintenance Diets are given below.

Every once in a while I see a patient who has been in the Out-Patient Department of the Massachusetts General Hospital and have been impressed by the excellence of the scheme there adopted in the treatment of poor diabetics. The method which they employ with many patients is not based upon weights but largely upon portions, tablespoonfuls, and with it they secure excellent results.

1. **Reappearance of Glycosuria.**—Glycosuria frequently disappears while the diet is being increased. For this reason it is often well to disregard a few tenths of sugar in the urine when the patient is upon a low maintenance diet, because this will very likely vanish as the diet progresses. This is readily explained first because the increased diet is still one of undernutrition and second because the patient is regaining tolerance for carbohydrate.

TABLE 211.—FOOD EQUIVALENTS NECESSARY FOR TEST AND MAINTENANCE DIETS.

Food.	Weight, gms.	C.	P.	F.	Approximate equivalent.
5 per cent vegetables (3 to 5 per cent)	300	10	5	0	Three moderate portions
Orange	300	30	0	0	Three small oranges
Oatmeal, dry weight	30	20	5	2	One large saucerful
Potato	240	48	8	0	Two medium sized potatoes
Cream	30	1	1	6	Two tablespoonfuls
Bacon	30	0	5	15	Four crisp strips
Butter	30	0	0	25	Three medium portions
Meat	90	0	24	15	One moderate portion
Bread	25	15	2.5	0	$3 \times 2\frac{1}{2} \times \frac{3}{4}$ inches.[1]

[1] The patient may be given a block of this size, metric equivalents 7.6 x 6.3 x 1.9 centimeters.

Elderly patients with arteriosclerosis, particularly those with gangrene, often show this feature in a striking fashion. With the elderly the reaction to a change in diet takes place far more slowly than with the young. Perhaps this is a protective mechanism, because when the sugar is readily reduced in an elderly person serious symptoms may occur such, for example, as the hypoglycemia reported with Case No. 2716 on p. 218. How serious this is for the heart we shall have occasion to comment upon later.

The second alternative, namely, an increase in tolerance during treatment, is more important and especially so with cases who are receiving insulin. Case No. 2962 gained tolerance after discharge and an insulin reaction thereupon developed. This is the reason why so much caution should be taken to secure a test of the blood sugar in the late forenoon within one or two days before the discharge of the patient. Such a test usually gives the lowest value for the twenty-four hours in patients taking insulin.

The return of glycosuria in the course of treatment demands action. If the patient is upon Maintenance Diets, the simplest plan is to recede by a day when the restriction of carbohydrate and of calories may immediately clear the urine. If this is not successful still further recession may be tried. However, since

TABLE 212.—THE SIMPLICITY OF THE TREATMENT OF DIABETES WITH TEST AND MAINTENANCE DIETS.

CASE NO. 3323, WOMAN, AGED 52.1 YEARS, DURATION 4.7 YEARS.

Day.	Wgt. lbs. net.	Urine.		Blood sugar, per cent.	Diet.				Diet orders.	Insulin units.
		Diacetic.	Sugar, per cent.		C. gr.	P. gr.	F. gr.	Cal.		
1923										
Aug. 21	117½	++++	9.1	....	33	13	15	319	T.D. 1	0–0–1
" 22	118¼	+++	4.0	0.30	101	35	43	931	T.D. 1	2–4–5
" 23	118	0	0.2	....	66	24	37	693	T.D. 2	5–6–7
" 24	119½	0	0.3	....	44	39	81	1061	C 4 PF6 20% Cr. 120	8–9–10
" 25	120	0	0	....	48	43	105	1309	C 4 PF6 20% Cr. 240	10–10–10
" 26	120	0	0	....	58	54	124	1564	C 5 PF7 20% Cr. 240	10–10–10
" 27	120	0	0	0.23	58	54	137	1681	ditto	10–10–10
" 28	119¾	0	0	....	58	54	137	1681	ditto	10–10–10
" 29	120¾	0	0	....	58	54	137	1681	ditto	10–10–10
" 30	121½	0	0	....	58	51	98	1381	ditto	10–10–10
" 31	121½	0	0	....	58	53	136	1668	ditto	15–0–10
1926										
Mar. 31	132	0	0	....	78	60	130	1722	.....	10–0–5

CASE NO. 3324, BOY, AGED 12.6 YEARS, DURATION THREE WEEKS.

HEIGHT AUGUST 1923, 61 INCHES; MAY 1925, 62 INCHES.

1923										
Aug. 23	76¼	++	9.0	....	63	23	31	623	T.D. 1	0–1–2
" 24	75¾	+	2.0	0.21	66	24	37	693	T.D. 2	3–4–5
" 25	76¾	0	0.1	....	64	46	82	1178	C 6 PF6	5–5–5
" 26	78¼	0	0.1	....	73	44	83	1219	C 7 PF6	5–5–5
" 27	79	0	0	....	84	45	84	1272	C 8 PF6	8–0–7
" 28	79½	0	0	0.10	96	47	84	1328	C 9 PF6	8–0–7
" 29	79½	0	0	....	106	47	84	1368	C10 PF6	8–0–7
" 30	80½	0	0	....	107	54	89	1445	C10 PF7	8–0–7
" 31	80¾	0	0	....	119	55	89	1497	C10½ PF7	8–0–7
Sept. 1	81¼	0	0	....	131	60	89	1565	C11 PF7	8–0–7
" 2	79½	0	0	....	131	58	89	1557	C11 PF7	8–0–7
" 3	80¾	0	0	....	131	58	89	1557	C11 PF7	8–0–7
1924										
Aug. 25	81	0	0.1	0.11	68	64	130	1698		5–0–5
1926										
Oct.	105	.....	...	...	100	...	...	....	.....	12–0–12

the introduction of single specimen days, that is, the testing of each specimen of urine throughout the twenty-four hours, it frequently comes to light that the reason for the appearance of the sugar was simply due to the unbalanced diet. Correcting this by shifting the carbohydrate from the offending meal to another often solves the difficulty. In general less carbohydrate should be given

at breakfast than at the other two meals even if the largest dose of insulin is before breakfast. Perhaps the patient should take insulin fifteen to thirty minutes earlier before a meal; perhaps it should be given in a fresh place; perhaps he requires more exercise or there may be an infection or an error in diet. The adjustment is made as indicated when insulin is employed along with the diet as shown in Table 212.

The return of sugar demands fasting whenever there is the slightest suspicion that the diet has been broken by design. This was the rule when the treatment by fasting was first adopted. It is a pity now that it is not as strictly enforced, and I confess I seldom enforce it, but it works so advantageously that it should be done. With children confiement to bed for a few hours with a low diet works wonders. In hospitals it simplifies the treatment enormously. So soon as it is understood that the reappearance of sugar means a fast until glycosuria disappears from the twenty-four-hour quantity of urine, there is little tendency to break over the diet. Furthermore, most patients are thrifty enough to see the disadvantage of paying their board with no return. The rule must be rigidly enforced with children, because with them disobedience means death.

2. **Determination of Tolerance for Protein.**—Protein to the extent of 1 gram per kilogram body weight is borne by nearly all patients and I am very loath to allow the protein to remain permanently below this figure save in the elderly and those with impaired kidneys. By further restricting the carbohydrate either temporarily or permanently this can usually be avoided. It is always necessary to bear in mind that one food which the diabetic patient cannot do without is protein and to it everything else must be subordinate. Body protein must be spared. Newburgh and Marsh emphasized the importance of fat in this regard. (See p. 603.)

3. **The Caloric Needs of the Patient.**—The number of calories which a diabetic requires varies not only with each case, but varies with each case each day. Schematic rules do not hold. This will be seen in Table 190, in which the great variation in the basal metabolism of diabetics is shown. There it will be found that the average caloric needs were essentially the same as for a large group of normal men and women, about 25 calories per kilogram body weight reckoned per twenty-four hours.[1] Great variations in caloric requirements are also shown in this table since they vary from 19 calories to 41 calories per kilogram body weight. If this variation exists while at rest, how much

[1] The error should not be made of concluding that an energy loss of 25 calories per kilogram body weight in the fasting state can be replaced by a diet with the corresponding number of calories. In reality a considerably greater number of calories would be required, due to the specific dynamic action of the food ingested.

more it must exist during the various activities of different individuals! Furthermore, one must remember that the number of calories consumed per hour varies enormously. During sleep, Benedict's fasting man burned 1 calorie per kilogram body weight per hour the day before the beginning of the experiment, while during the daytime and awake although still at rest, the number of calories rose to 1.05. During the fast while asleep the metabolism on the same basis dropped to 0.85 calorie, and when awake to 0.95 calorie. In the previous section it has been pointed out that an individual weighing 60 kilos walking at the rate of 2 miles per hour would require twice and at 4 miles an hour thrice the calories of the standing metabolism which in turn is 12 per cent more than in the horizontal position. Habits of individuals vary widely. Some are quiet and some are active. All these considerations should be clearly borne in mind by doctors and patients in order not to allow themselves to be held too rigidly by any caloric fetish. Patients coming for treatment with severe acidosis consume from 10 to 20 per cent more calories per kilogram body weight than patients after they have become sugar- and acid-free. How low the caloric requirements go is well illustrated by Case No. 1085 (see p. 216) and by Case No. 866 (see p. 63). The basal metabolism of a fat inactive woman of 220 pounds is but slightly greater than that of an alert individual weighing half as much.

TABLE 213.—TABULATION OF DIABETIC DIET OF A MAN, AGED FIFTY-TWO YEARS, FOR FIFTEEN MONTHS (CASE NO. 2207). (See p. 574.)

Date.	Carbohydrate.	Protein.	Fat.	Calories.	Remarks.
Oct. 14, 1921	126.45	95.69	124.99	2,015	Living in country; some golf.
Nov. 15, 1921	155.90	86.73	115.55	2,010	Living in country; some golf.
Dec. 14, 1921	121.01	66.59	137.50	1,988	Living in country; some exercise.
Jan. 18, 1922	135.03	75.16	118.50	1,908	Living in country; some exercise.
Feb. 19, 1922	119.78	107.36	116.16	1,953	Living in country; some exercise.
Mar. 14, 1922	109.81	68.47	87.83	1,502*	At Atlantic City; some exercise.
April 16, 1922	104.16	90.16	125.33	1,907	Living in country; some golf.
May 15, 1922	125.20	100.03	123.83	2,015	Living in country; some golf daily.
June 16, 1922	116.54	61.45*	121.49	1,805	Living at seashore cottage; no golf.
July 24, 1922	98.28	101.61	138.33	2,044	Living in country; golf daily.
Aug. 15, 1922	143.50	114.33	144.00	2,327	Motoring and playing some golf.
Sept. 16, 1922	113.48	110.66	133.00	2,091	Living in country; golf daily.
Oct. 15, 1922	106.80	109.30	106.16	1,819	Living in country; some golf.
Nov. 14, 1922	76.08*	73.66	113.83	1,623	Living in N. Y. City; no golf; very little exercise.
Dec. 14, 1922	103.58	86.33	93.99*	1,569	Living in N. Y. City; no golf very little exercise.
Averages	117.00	90.00	120.00	1,905	

* Sugar-free throughout whole period. Weight from 155 to 160 pounds, naked.

The caloric requirements of patients over long periods of time were determined with unusual accuracy in 2 cases. The first was Mrs. P., Case No. 1541, who had suffered a hemiplegia. She was constantly under the strict supervision of one of my nurses trained in diabetes. Obviously, in this patient exercise was greatly curtailed and during one year she maintained her weight while living on a diet computed to be 20 calories per kilogram body weight.

Another patient, Case No. 2207, aged fifty-two years, submitted to me Table 213 on page 573. The weight of this patient varied from 155 to 160 pounds, 70 to 73 kilograms. His average daily diet amounted to 27 calories per kilogram body weight, the maximum being 32 calories per kilogram body weight and the minimum 21 calories per kilogram body weight.

4. **The Management of Mild Cases of Diabetes.**—The mild case of diabetes is the case which demands the most energetic treatment, but hitherto has received the least. These cases are analogous to the cases of incipient tuberculosis. As in tuberculosis, a "cure" may not be effected, but the disease is held in check. Emphasis should be placed on freedom from glycosuria. Naunyn's dictum that "many a severe case was originally mild, but neglected," should not be forgotten.

These patients should be taught to take long vacations, secure an abundance of sleep, avoid excess in mental and physical labor, shun obesity, and provide for daily exercise. It is best to be frank with such patients, and warn them of the danger of neglecting treatment.

The diet of such patients is not a great hardship though often it is resented more than a closely limited diet by the severe diabetic. With these individuals it is hard to have patience.

Formerly the reduction of carbohydrate to 100 grams would often suffice to stop the glycosuria. In our enthusiasm for new methods it should not be forgotten that even in the past good results were obtained with the majority of diabetics, and that gradual restriction of carbohydrate was the means employed. Incidentally, this is good proof that most diabetics are not severe. The simple omission of butter, cream, or both for a time, will lead to a great reduction in the sugar excreted, which will also be favored if the protein is limited to between 1 gram and 1½ grams per kilogram body weight. Combined with the above the exclusion of actual sugar from the dietary and the substitution of potato (20 per cent carbohydrate) for bread (60 per cent carbohydrate) will frequently secure a sugar-free urine. It is onerous for a patient to eat 100 grams of starch in the form of potato, but enjoyable to consume it as bread. This method of treatment is very successful with my good-natured and usually obedient, fat doctor-patients.

The milder cases of diabetes in a few weeks attain a tolerance of more than 100 grams carbohydrate. Such cases should limit the quantity of carbohydrate in their diet for years, even though no signs of sugar appear. It is interesting to note that many of these patients like Case No. 1287, feel better and have less digestive trouble if the quantity of carbohydrate is held at about 125 grams to 150 grams even though they tolerate more. Such individuals live apparently in perfect health, and there is always satisfaction in the belief, and I think justification for it, that treatment has prevented the progress of the disease. Mention of these cases is made in the discussion of the Cases of Twenty-five or More Years' Duration, p. 897.

5. **The Management of Severe Cases of Diabetes.**—It would be wrong to give the impression that the treatment of diabetes is free from anxiety. It is both simpler and yet more complicated: simpler because the laws of diet and insulin are better understood; more complicated because of the dangers of hypoglycemia from too much insulin and exercise or too little carbohydrate, or because of approaching coma due to too little insulin. These children, charming though they be, and the adults whose cardiac incompetence is always in the background, still cause worry to the physician and even more than heretofore, because if death ensues it is so often unnecessary. The physician who treats severe diabetes successfully must constantly be in as close touch with his patient as any family doctor. Indeed diabetes is developing new opportunities for the latter.

The severe diabetic requires hospital care. The chances are that he is not a severe diabetic and the hospital is the place in which to find out. All kinds of infections, acute and chronic, must be eliminated, the element of hyperthyroidism must be excluded and cancer of the pancreas or elsewhere and pancreatitis as well. Exercise may have been neglected, mistakes with insulin may have been made, and joy returns when the 80 units previously injected in one spot are reduced in a week to 43 units injected into several spots and carbohydrate 15 grams added to the diet. The patient must demonstrate the trust placed in him. Be slow to acknowledge a diabetic severe and never rest content with this classification.

Having planned what seems to be an ideal diet and insulin dosage, do not take the case too seriously but keep the patient upon it for a few weeks and then ask him to return for a still shorter period of observation. Both you and he may make discoveries in the meantime.

What is the ideal diet for a severe diabetic adult? Calories sufficient to maintain weight within 10 per cent of normal, not less than protein $\frac{2}{3}$ gram per kilogram body weight, and 50 grams of carbohydrate. (Indeed I have no diabetic today taking only 50 grams.)

The carbohydrate would be given largely in vegetables, fruit, and cream, perhaps a little oatmeal. Jonas has demonstrated the advantage of foods with low percentage of carbohydrate. The breakfast would contain one-fourth of the carbohydrate and the balance would be divided between noon and night. Additional tolerance can be obtained by giving to these patients so-called "activating" carbohydrate meals. Two or 3 grams of carbohydrate may be given an hour before breakfast and twice as much in the late forenoon and perhaps upon retiring. The stimulus of a little carbohydrate to the utilization of a larger quantity of carbohydrate in a subsequent meal is definite. The possibility of good effects from these "activating" carbohydrate meals came to my attention through the work of Benedict and Osterberg.[1] H. Gray[2] proved its efficacy with several of my patients. Case No. 1542 relied upon such expedients to hold out during the nine months before insulin arrived. The question, however, has attracted attention for years and the literature has recently been summarized by Odin.[3] Bang[4] with animals, Staub[5] and Traugott[6] with human beings, have shown that a carbohydrate-free diet lowers tolerance for carbohydrate. Kageura[7] reached the same conclusion from experiments on animals and men and so did Malmros,[8] Stenstrom,[9] Aldersberg and Porges,[10] and Odin. As Stäubli[11] brought out long ago, too great importance must not be attached to a slight hyperglycemia. It may soon vanish; it does not always indicate a further reduction in carbohydrate. With Odin, however, one can agree that the first rule of medicine is to spare a diseased function, but after time has been allowed for its recuperation, the function should be stimulated to exert its power.

In practice the interpolation of a single fast day often rid the patient of sugar and prior to the introduction of insulin not one, but several were employed. For my patients a day without food accomplished at that time what nothing hitherto had done, though fortunately now it is rendered unnecessary, thanks to insulin. The introduction of fasting in the routine of dietetic treatment has been of inestimable value in prolonging the lives of several children so

[1] Benedict and Osterberg: Jour. Biol. Chem., 1918, **34**, 217.
[2] Gray: Boston Med. and Surg. Jour., 1922, **186**, 763.
[3] Odin: Acta Med. Scand., 1927, Supp. 18, p. 388.
[4] Bang: Biochem. Ztschr., 1913, **92**, 344.
[5] Staub: Ztschr. f. klin. Med., 1921, **91**, 44; 1922, **93**, 89.
[6] Traugott: Klin. Wchnschr., 1922, **1**, 892; Ztschr. f. exp. klin. Med., 1923, **94**, 282.
[7] Kageura: Jour. Biochem., 1922, **1**, 333; also ibid., 1923, **2**, 341.
[8] Malmros: Acta med. Scand., 1925, **62**, 294; Tagung d. Norddeutschen Gesell. f. inn. Med., Lund, 1926.
[9] Stenstrom: Ibid.
[10] Aldersberg and Porges: Klin. Wchnschr., 1926, **5**, 1451, 1508.
[11] Stäubli: Deutsch. Arch. f. klin. Med., 1908, **93**, 107.

that they preserved for years the spark of life. The children who were fed for comfort died. The children who were kept sugar-free with painstaking adherence to the principles of undernutrition are here today. I do not want to forget the advantages which have accrued to the severest of my patients as a result of an occasional day without food. It would appear that a little carbohydrate stimulated the islands of Langerhans to increased secretion. This is important and confirms me in the desirability of giving diabetics the carbohydrate which they can utilize rather than arbitrarily condemning them for life to a carbohydrate which is far, far below their original capacity to burn. It is not yet possible to say that if the carbohydrate is radically restricted for weeks, months, or years to a point below what can be burned, the ability to burn carbohydrate will also permanently fall. The usefulness of activating carbohydrate meals, therefore, may be of a more general importance than in the immediate effects produced.

The carbohydrate ration of a severe diabetic without insulin is what he can tolerate, but the protein ration can be more definitely predicated. It should not fall below $\frac{2}{3}$ gram per kilogram body weight, or should it rise above 1 gram per kilogram body weight. Only by restricting the protein to this minimum was it possible to supply the diabetic with the maximum calories in the form of fat without the production of acidosis. If the severe diabetic was not sugar-free with maintenance calories distributed between carbohydrate, protein, and fat, the only recourse for him was to undergo undernutrition to such an extent that his metabolism was reduced to such a level that a smaller quantity of carbohydrate, protein and fat would hold him in equilibrium.

What is the ideal amount of insulin for a severe diabetic adult? Enough to make him a happy and useful member of society. Few need over 50 units, and I do not think there are 10 patients among my 2000, more or less, using insulin who are taking 60 units. Additional units give far less return in carbohydrate assimilated. As a rule adjustment of insulin and diet will allow any patients, no matter how severe, to take 100 grams carbohydrate. Obviously these remarks do not apply to patients with infections. Even at the height of his mastoid infection, with 85 units of insulin, Stanley L., Case No. 2680, aged 13.1 years, with diabetes of 6.5 years duration, maintained a normal blood-fat, a blood sugar varying between 0.07 and 0.48 per cent in twenty-four hours, with carbohydrate 64 grams, but his urine contained 50 grams sugar. Yet the surgeon said he had never before had a patient, either diabetic or non-diabetic, show as great reparative power. (See p. 712.)

Miss M., Case No. 1542, my first insulin case and then considered my severest diabetic, age 37.1 years at onset in July, 1917, on August

7, 1922, had a tolerance for carbohydrate 7 grams, protein 29 grams, fat 83 grams. She has long been at work. Her original weight fell from 155 pounds to 69 pounds, but in November, 1927, was 143 pounds, to my regret. Catamenia, absent for six years, has returned. She is not often sugar-free. Her diet is 56 grams carbohydrate, the insulin 45 units in, March 1928.

It is not so much the quantity of insulin as it is the intelligence with which it is given. Less is required with good manipulation of the syringe, with variation of the site of injection, with several rather than a single dose, with distribution of the dosage and frequency according to the time of day the blood sugar is highest. For these severe cases before breakfast and the evening meal and upon retiring are the choice. Jonas[1] has shown a noon dose is theoretically avoidable, and I have usually found this true. The distribution of quantity of carbohydrate to dose is not as necessary as one would imagine.

Severe cases of diabetes cause the most worry at the beginning of treatment. An infection, a gastro-intestinal upset, a careless alteration of diet, anxiety, excitement, overexertion, a mild intercurrent disease, may favor the outbreak of coma.

For these severe cases a trained diabetic nurse permanently in charge of the patient is of the greatest assistance to the patient and family. Any diabetic who can afford the luxury of a diabetic nurse is fortunate. It is the best insurance he can take out for his life. Several of my diabetic cases consult me but twice a year because they depend upon their nurses. If a nurse is not available, success in treatment depends upon the thorough education of the patient. The wise live long; the ignorant succumb early.

Case No. 632 has faithfully carried out treatment for ten years and his course is an encouragement to all. In fact most of the first severe cases treated with insulin both in this and other clinics, have been "pedigreed" diabetics, who by their own tenacity have kept life in the body. I have never seen a diabetic patient do well who had wholly given up diet. The family, the friends, the patient, and the doctor will all get along more comfortably if the diet throughout the whole course of the disease is kept at a point where sugar remains absent from the urine. The very exceptional diabetic may live for years despite glycosuria and hyperglycemia. Such evidence is disturbing to the conscientious patient and doctor, but it occurs so rarely that it should not alter the rule of adherence to orthodox treatment which on the average yields the best results.

Labbé[2] and Høst[3] each report good results in series of cases treated

[1] Jonas: Arch. Int. Med., 1925, **35**, 289.
[2] Labbé: Annal. de Med., 1927, **22**, 121.
[3] Høst: Norsk Mag. f. Lægevidensk., 1927, **88**, 561.

with insulin over a long period. The diabetic remains vulnerable, particularly to infections. Certain cases lead Labbé to hope for cure through functional regeneration.

6. **Utilization of Exercise in Treatment.**—The effect of exercise upon the utilization of carbohydrate has excited interest for many years. Von Noorden[1] referring to this subject, writes: "Wide individual differences exist with regard to this matter. It is found that some patients can tolerate much more carbohydrate when taking plenty of exercise; with others this is not the case, muscular work doing them more harm than good." Miss H. B. McKay was the first nurse to write me that she regulated her patient's insulin by the exercise he intended to take. The patient, Case No. 2419, developed diabetes at the age of 14.6 years, in 1920. He is in good health, height 72¾ inches, weight 139 pounds, and at work January, 1928. His diet is carbohydrate 90 grams, protein 75 grams, fat 130 grams, insulin 50 units. Last summer she wrote: "I have to vary his insulin according to the exercise he gets. When he does not have a chance to play golf, he takes 30 units, 16 in the morning and 14 in the afternoon, but when he has a chance to play golf, 14 in the morning and 10 in the afternoon keep him sugar-free."

Lawrence[2] found the effect of exercise in increasing the action of insulin was greatest at the maximum period of insulin activity. This is why exercise plus insulin so frequently cause insulin reactions and particularly do so if the next meal is postponed.

Exercise out of bed and in bed is essential for the diabetic. His muscles live on sugar and help him utilize it. Our hospital cases suffer from lack of exercise, and at the Deaconess a gymnasium is being made ready for them and will supplement our School Room, Dentist's Office, and "Beauty Parlor for Diabetic Feet" in their care. Insulin reactions as a result of exercise attest its worth in lowering the blood sugar. Lack of exercise in hospitals often makes a diabetic appear worse than he really is and, counting on the aid of exercise in the patient's home, I often discharge him, even with glycosuria, at a time which to many might seem premature. The disarrangement of a patient's routine when transferred to a hospital often makes it extremely difficult to determine his true state. Even before insulin the value of exercise was appreciated. Case No. 352, Major W., wrote: "First, it is very hard to start the exercise, and the less one feels inclined to start the more one needs it. Second, it is neither necessary nor desirable that it should be violent. I found a quiet ride of an hour, walking or jogging after taking something on the stomach, started up my old metabolism for the whole

[1] Von Noorden: Diabetes Mellitus, E. B. Treat, 1905, p. 177.
[2] Lawrence: Brit. Med. Jour., 1926, i, 648.

day. If I rode hard I got tired out." Various patients on mountain hikes have tolerated unusual quantities of carbohydrate.

The following clinical observations are of interest: Case No. 112, a doctor and a good observer, noticed that the quantity of sugar in the urine always decreased while on hard camping trips in Maine, although the diet contained the same, or probably more, carbohydrate than when he was at home. Case No. 22, a Harvard professor, said to me in 1901 that "mental work makes sugar, manual work burns it up." Case No. 511, shows sugar when hard at work in the city, but when quite as occupied with mental work in the country, but with more exercise and a similar diet, shows no sugar. I recall instances of diabetics who were able to carry on severe muscular labor, although the diabetes was of extreme severity. One striking case of this type was a railroad inspector who traversed several times a day alone in a handcar many miles of railway, and yet maintained fair health, much to the astonishment of his physician and myself. I was always impressed in former days of treatment by the better results frequently obtained by ambulatory as compared with the hospital treatment at that time, provided the same degree of attention was given to the details of the diet and hygiene of the patient.

These practical demonstrations, I confess, do not conform to the experiments of Richardson and Levine[1] who found that the respiratory quotient of the exercising diabetic is depressed below the basal level unless we assume that these patients had too little a storage of carbohydrate available or were unable to manufacture a sufficient quantity out of fat.

Allen[2] has found that diabetic dogs with a known constant limit for tolerance of carbohydrate or protein upon vigorous exercise in a treadmill showed a marked increase in tolerance, as demonstrated both by the sugar in the urine and in the blood. He further says that dogs which have for months regularly shown glycosuria whenever they were given 100 grams of bread, on exercise became able to take 200 grams of bread as a regular daily ration with glycosuria. It is astonishing how much exercise a diabetic in training can take. One of my severe cases living on a strict diet several years ago walked between 20 and 30 miles in one day. H. H., Case No. 1889, while taking insulin walked 10 miles a day and occasionally thereby accelerated an hypoglycemic reaction. Since taking insulin Case No. 632 has raised his standard of muscular efficiency from 71 per cent up to 89 per cent according to measurements of R. Fitz. The fact that undernutrition lowers muscular strength, and, when injudiciously employed as it was at first, allowed

[1] Richardson and Levine: Jour. Biol. Chem., 1925, **66**, 161.
[2] Allen: Boston Med. and Surg. Jour., 1915, **173**, 743.

the patients to fall greatly below par must have seriously handicapped the good results it would otherwise have produced. This lack of physical fitness was brought out by Root and Miles.[1] I have never forgotten the remark of Dr. Sabine, of Brookline, that in the course of his long practice he had observed that those of his patients who had taken active camping trips in the woods bore the stress of modern life best. By this means exercise was combined with mental relaxation. That the good effects of each last for months is not hard to believe. It is only natural to conclude that if the muscles, in which is stored one-half of the carbohydrate of the body, are kept in good condition by training, a favorable effect must be exercised upon the general metabolism of carbohydrate. The man who, in middle life, gives up hard physical work and is promoted to an office chair with increased mental worry is exposed to diabetes. It is not uncommon to hear of diabetes developing soon after exercise is omitted, but I do not remember to have heard of it developing just after exercise was begun.

C. SUMMARIES OF THE TREATMENT EMPLOYED IN FIVE SUCCESSIVE GROUPS OF CASES.

The treatment of diabetes is changing so rapidly that it is difficult to grasp its essential features from a study of individual cases. Consequently, in the following tables are summarized the treatment of five groups of cases of diabetes, each consisting of 30 cases seen in chronological periods between 1915 and 1927. The composition of the diet during the first and last weeks of hospital stay is given and for comparison is calculated per kilogram body weight. The duration of the disease to death or of the living cases to July 1, 1927, shows the results obtained. Finally, the type of preliminary treatment is indicated, *i. e.*, whether it commenced with fasting or with diminution of fat and protein and possibly followed by a fast, though actual fasting was not often used, or whether it was started with test diets together with insulin, as shown first in 1923 and again in 1927.

In the last three columns the question of acidosis is considered. In the early cases but few were without it, either developing it in the hospital or entering with it. In the fourth and fifth groups acidosis ceased to be a factor because of insulin. With design the cases of coma are not included in the summary.

The criteria for the selection of cases in the table for the first *four* groups were: (1) That the patients should have been over fifteen years of age; and (2) that they remained at least two weeks in the hospital. In the fifth group the patient's stay was shorter and

[1] Root and Miles: Jour. Metab. Res., 1922, **2**, 173.

TABLE 214.—THE TREATMENT OF THIRTY CASES OF DIABETES BETWEEN APRIL 6, 1915 AND MARCH 18, 1916.

Case No.	Age at onset, yrs.	Days in hospital	Weight in kilograms.		Average daily diet in hospital in grams.												Duration in years to July, 1927, or to death.	Fasting.	Treatment begun with exclusion of fat, preparatory treatment.	Acidosis.		
					First week.						Last week.									Present.		Absent during hospital stay.
			Entrance.	Exit.	Carbohydrate.	Protein.	Fat.	Alcohol.	Calories. Total.	Calories. Per kilo.	Carbohydrate.	Protein.	Fat.	Alcohol.	Calories. Total.	Calories. Per kilo.				Developed after entrance.	Decreased after entrance.	
263	34	17	62	59	6	16	16	12	326	5.0	9	28	49	5	762	12	14.8	+	..	+		
877	50	25	77	?	31	48	80	0	1037	13.0	53	51	89	0	1217	?	11.0	..	+	..		+
902	36	23	59	57	16	3	3	0	0	0.0	9	35	45	0	420	7	4.1	..	+	..	+	
908	20	20	43	45	12	7	7	0	66	2.0	36	41	69	0	725	15	10.2	..	+	..	+	
181[1]	44	63	50	49	12	0	0	5	8	0.2	2	46	38	10	591	12	11.3	..	+	..	+	
912	40	15	60	57	35	22	18	0	389	6.0	43	49	49	0	778	14	....[3]	..	+	..		
919	47	25	53	50	28	5	2	3	164	3.0	2	44	59	2	722	14	21.0	..	+	..		+
552[1]	29	34	43	39	5	4	2	13	193	4.0	25	52	61	0	740	19	10.5	..	+	..	+	+
935	46	27	53	48	12	16	4	0	148	3.0	17	27	38	0	516	11	3.7	+	..	+		
955	47	27	84	70	21	30	23	0	409	5.0	67	76	93	0	1384	20	14.4	..	+	..	+	
953	18	19	74	76	10	20	9	0	188	3.0	27	67	60	0	973	13	7.0	+	..	..	+	
958[2]	30	21	44	43	7	11	5	0	105	2.0	28	55	58	0	857	20	11.7	+	..	..	+	
960[2]	51	48	74	68	19	27	9	0	251	3.0	17	49	115	0	1191	18	22.5	..	+	+		
965[2]	46	36	90	85	6	14	7	0	161	2.0	43	96	115	2	1592	19	14.9	+	..	+		
966[1]	39	24	53	55	28	1	0	0	112	2.0	5	54	79	0	971	18	1.0	..	+	..	+	
969	42	23	52	55	15	30	18	0	338	7.0	20	57	80	0	1026	19	8.2	+	..	..		+
560[1]	66	34	75	69	19	31	11	1	264	4.0	43	67	98	0	1317	19	5.6	..	+	+		
684[1]	55	34	44	45	6	6	2	11	148	3.0	19	28	31	0	467	10	10.6	+	..	..	+	
765[1]	22	30	40	37	13	9	3	0	118	3.0	0	45	69	0	795	22	2.3	+	..	..	+	
970[2]	59	16	92	89	14	28	14	0	281	3.0	41	65	107	0	1322	15	11.6	+	..	..	..	+
983[2]	55	25	90	87	39	14	3	0	146	2.0	40	75	55	0	971	11	11.6	..	+	..	+	
821[1]	23	36	54	48	4	11	5	0	108	2.0	1	70	97	0	1157	24	2.4	+	..	..	+	
996[1]	62	27	48	47	19	26	13	0	310	6.0	3	44	77	0	876	19	1.8	..	+	..	+	
981	28	20	43	41	11	21	12	0	236	5.0	32	48	92	0	1150	28	2.8	+	..	+		
994[2]	15	19	60	57	41	41	35	0	639	11.0	80	65	117	0	1617	28	13.4	+	..	+		
1005[1]	31	88	33	33	24	2	0	0	77	2.0	13	67	83	0	1075	33	6.3	..	+	..	+	
1008	41	49	51	49	40	8	1	0	192	4.0	11	50	74	0	921	19	15.0	..	+	..	..	+
1013	46	27	65	63	40	26	12	0	345	5.0	49	54	102	0	1329	21	3.9	..	+	..	..	+
1011	25	69	40	38	4	11	2	0	63	2.0	4	54	61	14	902	24	4.4	..	+	..	+	
1022	53	18	84	83	45	29	20	0	460	5.0	29	70	106	5	1397	17	20.0	..	+	..	..	+

[1] Died within eight months of discharge.

[2] Alive, July, 1927.

[3] Untraced.

TABLE 215.—THE TREATMENT OF THIRTY CASES OF DIABETES BETWEEN MARCH 19, 1916, AND JULY 19, 1916.

Case No.	Age at onset, yrs.	Days in hospital.	Weight in kilograms.		Average daily diet in hospital in grams.												Duration in years to July, 1927, or to death.	Fasting.	Treatment began with exclusion of fat, preparatory treatment.	Acidosis.		
					First week.						Last week.									Present.		Absent during hospital stay.
			Entrance.	Exit.	Carbohydrate.	Protein.	Fat.	Alcohol.	Calories. Total.	Calories. Per kilo.	Carbohydrate.	Protein.	Fat.	Alcohol.	Calories. Total.	Calories. Per kilo.				Developed after entrance.	Decreased after entrance.	
904[1]	40	45	62	57	18	16	6	6	244	4.0	7	38	51	71	1137	20	16.0	..	+	+		
1033	51	20	56	53	49	14	1	0	265	5.0	31	59	33	0	655	12	9.3	..	+	..	..	+
1024	69	41	55	52	28	12	0	10	235	4.0	18	57	92	12	1210	23	10.0	..	+	..	..	++
1028	29	24	59	55	6	18	4	9	198	3.0	38	63	42	8	886	16	2.3	+	..	..	..	
1029	33	17	53	51	0	9	2	11	127	2.0	21	59	74	0	809	16	4.6	+	..	..	+	
1030	64	23	75	71	21	30	12	0	312	4.0	73	69	129	0	1730	24	12.3	..	+	..	..	+
1032[2]	50	20	48	47	14	11	2	0	110	2.0	54	60	61	0	1012	22	21.5	..	+	+		
327	40	16	78	75	18	20	9	0	228	29.0	59	78	84	0	1330	18	9.8	+	..	..	..	+
1025[1]	21	27	43	40	2	1	0	0	13	0.3	8	48	64	0	811	20	1.6	+	..	..	+	
1036	52	21	74	66	21	27	15	0	322	4.0	34	82	110	0	1451	22	6.0	..	+	..	..	+
1038[2]	37	22	78	74	19	17	6	0	191	2.0	73	51	75	0	1177	16	14.0	+	..	+		
1041	59	20	51	52	20	23	7	0	234	5.0	32	61	87	0	1157	22	3.7	+	..	..	+	
1045	56	16	45	44	17	21	10	3	258	6.0	43	52	81	8	1165	27	2.4	+	..	..	..	+
1046	41	22	43	42	14	8	2	0	105	2.0	51	67	76	0	1153	28	2.5	+	..	..	..	+
1050	66	20	68	67	28	31	17	0	387	6.0	72	66	87	0	1120	17	10.3	..	+	..	..	++
1052[2]	57	25	74	72	53	49	34	0	716	10.0	55	64	121	0	1567	22	17.5	..	+	..	..	++
1054[2]	53	19	63	60	24	38	18	0	415	6.0	64	85	85	0	1343	22	11.6	+	..	..	..	++
875	46	20	46	45	41	16	4	0	274	6.0	110	42	102	0	1531	34	4.0	+	..	..	..	++
1066	38	20	32	32	21	11	0	0	129	4.0	29	56	76	0	1019	32	5.8	+	..	..	..	+
1058[1]	39	20	59	57	26	101	2	0	166	3.0	28	51	69	0	937	18	1.1	+	..	+		
1055	41	20	73	67	32	12	0	0	173	2.0	30	42	66	0	879	13	21.0	+	..	..	..	+
1063	71	25	63	61	59	123	2	0	300	5.0	31	78	119	0	1169	19	3.9	..	+	..	..	++
1061[2]	47	19	67	64	26	9	0	0	142	2.0	51	74	118	0	1277	20	15.0	..	+	..	..	++
1065[2]	44	16	98	96	51	30	14	0	447	5.0	85	75	124	0	1753	18	11.5	..	+	..	..	++
786	38	33	49	46	33	15	2	0	216	4.0	37	72	63	0	1004	22	3.4	..	+	..	+	
1079	54	17	59	56	19	17	10	0	230	4.0	71	48	73	0	1137	20	2.1	+	..	..	..	+
942[1]	30	48	40	38	28	7	0	0	140	4.0	8	41	54	0	677	18	1.3	..	+	..	+	
1085[1]	34	121	40	28	29	16	2	0	198	5.0	2	30	27	28	571	20	0.8	..	+	..	+	
1083[1]	54	21	57	55	4	10	5	0	101	2.0	32	67	120	0	1476	27	1.8	+	..	..	..	+
1084[1]	34	18	62	61	21	13	2	0	161	3.0	48	68	100	0	1377	23	3.0	+	..	..	..	+

[1] Died within eight months of discharge.

[2] Alive, July, 1927.

TABLE 216.—THE TREATMENT OF THIRTY CASES OF DIABETES BETWEEN JULY 20, 1916, AND FEBRUARY 2, 1917.

Case No.	Age at onset, yrs.	Days in hospital.	Weight in kilograms.		Average daily diet in hospital in grams.											Duration in years to July, 1927, or to death.	Fasting.	Treatment begun with exclusion of fat, preparatory treatment.	Acidosis.		
					First week.						Last week.								Present.		Absent during hospital stay.
			Entrance.	Exit.	Carbohydrate.	Protein.	Fat.	Alcohol.	Calories. Total.	Calories. Per kilo.	Carbohydrate.	Protein.	Fat.	Alcohol.	Calories. Total.	Calories. Per kilo.				Developed after entrance.	Decreased after entrance.	
1090	18	13	55	53	45	25	11	0	364	7.0	67	55	76	0	1169	22	4.8	..	+	..	..	+
1088	55	34	64	64	63	44	56	0	933	15.0	97	48	82	0	1276	20	8.8	..	+	+	..	
1098[2]	47	13	70	70	55	46	16	0	616	9.0	70	61	76	0	1182	17	18.5	..	+	..	..	+
479	35	29	54	52	38	8	0	0	185	3.0	9	79	112	0	1362	26	7.0	..	+	..	..	
1094	55	35	72	71	26	33	9	0	321	4.0	72	81	141	0	1891	27	7.9	..	+	..	+	+
1034	36	45	51	40	0	7	0	0	27	0.5	24	50	87	0	1078	27	7.0	+	..	..	..	+
1101	51	41	53	54	25	18	3	0	203	4.0	14	66	125	0	1436	26	8.8	..	+	..	+	
1099	51	15	60	60	23	30	11	0	313	5.0	40	71	109	0	1437	24	3.4	..	+	..	+	
1102	21	59	49	45	23	12	1	0	154	3.0	27	47	77	0	993	22	9.0	..	+	..	..	+
1110[2]	61	14	58	57	62	43	24	0	637	11.0	103	69	76	0	1368	24	14.5	..	+	..	..	
1114	27	34	49	50	1	7	0	6	78	2.0	2	68	79	19	1137	23	2.9	+	..	..	+	
1125	34	27	36	37	21	17	9	0	226	6.0	20	50	89	0	1087	29	8.8	+	..	..	+	
1130	21	20	43	41	4	5	7	0	98	2.0	6	36	84	0	922	23	2.4	+	..	..	+	
815	59	16	55	57	15	32	68	0	799	15.0	38	59	159	0	1819	33	4.7	+	..	..	..	+
1131	27	15	54	54	25	23	16	0	342	6.0	91	77	70	0	1303	24	2.6	..	+	..	..	+
1134	24	35	67	64	25	24	16	0	344	5.0	167	92	115	0	2071	32	1.3	..	+	..	..	+
1159	39	43	41	36	14	5	0	0	74	2.0	7	44	45	9	679	19	12.0	..	+	..	..	+
1160	24	34	69	68	26	4	0	0	122	2.0	24	62	69	0	964	14	1.2	..	+	..	..	+
1180	40	20	65	62	11	18	3	0	150	2.0	26	61	95	0	1199	19	19.3	..	+	..	..	+
1157	59	20	54	57	32	44	25	0	535	10.0	32	64	102	4	1332	23	7.0	..	+	..	..	+
1171[2]	59	16	82	80	60	50	18	0	601	7.0	87	83	104	0	1619	20	10.7	..	+	..	..	+
1164	52	26	58	54	26	35	24	0	470	8.0	38	38	75	0	985	18	15.5	..	+	..	..	+
1195	42	34	34	35	20	8	0	0	113	3.0	31	45	76	0	982	28	3.6	..	+	..	+	
1196	39	69	44	44	0	27	29	13	463	11.0	4	65	77	30	1101	25	8.0	+	..	..	+	
1193	49	22	68	66	19	23	10	9	317	5.0	49	61	100	0	1338	20	..[1]	..	+	..	+	
1214	50	27	67	62	15	19	9	0	222	3.0	19	30	52	0	675	11	11.3	..	+	+	..	
1217[2]	48	13	63	62	49	31	26	0	553	9.0	44	53	75	0	1078	17	12.3	..	+	..	..	+
1218	55	30	39	38	16	13	2	0	135	3.0	16	51	85	0	1030	27	2.7	..	+	..	+	
1226	33	28	52	49	27	13	1	0	168	3.0	13	50	90	0	1103	23	1.5	..	+	..	+	
1228[2]	42	27	56	52	49	55	75	2	1108	20.0	55	70	104	15	1544	30	10.9	..	+	..	..	+

[1] Untraced.

[2] Alive, July, 1927

TABLE 217.—THE TREATMENT WITH INSULIN OF THIRTY CASES BETWEEN FEBRUARY AND MAY, 1923.

Case No.	Age at onset, years.	Days in hospital.	Weight in kilograms.		Average daily diet in hospital in grams.						Last week.						Duration in years to July, 1927.	Treatment begun with:	
					First week.													Test diets.	Insulin.
			Entrance.	Exit.	Carbohydrate.	Protein.	Fat.	Calories.		Insulin, average units, daily.	Carbohydrate.	Protein.	Fat.	Calories.		Insulin, average units, daily			
								Total.[1]	Per kilo.					Total.	Per kilo.				
812[2]	31	16	54.0	54.7	97	55	89	1409	26.0	5	107	62	119	1747	32.0	8	12.6	T. D. 2	2
1182[2]	33	23	76.3	75.7	75	46	93	1321	15.5	9	111	74	123	1847	24.0	10	14.0	T. D. 2	2
1579[2]	50	16	89.7	89.7	44	35	61	856	9.5	11	78	72	135	1815	20.5	6	8.0	S. T. D. 2[1]	2
1609[2]	11	15	37.8	38.6	49	32	52	789	21.0	11	48	49	113	1400	36.5	13	10.0	T. D. 3	3
1705[2]	21	19	64.7	61.7	35	20	35	537	8.5	15	77	65	130	1740	28.0	15	7.7	T. D. 2	15
1887	15	26	24.6	26.7	50	32	58	853	34.0	14	51	43	114	1394	24.5	21	8.0	T. D. 2	8
1947	53	28	46.3	45.2	45	28	49	736	16.5	14	58	54	142	1730	38.5	17	3.9	T. D. 3	10
2266	58	19	35.0	36.0	44	32	68	915	11.5	8	48	47	103	1303	36.0	11	5.1	T. D. 3	0
2319[2]	54	20	61.3	62.7	48	56	88	1207	20.0	7	50	57	139	1550	24.5	15	13.0	..	0
2420	51	16	38.3	40.1	50	41	79	1070	28.0	9	78	56	112	1544	39.0	13	4.0	C_3PF_5	2
2448[3]	18	17	44.0	50.7	39	31	73	936	20.0	31	38	43	123	1433	29.0	28	5.6	Acidosis	30
2476[2]	32	36	56.1	57.9	40	39	76	1001	17.5	17	43	60	152	1782	30.5	14	10.3	T. D. 2	2
2588[2]	33	14	33.1	30.0	44	35	71	972	30.0	9	56	46	105	1402	46.0	10	6.2	T. D. 3	1
2793	65	14	67.6	70.6	69	48	96	1333	19.5	12	111	67	131	1894	29.0	9	4.8	C_6PF_6	5
2801	15	277	45.8	43.4	37	21	4	270	6.0	0	49	63	144	1744	40.0	35	1.2	Acidosis	0
2854[2]	42	14	43.8	46.3	64	51	85	1215	27.0	9	88	64	115	1643	36.0	10	7.5	C_8PF_7	3
2955	64	29	45.6	47.8	44	51	101	1289	28.0	9	60	62	151	1847	46.5	14	5.3	C_4PF_7	2
3034	39	26	35.4	36.3	72	44	70	1099	30.5	12	66	54	102	1400	45.0	10	2.3	S. T. D. 1	3
3064[2]	45	16	55.8	53.0	53	40	76	1053	19.0	10	48	50	110	1382	25.5	10	5.2	S. T. D. 2	2
3067[2]	39	18	56.6	58.2	64	34	54	872	15.5	13	48	57	127	1558	27.0	12	5.9	T. D. 1	3
3068	10	18	24.5	25.4	51	31	50	781	31.0	10	65	45	80	1160	45.5	10	1.7	S. T. D. 2	3
3071[2]	50	15	63.9	62.5	56	32	74	1010	63.0	9	68	41	130	1606	63.0	10	7.4	T. D. 2	3
3073	25	16	75.8	76.7	66	57	97	1368	17.5	10	100	81	142	2002	26.0	8	2.2	S. T. D. 2	5
3077[2]	44	14	69.9	70.2	60	45	78	1098	15.5	6	72	64	130	1713	24.5	8	7.1	T. D. 2	2
3086[2]	18	14	60.7	61.1	57	51	93	1266	21.0	11	130	71	131	1985	32.5	10	4.5	S. T. D. 3	5
3092	35	23	39.0	41.8	78	40	63	1033	26.0	5	87	48	108	1515	36.0	10	2.1	C_4PF_5	3
3096[2]	61	26	55.1	56.3	49	38	79	911	16.0	9	68	49	130	1631	29.0	10	6.0	S. T. D. 3	3
3118	44	17	60.8	60.8	49	22	35	603	10.0	9	89	65	118	1675	27.5	12	2.1	T. D. 2	5
3121[2]	26	16	55.3	54.0	39	22	39	593	11.0	13	77	67	108	1549	29.0	15	5.3	T. D. 2	3
3124[2]	38	23	60.2	59.2	27	23	41	563	16.0	0	60	63	134	1699	28.5	10	5.8	..	0

[1] S. T. D signifies Surgical Test Diets. These were similar to the Maintenance Diets which have now replaced them.

[2] Alive, July, 1927

TABLE 218.—THE TREATMENT WITH INSULIN OF 30 CASES IN 1927.

Case No.	Age at onset, years.	Days in hospital.	Weight in kilograms.		Average daily diet in hospital in grams.												Duration in years to July, 1927.	Treatment begun with:	
					First week.						Last week.								
								Calories.						Calories.					
			Entrance.	Exit.	Carbohydrate.	Protein.	Fat.	Total.	Per kilo.	Insulin, average daily dose.	Carbohydrate.	Protein.	Fat.	Total.	Per kilo.	Insulin, average daily dose.		Diet.	Insulin units.
4516	38.0	8	41	40	85	51	97	1420	36	27	88	59	122	1682	42	35	4.8	C^8PF^8	20
4978	16.0	16	64	62	76	54	100	1383	22	40	63	64	104	1426	23	56	3.0	C^8PF^8	35
5181	20.1	10	46	49	89	56	88	1370	30	25	84	55	88	1348	26	43	2.0	C^8PF^8	15
5277	57.4	10	66	67	74	54	87	1295	20	10	89	61	106	1553	23	10	10.4	C^7PF^7	10
5520	27.3	8	67	68	91	75	135	1880	28	20	108	77	135	1955	29	26	3.8	$C^{10}PF^{10}$	20
5582	21.0	9	46	47	88	66	116	1660	36	40	86	66	116	1647	35	43	0.6	C^8PF^8	35
5584	55.9	9	58	59	76	61	100	1446	25	25	101	68	117	1725	29	29	4.5	C^7PF^7	30
5608	46.4	115	..	..	92	47	88	1348	..	35	99	62	111	1643	..	10	11.5	C^9PF^9	35
5629	45.3	76	..	..	93	52	95	1438	..	10	107	55	82	1409	..	15	16.5	C^8PF^8	10
5707	14.1	14	71	70	79	69	120	1451	20	20	98	80	123	1819	26	28	1.6	C^7PF^7	20
5717	53.5	10	48	47	75	51	90	1294	27	26	99	57	99	1412	30	13	3.7	C^6PF^6	45
5740	67.0	7	54	55	74	46	84	1239	23	11	84	55	108	1525	28	20	1.1	C^7PF^7	20
5973	22.9	10	52	50	80	58	111	1583	37	14	108	61	112	1642	33	10	27.0	C^7PF^7	15
5974	44.0	14	95	96	109	78	135	2001	21	5	152	81	135	2147	24	0	10.4	$C^{10}PF^{10}$	0
5985	48.5	7	56	57	92	62	76	1509	27	5	86	67	117	1667	29	15	6.5	C^9PF^9	0
6000	48.4	13	69	..	78	42	75	1039	15	21	78	58	111	1543	..	24	12.5	C^7PF^7	15
6003	53.6	9	57	56	135	67	111	1807	32	16	135	67	111	1807	32	15	3.0	$C^{11}PF^{11}$	25
6013	66.1	11	75	74	88	62	115	1619	27	14	98	68	118	1722	23	15	0.2	C^7PF^7	20
6021	66.7	11	35	39	88	38	63	1065	30	24	95	55	90	1412	36	19	0.8	C^9PF^9	15
6028	57.0	11	78	78	96	52	121	1470	19	15	118	65	121	1818	23	15	2.5	C^9PF^9	15
6030	40.7	15	45	46	60	37	41	758	17	35	76	62	108	1524	33	34	1.5	Acidosis	70
6033	21.3	11	41	45	74	57	89	1341	33	21	81	75	123	1725	39	24	0.1	C^7PF^7	15
6037	53.4	6	65	66	79	53	90	1336	26	15	95	58	101	1521	23	8	15.0	C^7PF^7	15
6042	62.0	9	63	64	87	56	90	1376	22	15	98	59	118	1688	26	14	2.3	C^7PF^7	15
6044	58.7	11	67	64	78	56	101	1442	22	15	98	58	124	1750	27	15	2.5	C^7PF^7	15
6046	68.9	9	61	62	113	60	118	1746	29	15	115	61	124	1820	30	14	5.3	$C^{10}PF^{10}$	15
6050	59.1	12	62	62	91	53	104	1516	25	18	84	45	111	1515	25	20	5.5	C^8PF^8	15
6057	58.3	9	63	64	76	56	102	1449	23	15	78	63	125	1678	27	16	5.2	C^7PF^7	15
6058	20.3	8	53	54	74	61	91	1395	23	25	78	65	112	1576	25	30	0.6	C^7PF^7	15
6105	62.8	8	62	63	83	56	99	1446	23	15	98	58	124	1740	28	11	3.7	C^7PF^7	15

TABLE 219.—SUMMARY OF TABLES 214, 215, 216, 217 AND 218 SHOWING THE TREATMENT OF FIVE GROUPS OF 30 CASES EACH OF DIABETES AT SUCCESSIVE PERIODS.

Group.	Date.	Age at onset, years.	Average number of days in hospital.	Weight in kilograms.			Average daily diet in hospital in grams.												Duration in years to July 1, 1927, or to death.	Treatment begun with:		Acidosis.		
							First week.						Last week.											
											Calories.						Calories.							
				Entrance.	Exit.	Gain or loss.	Carbohydrate.	Protein.	Fat.	Alcohol.	Total.	Per kilo.	Carbohydrate.	Protein.	Fat.	Alcohol.	Total.	Per kilo.		Fasting.	Exclusion of fat. Preparatory treatment.	Present.		Absent during hospital stay
																						Developed after entrance.	Decreased after entrance.	
I.	1915, to 1916	40	33	60	57	−3.07	19	17	11	2	243	4	26	54	75	1	992	18	9.6	12	18	7	15	8
II.	1916	46	23	59	56	−2.87	25	24	6	1	234	4	43	60	82	4	1151	21	7.7	16	14	4	6	20
III.	1916, to 1917	42	28	56	54	−1.60	27	24	16	1	356	6	43	60	90	3	1239	23	7.9	6	24	2	12	16
																				Insulin, average units daily.				
																				First week.	Last week.			
IV.	1923,	37	19[1]	52.6	53.1	+0.50	53	38	67	..	965	21	71	58	123	..	1623	33.5	6.2	10	13			
V.	1927	46	16[2]	59	59.4	+0.4	86	57	98	..	1438	24.4	96	60	113	..	1665	28	5.6	19	21			

[1] Not including No. 2801, who stayed in hospital two hundred and seventy-seven days.
The average duration of hospital stay of 100 cases treated without insulin, just prior to August 7, 1922, was 12 days and of 100 cases treated with insulin, prior to August 7, 1923, was ten days.

[2] Including 2 cases whose average hospital stay was ninety-five days, because of acute infection of hip joint in one instance and chronic cardiac failure in the other. *Excluding* these 2 cases, the average hospital stay was ten days.

instead of a week the periods are for the first four and the last four days. All cases recorded in these tables left the hospital alive except Case No. 904, who died with a carbuncle. It is hoped that the introduction of this method of presenting results of treatment will prove a valuable innovation in our management of diabetes. Undertaken with little conception as to what the average results would be, it showed quite clearly the errors of the past and indicates where the weak places in modern diabetic treatment lie.

1. **Body Weight.**—Weight was lost by all groups save the fourth and fifth, which were treated with insulin. In the first and second groups the losses amounted to 3.07 and 2.87 kilograms, respectively, but it will be noticed in the third group the loss was but 1.6 kilograms per patient. With the fourth and fifth, or insulin groups, the steadily decreasing loss was changed to a slight gain of 0.5 kilogram and 0.4 kilogram, respectively.

During the stay of the first group of patients treated, the loss of weight per day per patient was approximately 100 grams, in the second group 125 grams, and in the third group 57 grams. If this loss of weight should arbitrarily be reckoned in caloric equivalent as described on page 275, allowing 3300 calories for each kilogram lost, it would be equivalent to 10,131, 9471, and 5280 calories respectively. Since the average weight of the patients was 60, 59, and 56 kilograms, this would represent the equivalent of 5.1, 7.5, and 3.3 calories per kilogram body weight per day. Add to these endogenous calories those of exogenous origin ingested and the calories in the four groups are almost identical.

2. **Body Protein.**—Desire to protect body protein by exogenous protein unfortunately failed in preinsulin days. Today all realize this could have been done by fat. In the early group the protein per day per patient for the first week was but 17 grams or less than 0.33 gram per kilogram body weight. During the last week it was 0.9 gram per kilogram body weight. In the two later series the figures change, and in the first week the protein almost reached 0.5 gram per kilogram body weight, and in the last week was fully 1 gram. The insulin cases in the fourth group received 1.1 grams protein per kilogram and in the fifth group 1 gram per kilogram.

3. **Total Calories.**—The gain in calories given the patients in the last week of the third group was distinct. Writing in 1917, my comment was, "At the present time the patients certainly go home in better condition and with lower blood sugars than two years ago. Still the melancholy fact remains that the patients leave the hospital with 23 calories instead of a permanent, self-sustaining diet. A gain in 3 or 4 calories per kilo would mean everything to diabetic patients. The shortage in calories now is in great part due to the weekly 'fasting' day or 'half' day, and the

21 and 23 calories respectively per kilo which the last group of patients daily received on leaving the hospital were chiefly taken by them during six days." Who of us at that time dared to believe that insulin was so near? Looking at the insulin group the metamorphosis of diabetic treatment is apparent. The caloric intake of the diabetic has been raised 64 per cent over that in the first period, 1915, and 31 per cent over that of the third period ending in 1917. Today there is the danger of giving too many calories rather than too few.

4. **Duration of Disease.**—Years enough have elapsed to allow an inventory of the length of the disease in the early groups of patients and a hint as to that in the fourth group. The fifth group simply reflects the patients recently at the hospital, although it errs in excluding the surgical diabetics.

D. FOLLOW-UP METHODS.

Almost any physician can get his diabetic patients sugar-free, but to keep these patients sugar-free and in good health is an art. A doctor's ambition should be not to see how large a number of diabetic patients he can have, but how many he can keep in good condition. The education of the patient is the basis for success along this line, and this must begin at the very start. Upon finding that the mortality among patients was largely due to ignorance the importance of this aspect of treatment became evident. Insulin makes education even more necessary.

Patients must be taught from the first that the preliminary treatment represents only a beginning of treatment; that treatment lasts for life; that whenever sugar or acidosis returns or unusual loss of weight occurs and they are unable to control these phenomena, they must report to a physician. The physician, too, must do everything in his power to keep in touch with his patients at regular intervals. Of course, this is quite difficult because he is laid open to the suspicion of seeking practice; but it is better to run the chance of a misunderstanding on this score in 1 case than to let 10 other cases perish. One of the chief advantages of modern treatment is that it is less costly than former methods, because when once trained, there is less necessity to consult the physician at frequent intervals.

Doctors who have patients temporarily under their care in hospitals owe it to their patients to keep the family physician in touch with the method of treatment employed. Formerly a copy of the chart at the end of the hospital stay was sent to the physician, but this is not sufficient. Weekly reports, made out by the patients themselves are preferable and should be sent home. It is just

as essential, in fact even more so, to educate the doctor as the patient. If a physician sends a diabetic patient to a hospital for treatment, from the reports he receives he should gain enough help to enable him to treat other similar cases at home. A patient with exophthalmic goiter sent to the Mayo Clinic, prior to 1917, led to the receipt of *four* unsolicited reports upon her progress.

The safest plan for a diabetic is to see a doctor once a month or, in lieu of a visit, send a brief report. Patients who follow this rule do the best. It is the patient who does not report who develops coma, and it is the patient whose feet are not examined at each visit who neglects to care for them and develops gangrene. A diabetic seldom shows dirty feet to a doctor twice.

When a diabetic patient shows acidosis he should be seen again by a physician within twenty-four hours, and this holds also when glycosuria is 3 per cent or the blood sugar is 0.30 per cent or above. When the blood sugar is 0.25 to 0.29 per cent, he should report within three days, and when it is 0.20 to 0.24 per cent, within one week.

The urine should be kept sugar-free throughout the day. The aim should be to keep the percentage of sugar in the blood normal before and after meals, but exceptions will arise in cases with infections or hyperthyroidism, or pituitary involvement, and occasionally in nephritis, hypertension, arteriosclerosis, and cancer of the pancreas.

The million diabetics in this country should be looked upon as a trust placed in the doctors' hands for conservation and development. The lives of the diabetics must be preserved, but they must yield dividends of health for all. These patients are under constant supervision. Here is the opportunity for health examinations on a vast scale. What other such select group of adult individuals exists which can demonstrate better the efficacy of preventive medicine, the success of prompt surgical intervention in acute and chronic surgical affections, including cancer, the effect of early diagnosis of tuberculosis and, in fact, all other medical ills which can be thwarted or cured. What a trust! The public and the patients, too, will watch our administration of it with critical eyes.

E. SPECIAL DIETETIC METHODS.

1. **High-carbohydrate Diet.**—The normal diet for an adult with moderate activity consists of carbohydrate 4 to 5 grams, protein 1.25 grams, and fat 1 gram, or a total of 30 to 34 calories per kilogram body weight. A common diet in diabetes is carbohydrate 1 gram, protein 1 gram, and fat 2.5 grams, or 30 calories per kilogram body weight, but I think a better diet would be carbohydrate

1.5 grams, protein 1.25 grams, and fat 2.0 grams, 29 calories per kilogram body weight.

The radical modification of the diet which diabetes entails has always attracted my attention and in addition, during the last few years (written first in 1923, but revised for this edition), the following considerations have been influential: (1) That in those countries where the diet consists largely of carbohydrate, the diabetes is mild; (2) that the diets of those diabetics who live longest, whether they show sugar or not, are those whose carbohydrate has never been long reduced to a very low quantity; (3) that as yet few cases have been published who have lived constantly, either in or outside of institutions, upon very low-carbohydrate and high-fat diets and still fewer upon a very low-carbohydrate but high-protein-fat diet and attained an average duration of their diabetes equivalent to the 5.4 years recorded for my own 806 fatal cases between June, 1914, and August, 1922. Of all my cases there is perhaps but one, Case No. 632, aged thirty-three years, who once lived for six years on approximately carbohydrate 28 grams, protein 79 grams, fat 133 grams, alcohol 15 grams; (4) that, given a diabetic in the last stage of inanition, he may gain a considerable lease of life when carbohydrate and protein are given freely; but this, however, is soon shortened by coma if much fat is also added; (5) that if the liver can be made to harbor any carbohydrate it is a protective phenomenon (witness the giving of carbohydrate freely to children prior to tonsillectomies and the resulting avoidance of acidosis); (6) that upon analysis of cases of coma it will be found that usually preceding its onset carbohydrate has been lowered and the protein and fat metabolized have been increased, whether from exogenous or endogenous sources; (7) that the work done by Benedict and the writer at the Nutrition Laboratory has shown that there is no diabetic so severe as to have completely lost the power of responding to carbohydrate by a failure to raise the respiratory quotient as a result of its administration; (8) that it is more rational to tend toward than to deviate from the standard diet of healthy people; and (9) finally, that experiments on animals and on normal and diabetic men show that a low-carbohydrate but high-protein-fat diet causes hyperglycemia and lowers at least temporarily the tolerance for carbohydrates. (See p. 200.)

My attention was drawn especially to a high-carbohydrate and low-fat diet by a little boy, George B., Case No. 2007, an only child, with diabetic heredity, who two years and six months after onset at 5.6 years of age continued to keep sugar-free on a diet of carbohydrate 178 grams, protein 75 grams, and fat 44 grams. The diagnosis was made by Dr. John Lovett Morse in the course of a *routine* examination on December 1, 1920, at 5.8 years of age, a short time

after the beginning of symptoms, when the urine showed a specific gravity of 1.035. It was 1.028 on the following day. The percentage of sugar on December 3, was 4.4 Ten days after the onset of symptoms he excreted but 3 grams of sugar, although his diet consisted of carbohydrate 102 grams, protein 58 grams, fat none, calories 640, and he was sugar-free the next day on carbohydrate 64 grams, protein 33 grams, fat none. From that time on his carbohydrate gradually increased until it reached 178 grams. The protein was raised from 33 grams to 75 grams, but the fat was constantly kept low. This little boy, George B., has been sugar-free except on a few occasions when he had an infection. He has, in seven years, gained 49 pounds in weight and 14 inches in height. Before the discovery of insulin the blood sugar remained normal, but by July, 1923, the tolerance fell to 120 grams. Insulin was begun in 1923, and he is now, 1928, taking 75 units with carbohydrate 141 grams, protein 79 grams, fat 94 grams. At his school he was passed as a healthy child, and he looks the picture of health. He sailed his boat in a regatta last summer with his dog for a companion and won the silver cup. His urine is tested five times daily and is usually kept free from sugar.

The diet of the once little boy, George B., however, has been broken only on the rarest occasion, and not another one of my patients has had such close care. The future of this child, therefore, should disclose the merits of this form of treatment. It is, however, fully realized (1) that faithful supervision of a diabetic case, provided the diet is not distinctly bad, *i. e.*, excessive, is so great a factor in treatment that it largely overcomes many minor dietetic faults; (2) that this child's diabetes was discovered extraordinarily early, and (3) that this case too has an hereditary element in his grandparents. Whether this boy is so very unusual, time will tell. (See p. 841.)

The example of this case suggested similar treatment for other cases, but none of these others has done quite so well. Case No. 2140, 20.8 years old at onset, who originally showed 7 per cent sugar with acidosis and later acquired a tolerance for carbohydrate 186 grams, protein 89 grams, fat 75 grams, fell out of the race when he ate 9 doughnuts one night. He later contracted tuberculosis and died of it in January, 1923, 1.9 years after onset of diabetes. Case No. 2052, aged seventeen and a half years at onset in November, 1920, thoughtlessly broke his diet by the addition of cream and thus jeopardized his future but is doing very well indeed, particularly since last autumn when he moved to an active life in the mountains. His diet contained in January, 1928, carbohydrate 140 grams; and his insulin dose was 50 units. Case No. 2095, aged 27.2 years at onset of diabetes in December, 1920, although

the urine of February 21, 1921, contained 9 per cent of sugar, took 175 grams of carbohydrate until he suffered an attack of jaundice. On March 12, 1928, his diet contained 184 grams of carbohydrate, the blood sugar was 0.16 per cent, and the insulin dose was 20 units.

Strangely enough by one of those coincidences so common in medicine, soon after George B. appeared I had the opportunity of observing for a few days a case similar in many respects—Jack R., Case No. 2661, who has been under the care of another physician from the beginning. This little boy is an only child, his diabetes was also diagnosed promptly after onset of symptoms—in September 1921—at the age of 5.1 years. The first specimen of urine, in October, 1921, showed 8 per cent sugar. On May 26, 1922, nine months after the onset of his diabetes, his diet was carbohydrate 36 grams, protein 42 grams, fat 114 grams, making the calories 1338 or exactly identical with those of George B. His fasting blood sugar on May 26 was 0.09 per cent, and on May 29, 0.07 per cent, and the blood fat was 0.71 per cent. His weight at onset was 17.1 kilograms and on May 26, 1922, was 16.9 kilograms. The urine at that time contained no sugar, but showed a positive test for acetone and for diacetic acid. The average of the twenty-four-hourly analyses of ammonia for five days was 0.53 gram and of nitrogen, 7.8 grams. He was reported on May 17, 1923, to be taking carbohydrate 70 grams, protein 70 grams, fat 143 grams, calories 1850, with 17.5 units of insulin daily. By July he was able to reduce the dose. The blood sugar on May 1 was 0.106 per cent. This child has not grown as well as George B. He has more trouble with insulin reactions. He is doing better now, June, 1927, with carbohydrate 72 grams, protein 60 grams, fat 113 grams, insulin 32 units. Since each child will be guarded by his parents with equally scrupulous care, their careers will be watched with aggressive vigilance.

It is only within half a generation that diets have been accurately controlled for months and years and the quantities of carbohydrate, protein, and fat recorded, and only within the last twelve years that the total quantity of food has been at all closely limited. In consequence it is only today that we are in a position to compare the effects of various diets, only today that we can begin to discuss how, for instance, it is best to distribute a given intake between the three food-stuffs. In point are the two "only" children cases described above. There are no two cases who are more likely to afford crucial evidence regarding the optimal carbohydrate-fat ratio, and as no data exist to prove which is the better of the diets prescribed for these two boys, one is forced to prescribe empirically. Which child is on the better diet? The last few sentences were written in 1923. Today I think the higher carbohydrate diet the better, but I believe Jack R. will gain tolerance—and he has for

on December 16, 1927, he was taking 93 grams carbohydrate and 26 units insulin.

Sansum in 1926 published an account of his experience with high-carbohydrate diets. I have seen his patients and can vouch for the wonderful recovery of two with diabetes and tuberculosis, he may have others, and in general for the excellent appearance of his remarkable group of diabetics. Under his painstaking constant care they are plainly doing well. He, too, recognizes they are overweight. (The fat depancreatized dog is more susceptible to acidosis than his lean companion.) It will be of great interest to learn the condition of these patients after they have had diabetes for seven years. It would be unfortunate if they moved from Dr. Sansum's neighborhood and so escaped from his detailed supervision. A brief summary of his method of treatment follows:

The diets employed by Sansum, Blatherwick, and Bowden[1] are essentially normal diets "Except for the omission of sugar and of foods actually sweetened with sugar—containing white bread, potatoes, milk, and large servings of fruit—these new diets contain 2 or more grams of carbohydrate to each gram ot fat. . . .

"The routine treatment of diabetes with the high-carbohydrate diets does not differ in any way from the usually accepted methods, except that more insulin is required. . .

"With our present diet plan, in addition to adequate protein, we are using 2 or more grams of carbohydrate to each gram of fat. As a routine we divide the total amount of food into equal amounts for each of the three meals of the day. Two doses of insulin are used, five-eighths of the total dose being given from fifteen to thirty minutes before breakfast and three-eighths at the same interval before supper with minor variations as necessary.

"Table 220 represents the routine diet formulas in use at the present time. These are varied somewhat to suit the individual needs of each patient. If he gains weight too fast, he usually prefers to eliminate a part of the fat only, thus increasing the ratio of carbohydrate to fat.

"Diet 1 is our acidosis diet and consists of 90 grams of oatmeal (dry weight), 300 cc. of skim milk and 1000 cc. of fruit juice. The oatmeal and skim milk are divided into three meals, and the fruit juice is given both with and between meals. . . .

"When the patient is free from acidosis, the remaining diets are used in the order listed, up to a maintenance level. Ample insulin is given, but no attempt is made to render the patient sugar-free on the acidosis diet. The patient is desugarized on Diet 2. He is kept comparatively quiet while on the low diet, lest he burn his

[1] Sansum, Blatherwick, and Bowden: Jour. Am. Med. Assn., 1926, **86**, 178. See also Colorado Med., 1927, **24**, 307.

body fat and thus precipitate an acidosis. If the case is not too severe, and especially if there is no acidosis, we often start with the diet at the supposed maintenance level, using either no insulin or a small dosage and gradually raising it to the required level. We thus eliminate the irksome days of partial starvation and inactivity.

TABLE 220.—ROUTINE DIET FORMULAS.

(Sansum, Blatherwick, and Bowden.)

Diet.	Carbohydrate.	Protein.	Fat.	Calories.
1. Acidosis	257	28	12	1248
2. 1000 calories	95	48	49	1013
3. 1500 calories	146	69	71	1499
4. 2000 calories	202	79	97	1997
5. 2200 calories	217	93	107	2203
6. 2500 calories	245	100	124	2496
7. 3000 calories	301	116	150	3018

"Table 221 presents a typical diet as served. Potatoes are generally used as the 20 per cent vegetable. Attention is especially directed to the large servings of fruit. . .

TABLE 221.—STANDARD DIET OF 2200 CALORIES.[1]

(Sansum, Blatherwick, and Bowden).

Type of food.	Breakfast.	Dinner.	Supper.	Grams.
3 per cent vegetable	...	250	250	500
6 per cent vegetable	...	...	100	100
20 per cent vegetable	...	125	...	125
Eggs	2	...	...	2
Bacon	15	...	...	15
Lean meat (15 per cent fat)	...	75	75	150
Butter	10	15	10	35
Bread	45	30	30	105
20 per cent cream	33	33	33	100
10 per cent fruit	250	250	300	800
Dry cereal	20	...	...	20
Whole milk	100	...	200	300"

With this method of treatment large doses of insulin have been employed by Sansum and his co-workers, the quantities reaching at times 200 units and usually well up towards 100 units. Insulin reactions occur, but are considered justifiable. "We believe that, when the blood sugar is kept lower than normal, the pancreas, relieved of the stimulating effect of a normally high blood sugar, will rest to a certain extent. For this reason we purposely overdose our patients by at least 10 units a day. This slight overdosage probably accounts for the fact that patients remain constantly sugar-free to a subnormal degree, even when foods are used at their average values. In this series of diets, the insulin requirement seemed to be proportional to the glucose of the diet. . .

[1] Carbohydrate, 217; protein, 93; fat, 107; calories, 2203.

"In many instances, both with insulin and non-insulin patients, we have frequently substituted carbohydrate for fat without the appearance of sugar in the urine in the non-insulin cases or without raising the insulin dosage in the insulin cases. We have also been able to substitute more than an equal number of grams of carbohydrate for the fat omitted. . .

"Thus far, we have found no definite relation between insulin and the various types of food, but in the measuring of food tolerances and the adjustment of the insulin dosages to new diets, we have had excellent results by assuming that 1 unit of insulin will burn on the average of 2 grams of food. If a patient has no tolerance and is placed on a diet containing 200 grams carbohydrate, 100 grams protein and 100 grams fat, or 400 grams of food, he will need 200 units of insulin daily. We have had a number of extremely severe diabetic patients to whom we have given doses nearly as high as this. . .

"From the patients' standpoint, the most striking advantage gained by the use of these high-carbohydrate diets has been the improvement in physical and mental activity. These new diets, with at least two parts of carbohydrate to each part of fat, afford such a margin of safety that the acetone type of acidosis can hardly occur, even when large amounts of sugar are passed in the urine."

In the original article it is said: "With the use of the high-carbohydrate diets, we have found no difficulty in keeping patients sugar-free and with a normal blood sugar. . . .

"The potatoes, milk, and fruits have enabled us to eliminate the acid-ash type of acidosis which we believe has been a cause of the high incidence of blood-vessel disease. . . .

"The patients lose their craving for forbidden foods, especially for the carbohydrates. . . .

"Theoretically, at least, and because of the entire freedom from acidosis, such diets should afford the patients the best opportunity for partial recovery."

One hesitates to comment upon an honest attempt to improve the treatment of diabetes by a new method. As I see the situation, Dr. Sansum and I agree in our antipathy to fat. I hope by old-fashioned methods and rather small doses of insulin with the help of the element of time to build up in my patients a tolerance for 100 grams or more of carbohydrate. Dr. Sansum is bolder, allows diabetics 200 grams of carbohydrate at the start and, with two to four times as much insulin as I employ, provides for its utilization and believes he is resting the diseased function of the pancreas, likewise with the hope that eventually regeneration of tissue will take place and permit the reduction of insulin. The evolution of each method depends upon implicit obedience on the part of the patient—a human factor—and anyone seeing patients treated by

either plan should not forget this aspect of the case in drawing conclusions. The time element should operate advantageously to the success of each method. Geyelin[1] uses quite liberal diets and he has lately described his method of treatment. Perhaps as good an example as I have had of the good effects of a high carbohydrate and restricted protein is Case No. 6213, a minister's wife who had seven children. At forty-six years of age she had a blood sugar of 0.40 per cent and a glycosuria of 4.8 per cent; five months later, January, 1928, she is sugar-free with a tolerance for 250 grams carbohydrate, 75 grams protein, and 100 grams fat, and 5 units insulin once a day.

Adlersberg and Porges[2] report increasing carbohydrate tolerance with a high carbohydrate and protein, but low-fat diet.

2. **Fasting Days.**—Only those who have cared for many patients by the older methods can appreciate the advance which Allen gave to diabetic therapy, with his introduction into general practice of fasting and undernutrition. Many years ago Naunyn strongly urged the use of starvation days in the treatment of diabetes. He repeatedly called attention to the advantages derived therefrom, and said one should not fear temporary undernutrition if thereby it was possible to remove the sugar from the urine. Such days were indicated in the treatment of the severest cases of diabetes, and in a case of moderate severity such a day would do what many days of low diet had failed to accomplish. Naunyn used these days to free the urine from glycosuria, to promote a tolerance for carbohydrates, and also to lower the acidosis. Von Noorden agreed with Naunyn that these days were never disadvantageous. He writes: "I make use of these, especially when there is high acetonuria. It is astonishing how strikingly the acetone falls on a hunger day. Its effect stretches out for a number of days later. In numerous severe cases a hunger day has been instituted every week with excellent results." A third reason existed for a starvation day, to wit, the patient's digestion was given a rest. Naunyn emphasized the value of a low caloric intake. Hodgson, too, is precise upon this point. He says: "Again it should be stated that the quantity of all food, even if it is carbohydrate-free, must be greatly restricted. The number of calories that the body ordinarily requires is no safe criterion of the amount of food that should be given a diabetic. It is not the quantity of food that should be metabolized, but the amount that can be metabolized that should determine the quantity given to the patient."

Hodgson should be given the credit of having published this

[1] Geyelin: Atlantic Med. Jour., 1926, **29**, 825; also Cecil: Text Book of Medicine, W. B. Saunders Company, 1927, p. 567.

[2] Adlersberg and Porges: Klin. Wchnschr., 1926, **5**, 1451; 1508; 1927, **6**, 2371.

article in 1911.[1] Guelpa[2] in 1910 reported his success in the treatment of diabetes by the employment of several days' fasting combined with purgation.

"1. There is absolutely no danger and no serious inconvenience in abstaining entirely from food for three or four days, or even longer; the period of abstinence, also, may be repeated several times without risk or inconvenience, if each day a large dose of a purgative is given to insure intestinal disinfection.

"2. While there may be some slight discomforts during the period of abstinence, these never persist after food is resumed. On the other hand, undoubted and durable benefits are always gained, in the shape of increased freedom of movement, greater clearness of ideas, amelioration of all congestive conditions, and a true feeling of general well-being. In a word, one is always better in all respects after the cure than before.

"3. The cure is a perfectly safe procedure if controlled by examinations of the blood and the urine. It insures the maximum of benefit being derived from any concomitant therapeutic measures."

Guelpa reports many cases of diabetes and the astonishingly good results which followed the method he employed. He deserves great credit for his originality and courage in applying this method as well as for his modesty, and his name should always receive a prominent place when fasting is mentioned.

The advantages of the fasting method at the outset of treatment are many: (1) It is a simple method and enables the practising physician to render all save exceptional cases of diabetes sugar-free and to keep them so. (2) The treatment is such that acidosis is almost invariably diminished rather than increased. (3) The method is suitable for a patient to learn, and he is thereby placed in a position to protect himself. (4) The expense of treatment to the patient is reduced because he can readily perform the urinary tests essential for treatment, and by keeping sugar-free, visits to a physician are rendered infrequent. (5) The responsibility of treatment rests upon the patient, and this makes the chances of his following directions far more probable. Others have employed fasting, but Allen proved prolonged fasting efficacious. Before he treated any human patients by fasting, he demonstrated that his method was useful for animals. Allen's experience convinced him that the glycosuria of even the severest types of diabetes might be cleared up advantageously by one initial fast, though it might be necessary to prolong it exceptionally for eight or ten days. And he goes on to say: "Broadly speaking, freedom from glycosuria seems obtainable in all cases of uncomplicated human dia-

[1] Hodgson: Jour. Am. Med. Assn., 1911, **57**, 1187.
[2] Guelpa: British Med. Jour., 1910, ii, 1050.

betes before there is danger of death from starvation. Even wasted and emaciated patients have borne fasting with apparent benefit, giving the impression that they have been suffering more from intoxication than from a lack of nutrition;" and in another place, "among the patients treated thus far during a variable number of months, in the hospital and at home, spontaneous downward progress has not yet been observed."

During the last years, 1926–1927, I do not remember to have used "fasting" with a single patient, but it is a keen weapon which will serve one in emergency. The principle of undernutrition which underlies the method I use constantly. Excess of food brings on diabetes, excess of food makes it worse; the normally nourished or slightly undernourished patient does the best.

The method which I formerly found worked best when fasting seemed required was as follows:

Preparation for Fasting.—In severe, long-standing, complicated, obese, and elderly cases, as well as in all cases with acidosis or in any case if desired, without otherwise changing habits of diet, omit fat, after two days omit protein, and then halve the carbohydrate daily until the patient is taking only 10 grams; then fast. In other cases begin fasting at once. It is not only more rational but it is easier to prevent acidosis than to treat it. This is the reason for the preparation for fasting. The majority of diabetic patients show little acidosis upon fasting if protected in this way because they gain carbohydrate tolerance in the process, or if acidosis has been present it will decrease. (Table 216, p. 584.) On the other hand, it is not always easy to predict[1] what will occur, and an acidosis which has not been present may appear or an existing acidosis may grow worse. Therefore, it is safer to take pains to avoid the development of acidosis in those predisposed to it, for it is a sound rule of all treatment that patients coming to the physician in an endurable state must not be made worse or have their lives jeopardized by the therapeutic procedures adopted.

Individuals most predisposed to acidosis are those in whom the disease is of long duration. Changes in the diet and regimen of such patients are always dangerous, and particularly so in the cases of extraordinary length. Coma frequently occurs in early cases, but this is because of neglect, failure of diagnosis, or sudden restriction of carbohydrate. Treatment of such individuals should never be undertaken lightly nor without a full realization of the gravity involved. This has been illustrated by Cases Nos. 295, 304, and 310. These three were hereditary cases and this fact may have accounted for the long duration of their disease, which was nine, seven and

[1] Stillman: Am. Jour. Med. Sci., 1916, **151**, 505.

nineteen years respectively. They finally came under my supervision in a much debilitated condition. Even at that time the danger of changing the diet was appreciated, and unusual care was taken to prevent a fatal issue. Ultimately the 3 cases died in coma, 1 upon a sea voyage, 1 after unusual exertion, and 1 for reasons unknown, in periods of two and a half years, two months, and five months respectively, after being seen. Consequently, when Case No. 887 came for treatment in 1915, with a duration of the disease of twenty-nine years, unusual apprehension was felt. For nine days the patient was not allowed to make the slightest possible change in the regimen for, although she was wretched, she was alive. She was then admitted to the hospital, but with much foreboding, although no alarm was felt by other physicians, experienced in diabetes, who saw her. Table 222, shows the progress of the patient.

Fasting for nine days except for 150 grams of 5 per cent vegetables on one day failed to rid the urine of sugar save upon the second day after admission; indeed upon the ninth day the quantity of dextrose in the urine was 17 grams. On the following day, August 8, 3 eggs were allowed; on August 9, 3 eggs, lean meat 30 grams; on August 10, 200 grams of orange, about 15 grams oatmeal, and the whites of 3 eggs, but otherwise the patient took no food from her entrance to the hospital on July 30 to death on August 12 of coma. On autopsy the pancreas showed: fatty infiltration, moderate chronic interstitial pancreatitis, congenital deficiency in number of islands, apparent degeneration of those present. (J. E. Ash.)

This case constituted a distinct failure, but it taught me empirically to begin treatment with moderate undernutrition through the restriction of fat and protein and the very gradual reduction of carbohydrate. To my gratification such "preparatory" treatment made actual fasting seldom necessary and I learned that the inherent tolerance of the diabetic for carbohydrate was greater than I supposed he possessed.

The carbon-dioxide tension of the alveolar air remained between 32 and 26 mm. mercury tension until the day of death when it fell to 14 mm. mercury pressure. No great change took place in the quantity of sugar excreted. The D : N ratio was 3.73 to 1 the day before death. Two other features claim attention, first, the change in weight of the patient from 132 pounds to 122 pounds in ten days, and the low excretion of salt. On the other hand, there was an increase in the output of nitrogen which rose steadily from 6.5 grams to 17.6 grams two days before death, indicating the drain upon body protein.

The patient was wretched, it is true, when she entered the hospital but she was not excessively weak. With a gradual elimination of carbohydrate following the omission of protein and fat she

TABLE 222.—CASE NO. 887. DIABETES OF LONG DURATION WITH DEATH IN COMA AFTER FASTING.

Date, 1915.	Volume, cc.	Diacetic acid.	NaCl, gms.	Nitrogen, gms.	NH_3, total gms.	D:N ratio.	Total gms.	Carbohydrate.	Protein.	Fat.	Alcohol.	Calories.	Carbohydrate balance, gms.	$NaHCO_3$, gms.	Naked weight, pounds.	Pulse.	Blood sugar, per cent.	Alveolar air, CO_2 mm Hg.
July 21	..	++	..	..	..	..	4%											
26	3000	+++	..	21.3	3.7	..	72	37	..	..	..	..	−35	0				
							Entrance to Hospital.											
30–31	1350	++++	..	..	..	..	24	..	..	0	20	140	..	0	132	..	0.23	32
31, Aug. 1	1250	+	..	..	..	..	0	0	0	0	16	112	0	0	131	..	..	30
Aug. 1– 2	1650	0	..	..	..	..	10	5	2	0	2	42	− 5	0	131			
2– 3	1600	+	..	..	..	..	13	0	0	0	..	0	−13	0	128	..	..	28
3– 4	1500	+	..	6.5	2.4	1.85:1	12	0	0	0	25	175	−12	4	127	..	0.18	28
4– 5	2400[1]	+	..	8.6	2.8	2.79:1	24	0	0	0	32	224	−24	24	128	..	..	26
5– 6	3000	++	..	9.0	3.4	2.00:1	18	0	0	0	32	224	−18	24	127	..	0.15	28
6– 7	2800	+++	..	11.2	3.7	0.98:1	11	0	0	0	32	224	−11	36	127	..	0.19	26
7– 8	2900	++	..	11.9	4.0	1.43:1	17	0	0	0	8	56	−17	36	125	..	..	29
8– 9	2950	+++	..	11.2	3.8	1.52:1	17	0	18	15	24	375	−17	42	..	..	0.28	29
9–10	3900	+++	4.3	17.6	4.3	1.31:1	23	0	26	18	12	350	−23	30	122	..	0.21	28
10–11	1750	++++	2.8	6.5	1.7	2.15:1	14	..	..	..	..	..	−14	..	..	..	..	29
11–12	2900	+++	4.6	11.0	2.7	3.73:1	41	..	..	..	..	..	..	..	..	84–144	0.43	14
12							Death in Coma.									136–172		

[1] Notice increase in volume of urine presumably due to the washing-out of acid bodies coincident with the administration of sodium bicarbonate. Notice also the increase in acidosis when sodium bicarbonate was begun. Writing in 1928 one can see that the diabetes was by no means complete. See text for additional data.

might have shown a moderately large tolerance for carbohydrate. How could she have done otherwise if she had lived for twenty-nine years with the disease? With this modification of dietetic treatment and the omission of alkalis I should not anticipate a like catastrophe with a similar patient today even if insulin was not available.

The bowels must be thoroughly opened, but I do not believe in free catharsis. If the patient has not had a movement for several days, give an enema and another enema twelve or twenty-four hours later, but do not purge the patient. Gain enough is obtained if a movement is produced once in twenty-four hours when it has only been taking place once in seventy-two. In other words, do not upset any patient who is in a tolerable state.

Fasting is never so rigorous as doctors or patients expect. Patients are more ready to undergo it than physicians to prescribe it. Quite as often it is as much a relief to the patient as it is discomfort. This is in part due to the gradual decrease in polydipsia and polyuria. Headache occurs less frequently than would be expected, and is usually dispelled by a cup of coffee. Nausea almost never occurs unless a patient is given alkali or alcohol. Children bear it more easily than adults. Case No. 899 with onset at eighty, shunned it rightly, but she became sugar-free, lived to eat pie without glycosuria and died of hemiplegia at eighty-three years. It is always desirable to avoid fasting in the old.

Fasting does not seem like fasting to the patients when they receive coffee, tea, cracked cocoa shells, broths, and an unlimited supply of water. Warm drinks are preferable. If the quantity of urine, as it often does, falls to less than normal, the patients are urged to drink water freely. Clear meat broths are a great satisfaction. An analysis of the 1220 cc. of broths taken by Case No. 765 during three days showed the total amount of calories therein contained to be negligible. The advantage of broths is probably due in part to this, but to a considerable extent to the patient receiving salt by which he may maintain the equilibrium of body fluid.

It is surprising, though usually explainable, how variable is the period required to render the urine sugar-free. Frequently a urine which contains 7 per cent of sugar becomes free from sugar after fasting for four meals, and conversely, a urine with only 3 per cent of sugar may still retain traces after the patient has been deprived of food for three or four days. In general, cases seen soon after onset become sugar-free promptly, whereas the reverse is usually true for those of long duration. "In one case we may be dealing with fatigue; in the other exhaustion of an already weakened organ," according to Greeley.[1] However, Case

[1] Greeley: Boston Med. and Surg. Jour., 1916, **175**, 753.

No. 733, age at onset seventeen, was fasted twenty-six months later, when he showed 6.6 per cent of sugar and became sugar-free in two days. The explanation in this instance was apparently the fact that the case was remarkably mild, being of the obesity type; in fact, the patient's highest weight—196 pounds—was reached when he first came under observation, and during the preceding twenty-six months he had gained 26 pounds. Children showing large amounts of sugar have also become sugar-free very promptly when the duration has been only a few weeks. Cases of long standing appear to become sugar-free more quickly with a gradually limited diet than with an immediate fast. This is probably due to the avoidance of acidosis.

Many clinicians of the old school advantageously fasted their diabetics one day a week and this has given the cue to intermittent fasting. Very few of my patients were ever subjected to a fast of more than four days. No patient has undergone a fast exceeding nine days. The apparent reason for the persistence of sugar in this case, Case No. 610, who fasted the nine days, was the presence of a vulvar abscess and the harmfulness of a slight infection was just beginning to be appreciated. This patient was erroneously supposed to possess a carbohydrate tolerance of only 2 grams for the subsequent year, but upon readmission to the hospital in May, 1916, and upon the institution of routine treatment, she became sugar-free in one day and the tolerance rose to 55 grams carbohydrate and an equal quantity of protein, and the total calories rapidly increased to over 20 per kilogram body weight.

Since the advent of insulin no patient has been fasted at all. Fasting untangled many complexities of diabetes, but it was dreadful to see the patients. The best description of the results of fasting and insulin was written by the Prophet Ezekiel. See Ezekiel 37: 1–10.

Favorable results with fasting are recorded from Minkowski's Clinic by Gooke[1] and in France by Rathery,[2] who prefers to use Guelpa's purgation with the fasting.

3. Treatment with Low-carbohydrate and Low-protein and High-fat Diets.—(Newburgh and Marsh[3] and Petrén.[4]) "When a patient enters the clinic, he is placed on a diet containing from 900 to 1000 calories of which about 90 grams is fat, 10 grams is protein, and 14 grams is carbohydrate. After the patient has been sugar-free for one or two weeks, his diet is increased to about

[1] Gooke: Arch. f. Verdauungs-Krank., 1922, **78**, 853.

[2] Rathery: Bull. Acad. de Méd., 1921, **85**, 262.

[3] Newburgh and Marsh: Arch. Int. Med., 1920, **26**, 647; ibid., 1921, **27**, 699 (Blood Sugar); ibid., 1922, **29**, 97 (Urinary Nitrogen); ibid., 1923, **31**, 3 (Fat Lipemia); ibid., 1923, **31**, 455.

[4] Petrén: Münch. Med. Wchnschr., 1927, **74**, 1123. See also p. 607.

1400 calories, of which 140 grams is fat, 28 grams is protein, and from 15 to 20 grams is carbohydrate. In the case of small individuals this diet is sufficient for prolonged use, and some of them are discharged with instructions to continue it. For larger persons, after another period of trial, a second increase is made, reaching 1800 calories, containing 170 grams of fat, from 30 to 40 grams of protein, and from 25 to 30 grams carbohydrate. Further additions up to 2500 calories may be made to suit individual cases (Table 223.)

TABLE 223.—NEWBURGH-MARSH DIETS.

Carbohydrate.	Protein.	Fat.	Calories.
14	10	90	900
15–20	28	140	1400
25–30	30–40	170	1800
			2500

"In order to prove that our procedure is an improvement over the usual method, we must show (1) that glycosuria is avoided in severe diabetes; (2) that this diet does not precipitate acidosis; (3) that nitrogen equilibrium is maintained; and (4) that the patients are able to lead at least a moderately active, comfortable life."

The courage of Newburgh and Marsh, and of Petrén in giving a diet of high fat, with low carbohydrate and protein should be recognized. They have demonstrated that diabetic patients protected by a diet of undernutrition even largely composed of fat will not develop coma. Even before ketogenic-antiketogenic ratios were promulgated they showed empirically the advantage of low protein made possible by adequate calories in the form of fat in the prevention of acidosis. Their diabetic creed is sound. They believe the urine should be sugar-free, they endeavor to keep the blood sugar normal, and they have given no alkalis.

These results Newburgh and Marsh present in Table 224. The table shows that the percentage of deaths of patients who have been treated in Ann Arbor or in Boston is about the same. It requires a great deal of intelligence to live on a low-carbohydrate, low-protein, and high-fat diet. The dangers of breaking over such a diet by increasing fat are far greater than the dangers of breaking over a diet by increasing carbohydrate. The patient who breaks over only in carbohydrate pays an immediate penalty and is warned by increased urination; the patient who breaks over only in fat and protein is not warned and dies.

Undernutrition is the explanation of the success of the Newburgh-Marsh diet. A patient of 60 kilograms body weight, receiving their first diet of 900 calories, is on half rations. Only when one to two weeks of undernutrition with this diet has made the urine of the patient sugar-free, is he advanced to the next diet of 1400

calories, which is about sufficient for the requirements of basal metabolism. Thereafter those patients who can tolerate it are given an increased diet, ranging to 1800 calories or 30 calories per kilogram body weight or even more, but the carbohydrate is never raised over 40 grams.

TABLE 224.—DIABETIC PATIENTS TREATED FROM APRIL 1, 1919 TO DECEMBER 31, 1921, ON JANUARY 1, 1922.

	Newburgh and Marsh.		Joslin.	
	Number	Per cent.	Number	Per cent.
Cases, total	124	100	536	100
Cases, traced	117	94	508	95
Deaths in hospital	10	8	11	2
Deaths in and outside hospital	26	21	118	23

The diabetic's complaint against the Newburgh-Marsh diet is based upon its inflexibility. "There has been no selection of cases—every patient entering the service has been placed on this regimen." In other words, the mild, the moderate, and the severe diabetic, the old and the young diabetic, the diabetic with and the diabetic without acidosis, all are subjected to the same treatment. It is true that this shows the safety with which undernutrition can be invoked, and temporarily undernutrition will not harm either the mild or the severe case. With this factor of the diet there can be no objection. The innocent diabetic can well register his complaint against being sentenced for life, and this might be for over twenty years, see p. 897, to a diet of 35 to 40 grams of carbohydrate. A life sentence takes away all hope, it ignores the possibility of the patient's having a tolerance for a much higher quantity of carbohydrate as well as a restoration of tolerance for carbohydrate.

In a subsequent paper,[1] the writers modify their procedure "because of the small body mass of children their total calories are reduced, but the portions of foodstuffs used are the same. After the adult patient is desugarized, his diet is increased by steps until he is receiving 0.67 gram protein and from 30 to 40 calories per kilogram body weight or sometimes a little more than this. In children more protein and more calories per kilogram body weight are allowed." Subsequently McClellan and Hannon[2] showed that a low-protein diet was tolerated by a patient for one hundred and six days without evident ill effects. Indeed fat served to spare protein as efficiently as carbohydrate.

The abolishment of glycosuria was attained, according to New-

[1] Newburgh and Marsh: Arch. Int. Med., 1923, **31**, 455; 1921, **27**, 699.
[2] McClellan and Hannon: Soc. Exp. Biol. and Med., 1926, **23**, 817.

burgh and Marsh, in all cases coming for treatment, save a few justifiable exceptions. Such a demonstration merits attention and shows how useful moderate undernutrition is when combined with the low carbohydrate and low protein.

The reduction of the percentage of sugar in the blood to nearly normal was also attained in the vast majority of cases.

The fat in the blood decreased in 12 of the cases studied by Newburgh and Marsh during the period of observation while they were upon the diets of low carbohydrate, low protein, and high fat. The average fat in the blood at the time of the first observation was 2.1 per cent and at the last observation, 1.1 per cent, or about 25 per cent above Bloor's normal. The interval between observations averaged eighty-one days, being in one case three hundred and ninety-five days.

The ability of a diabetic patient to subsist upon a diet which does not exceed 35 grams of carbohydrate and 0.66 protein grams, per kilogram body weight, for a period of ten years, irrespective of the quantity of fat, has not been demonstrated. In my experience with considerable numbers of diabetics I have known of no patient who has lived upon as low a diet as 35 grams of carbohydrate for ten years, even though the protein has been considerably higher than $\frac{2}{3}$ of a gram per kilogram body weight.

The advantages of a low-protein diet in the treatment of diabetes have been shown to be most advantageous both in the Ann Arbor and Lund clinics. From both sources it has been demonstrated that diabetics can be in nitrogenous equilibrium when the protein falls to as low as 0.66 gram per kilogram body weight, provided certain other conditions are satisfied. These are the presence of sufficient total calories in the ingested food. Whereas carbohydrate is more efficient in sparing protein than is fat, but compare McClellan and Hannon, p. 605, it is possible to use fat in far higher quantities than was previously supposed to be possible. It has generally been believed that for fat to be effective in sparing protein the carbohydrate calories must not fall below 10 per cent of the total calories, but Newburgh and Marsh found only 3.8 per cent in the form of carbohydrate necessary. Their evidence is somewhat invalidated by the work of DuBois and Richardson who showed that it is not the quantity of carbohydrate, protein, and fat *given* the patient but that which is *burned*, as proven by calorimetric determinations, which is the deciding factor. Both Petrén and Newburgh and Marsh give extraordinarily low values for the urinary nitrogen excretion of their patients. Thus Newburgh and Marsh record that Case No. 4, weighing 92 pounds, ingested 4.49 grams nitrogen daily for five days. Of this but 1.21 grams were excreted in the urine and 1.15 grams excreted in the stools, there being a nitrogen

retention of 2.13 grams. That an individual on 28.06 grams of protein should maintain a positive nitrogen balance for nearly one-half of this amount daily appears inconceivable, as does also the possibility of the excretion of nitrogen in the urine falling to approximately the same level as the excretion of nitrogen in the feces. There is ground for doubting the analyses; those of Petrén[1] are similar, but how they can occur should be explained. Recently Millard Smith[2] has maintained a non-diabetic patient with nephritis for six months on 0.26 gram protein per kilogram body weight.

Petrén is fully as enthusiastic an advocate of an extremely low-protein diet in diabetes. He treats his severe diabetics (blood sugar 0.24 per cent or more) with a diet consisting almost exclusively of fat and vegetables with protein so low that the nitrogen in the twenty-four-hour urine falls 2 or 3 grams or even less. He uses 5 per cent vegetables, employs the inulin group freely and fruits containing carbohydrate of 5 per cent or less. The amount of vegetables seldom exceeds a kilogram. Fat is furnished by butter and lard, and the amount seldom exceeds 300 grams, but the patients are urged to take 200 grams. Not over 150 cc. of 20 per cent cream is allowed. The essentials of the diet are an assured liberal amount of calories furnished by high fat, very little carbohydrate and that chiefly in the form of vegetables and fruits, and a minimum quantity of protein. In addition he gives wine. Interspersed with the diet are one or more fast days a week if the blood sugar does not fall below 0.12 per cent, which he considers pathological. Also butter days are given, and the amount of butter may be 200 grams. All patients receive opium. "Alle Patienten haben ohne Ausnahme Opium erhalten, und zwar dreimal täglich 7 bis 10 Tropfen Tinctura opii."

Insulin is used in small doses with the idea (1) that if the patient falls short of it or gives it up he will be in less danger and (2) that if an infection supervenes larger doses are required, and if he has been accustomed to large doses still larger might be without effect, and (3) that with large doses it is more difficult to keep the blood sugar normal. This diet is for the temporary treatment of the severe cases and for weeks rather than for months, though he adheres to low protein indefinitely. He believes this produces a marked diminution of hyperglycemia and ketosis and that his patients feel well on it and do not complain of weakness.

[1] Petrén: Diabetes-Studier, Kopenhagen, Glydendalske, 1923. Of these the following may be cited: Verhand. d. XXXIV Kong. d. Deutch. Gesell. f. inn. Med., 1922; Acta Med. Scand., Suppl. 3, 101, 112; Verd. v. Staff.-Karnk., 1923, **8**, 5; Erg. d. Inn. Med. v. Kind., 1925, **28**, 92; Verd. u. Stoff.-Krank., 1927, **8**, Heft, 5, Auf 2; Studies on Diabetes, Jour. Metab. Res., 1924, **5**, 1; Handbuch d. Gesampt. Therp., Gustav Fischer, Jena, 1926, **1**, 827.

[2] Smith: Boston Med. and Surg. Jour., 1927, **196**, 941.

When the blood sugar is 0.18 per cent he considers a marked diminution in the intake of protein desirable, but emphasizes the need of recognizing the age of the patient and the duration of the disease. Under the age of thirty years one can adhere to the low protein, but when the patient is fifty years or over and the diabetes of several years' duration he advises against the use of the extremely low-protein diet unless the blood sugar is above 0.2 per cent. When the blood sugar has fallen under 0.12 per cent, and one to three weeks may be required for this purpose, the diet need not be as strenuous, because with insulin the sugar can be kept under 0.13 to 0.14 per cent. With old people Petrén is satisfied with a blood sugar of 0.13 to 0.14 per cent. He lays stress on a normal blood sugar with patients showing cerebral arteriosclerosis, because the cerebral disturbances may be contributing to the diabetes. If the blood sugar in these patients falls as low as 0.11 per cent, he immediately leaves off his insulin. As a rule, his patients eventually require 50 grams of bread.

If the patient shows a severe acidosis before the beginning of treatment, he advises such a patient to give up meat or fish for life. The great majority of his really severe cases eventually do not take more than 50 or 60 grams of meat and no eggs, or at the most two. He believes that if the patient is not placed upon a diet which his pancreas can take care of while in the hospital, then all hope of the patient ever taking such a diet himself after leaving the hospital is lost.

In relation to the question as to whether a restricted diet would not lead to the diminution in the production of insulin by the pancreas, he acknowledges this was proved on elderly people in his clinic by Odin. Odin gave for some weeks a diet consisting only of fat, vegetables, and cream. The later addition of a large grapefruit caused hyperglycemia. A similar result has also been noted by others with normals and with diabetics, and Malmros also noted the same in mild diabetics treated with fast days in Petrén's clinic. Bainbridge[1] found insulin more effective when rats were fed on a high-carbohydrate low-fat diet than upon a low-carbohydrate high-fat ration. Petrén takes account of this by increasing the carbohydrate in the diet later if the patient will tolerate it. He likes to have the blood sugar normal for fourteen days before any increase is made, and then such increases are very gradual, not more than 10 grams of bread every fourth day. He believes that harmful effects of tolerance tests upon patients show only in the immediate future.

As proof of regeneration of the pancreas Petrén cites the frequency of insulin reactions in returning patients.

[1] Bainbridge: Jour. Physiol., 1925, **60**, 293.

The treatment of coma in Petrén's clinic is without the administration of alkalis or glucose, but he gives carbohydrate in the form of vegetables and fats in large quantity. Among 75 attacks of coma occurring in 49 patients, there were 3 deaths, and he states that of 52 patients who were in the clinic during the last four years on account of coma 40 are still living.

In Table 225 he cites 15 cases in whom the average amount of nitrogen in the urine daily varies between 1.3 grams and 4.3 grams, the average being 2.87 grams. These patients received on the average a diet containing carbohydrate 50 grams, protein 18.7 grams (urinary nitrogen 2.87 × 6.25 + 0.75 allowed for feces), fat 218 grams.

TABLE 225.—DIET AND URINARY NITROGEN OF 15 CASES OF DIABETES (PETRÉN).

		Diet.			
No. cases.	Average number of days of treatment.	Nitrogen in urine, gms.	Average nitrogen, gms.	Carbohydrate.	Fat.	Body weight, kg.
15	30	2.87	4.3	50	218	73.3 to 73.5

These patients were on this diet for an average period of thirty days. The patients would hardly appear to be in the group of severe diabetics because of the 15 patients 8 weighed over 73.5 kilograms, and the lowest weight in the group was 52 kilograms.

The explanation of acidosis in elderly people Petrén considers to be "Kohlehydratkarenz." In addition he believes there is a certain threshold for nitrogen metabolism above which ketosis appears. If the nitrogen metabolism can be kept low this threshold ketosis will disappear or diminish and be negligible. This threshold is specific for the individual and will vary from time to time as the disease gets better or worse. The single difference between the ketosis of diabetics and normals depends on the peculiar sensibility of the diabetic to this nitrogenous metabolism which he considers the one characteristic peculiar to diabetes. The acidosis which follows the exclusion of carbohydrate from the diabetic diet he does not believe usually is severe and does not lead to coma except when it is added to the load of acidosis already resulting from the protein metabolism superthreshold for the particular patient. Therefore, the exclusion of carbohydrate is never serious unless a previous ketosis exists. No harm has resulted as a rule from giving fat to such patients while they were living on the minimal nitrogenous diet, but apparently the fat in the tissues of obese patients is not as harmless as the fat administered.

Petrén considers the chief virtue of his diet to be that he has shown that if carbohydrate is not completely excluded from the diet it is possible with his minimal protein to nourish the patient with a

large amount of fat and that even in severe ketosis a patient can be treated with fat in amounts sufficient to lower the nitrogenous metabolism.

The experiences of the World War are proof to Petrén of the advantage of a low-protein diet, because with the low-protein ration the diabetic mortality fell.

Recently Petrén has published a table of the diabetics treated at his Clinic in Lund between 1911 and 1919, and in this table has recorded those of this number alive in the year 1924 and the percentages of the dead who have died of diabetic conditions. He does not state what these are, but I have taken for granted he meant to include deaths from diabetic coma, deaths which on the death certificate are recorded "diabetes," and "deaths from gangrene." Furthermore, I have also taken for granted that the period included in the summary stops with January 1, 1919, rather than includes the whole of that year.

It occurred to me that a comparison of my own data with those of Petrén might be instructive in showing the results of treatment with our two different methods, my moderate fat *versus* Petrén's high fat.

TABLE 226.—DATA OF PETRÉN BASED UPON CASES TREATED BETWEEN 1911 AND 1919 (137 CASES TREATED BETWEEN 1911–1919; OF THESE 32, OR 23 PER CENT WERE ALIVE IN 1924).

Age at onset, years.	Cases.	Living, 1924.	Died of diabetes.[1]	
			Number.	Per cent.
1 to 20	31	..	31	100.0
21 to 35	34	4	30	88.2
36 to 55	57	18	39	68.4
56 to 70	15	10	5	33.3

For better comparison with Professor Petrén's figures my cases have been grouped in two tables. Table 227 shows the number of my true diabetics who were living on January 1, 1911, which was the end of my first thirteen years of practice. Table 228 strictly corresponds with Professor Petrén's series because it shows the new cases who consulted me between January 1, 1911 and January 1, 1919.

TABLE 227.—DATA OF AUTHOR FOR COMPARISON WITH PETRÉN'S DATA.

(One hundred and eighty-one old cases, *i. e.*, prior to 1911—were alive January 1, 1911; of these 175 were traced and 47, or 27 per cent, were alive January 1, 1924).

Age at onset	No. of cases.	Living in 1924.	Untraced 1924.	Died of diabetes.[1]	Per cent of diabetic deaths.
1 to 20	17	2	0	14	78
21 to 35	29	11	0	13	43
36 to 55	90	31	4	26	28
56 to 70	37	3	2	12	32
71 to 80	3	0	0	1	33
1 to 20	1, cause of death unknown—died before 1924.				
21 to 35	1, cause of death unknown—died before 1924.				
36 to 55	3, cause of death unknown—died before 1924.				

[1] Coma, gangrene, diabetes mellitus.

TABLE 228.—COMPARISON WITH PETRÉN'S TABLE.

(Nine hundred and sixty one new cases of diabetes mellitus between 1911–1919, and of these 947 were traced and 315, or 33 per cent, were alive in January, 1924.)

Age at onset,	No. of cases.	Living in 1924.	Un-traced.	Died of diabetes.[1]	Per cent of D. M. deaths.
1 to 20	127	12	1	98	77
21 to 35	167	47	2	78	47
36 to 55	474	206	9	132	28
56 to 70	164	45	2	47	29
71 to 80	20	5	0	2	10
Unknown	3				
35 to 55	3, cause of death unknown—died before 1924.				
56 to 70	3, cause of death unknown—died before 1924.				

[1] Coma, gangrene, diabetes mellitus.

In the first age group with onset of the disease under twenty years, Petrén had 21 cases and none were living in 1924 and all died of diabetes. Prior to 1911 I had 17 such cases, 2 patients were living in 1924, and 94 per cent of those who died, died of diabetes; whereas between 1911 and 1919, as shown in Table 227, there were 127 cases, and not only were 12 living in 1924, but unlike the figures of Petrén only 77 per cent died of diabetes. In the second age group, twenty-one to thirty-five years, Petrén had 34 cases with 4 living in 1924 or 12 per cent. I had 31 cases with 19 living or 29 per cent for the patients who came to me before 1911 and 167 cases and 47 living, or 28 per cent, for those between the 1911 and 1919. In the third period Petrén had 57 cases with 18 living, or 32 per cent, in comparison with my 100 cases with 25 living, or 25 per cent, prior to 1911 and 474 cases with 206 living, or 44 per cent, for the 1911–1919 series. Finally in the fourth age group, fifty-six to seventy years, Petrén had 15 cases with 10 living, or 66 per cent, compared with my 39 cases with 2 living, or 5 per cent, prior to 1911 and 164 cases with 45 living, or 27 per cent, for the longer period.

Summarizing all three tables it appears that 23 is the per cent of Petrén's cases living in 1924 as compared with 29 per cent of my cases prior to 1911 and 33 per cent for my cases between 1911 and 1919. It would seem, therefore, that my cases live distinctly longer. On the other hand, it is quite striking that Petrén's series of patients between fifty-six and seventy years of age outlived my patients and that a larger percentage of his cases succumbed to conditions he includes under the term diabetes. The conclusion might be justified that in middle life where one deals with the milder diabetic the extra calories, which fat provides, prolongs the patient's existence, whereas at an earlier age, when diabetes is more severe, extra fat shortens the duration because of death from coma.

4. **The Oatmeal Treatment.**—The use of oatmeal as a special form of treatment in diabetes was introduced by von Noorden in 1903.[1] The sudden disappearance of sugar from the urine, despite the administration of so much carbohydrate, was at first looked upon with awe. Gradually with a better understanding of the storage of carbohydrate in the body, its utilization or non-utilization, as disclosed by the respiratory quotient, and recognition of the low protein content of the oatmeal "cure," the mystery began to disappear. The experimental problems associated with it are so many that it deserves extended discussion. Formerly I occasionally employed it in the treatment of very severe cases of diabetes, but the apparent lack of the utilization of oatmeal as disclosed by the respiratory quotient discouraged extensive use of the same. Notwithstanding this fact, and although I have not treated a case in this manner for several years, the oatmeal treatment has taught us much.

The "cure" was originally prescribed by von Noorden[2] as follows: "The oat cure, as now prescribed by me, consists in the daily administration of 200 to 250 grams of oatmeal, best given in the form of gruel every two hours, and 200 to 300 grams of butter, and often about 100 grams of vegetable proteid or a few eggs may be taken in addition. Otherwise, nothing else is allowed, except black coffee, or tea, lemon juice, good old wine, or a little brandy or whisky. Such a diet is often disliked by the patient, but I have always succeeded in getting over this difficulty. After three or four days upon it the purpose for which it was intended is often found to have been attained; in other cases the same program must be repeated two or three times. It is apparently advisable to precede the oat cure with a few days of restricted diet, or even one or two vegetables days, for when the cure immediately supervenes upon a mixed diet the desired effect follows rather late.

"At the commencement of the oat-cure treatment one notices, it is true, even in the most favorable cases, an increase of the glycosuria; but after a few days the excretion of sugar diminishes and the acetonuria even more so. During the oat days the urine may often be quite free from sugar, and if it is not entirely free, one may be fairly certain that it will be so in the succeeding vegetable days." Table 229 gives the details of one such favorable case.

"The estimations made before the oat cure was begun show plainly enough that it is a case of severe glycosuria combined with excessive acetonuria. With the most restricted diet it had not been possible to bring the sugar below 40 grams; even on vegetable days more than 20 grams were excreted. In the course of the oatmeal

[1] Von Noorden: Berl. klin. Wchnschr., 1903, **40**, 817.
[2] Von Noorden: Diabetes Mellitus, E. B. Treat & Co., 1905, p. 190.

treatment the urine became free from sugar, and it remained so on the subsequent return to the restricted diet. It even appeared that small quantities of carbohydrate could be well tolerated, whereas for several months previously there had been no question of such a thing.[1]

TABLE 229.—VON NOORDEN'S ILLUSTRATION OF THE "OAT CURE."

Diet.	Sugar, gms.	Acetone, gms.	Ferric chloride reaction.	Ammonia, gms.
1. Strict diet	50.4	2.1	++	3.2
2. Strict diet	48.3	2.4	++	3.8
3. Strict diet	58.9	3.1	++	4.3
4. Vegetable day	28.2	2.1	++	2.9
5. Vegetable day	20.3	2.1	++	2.8
6. Oatmeal day	38.3	1.9	++	2.4
7. Oatmeal day	40.3	1.3	+	1.6
8. Oatmeal day	30.0	0.9	+	1.5
9. Oatmeal day	20.1	0.6	+	1.1
10. Vegetable day	8.0	0.8	+	1.3
11. Vegetable day	2.3	1.2	+	1.8
12. Oatmeal day	18.3	0.5	−	0.9
13. Oatmeal day	5.6	0.1	−	0.9
14. Oatmeal day	0	0.05	−	1.0
15. Vegetable day	0	0.1	−	0.8
16. Vegetable day	0	0.1	−	0.8
17. Strict diet	0	0.15	−	0.7
18. Strict diet	0	0.18	−	1.0
19. Strict diet and 20 gms. bread	0	0.12	−	0.9
20. Strict diet and 20 gms. bread	0	0.13	−	0.8

"I believe that a glance at Table 229, which is only one out of a large number showing the same thing, will suffice to show that a result has accrued which formerly would have been deemed impossible to obtain. Unfortunately, however, there are only relatively few cases in which the result is quite so surprisingly beneficial; in many others it is incomplete, although still satisfactory; in others again no result at all is obtained. The following fact is noteworthy: Cases in which the results of the treatment were most beneficial relate without exception to the very severe forms of glycosuria; many of them were in children or young people. On the other hand, the result was almost without exception a failure in cases of slight glycosuria, the exact opposite of what might *a priori* have been expected. The oat cure rendered me immense service in severe cases, and I may even say that I have often succeeded in fending off incipient coma by its use."

The positive proof of the value of an oatmeal day would be the demonstration that the carbohydrate in the oatmeal was oxidized in the body. As yet, such a proof has not been satisfactorily estab-

[1] From the data furnished in Table 229, this case would not appear severe today. This may be one reason why the improvement was so marked.

lished. It does not suffice to show that the sugar represented by the oatmeal does not appear in the urine during the oatmeal period. One should demonstrate a rise of the respiratory quotient following the use of oatmeal. This would appear an easy problem. Thus my own respiratory quotient before breakfast on September 30, 1914, was 0.82, but forty-five minutes later, after I had eaten 60 grams carbohydrate in the form of oatmeal it rose to 0.9. With diabetic patients the results were irregular but the evidence on the whole suggested a slight utilization by rise in respiratory quotient though a marked increase in metabolism. (See p. 312.)

Allen and DuBois[1] in studies upon several severe diabetics find "no special influence of oatmeal in diabetes. The respiratory exchange fails to account for all the carbohydrate that disappears. The behavior of the respiratory quotient showed no important difference on the first day and on the third day of the oatmeal treatment."

In the light of present knowledge the frequently striking successes of the oatmeal treatment in diabetes as practised during the last few years are seen to depend upon several factors of which the most important is the greatly restricted diet which preceded and followed the cure. A similar result could be obtained with any carbohydrate as Blum pointed out and as Klemperer's experiments with dextrose and Benedict's and my experiments with levulose show. During fasting the sugar level in the body is lowered and the body is therefore in a more favorable condition to store carbohydrate and possibly to utilize it than under ordinary circumstances; during the days of undernutrition acidosis decreased and that is favorable to the utilization of carbohydrate. Then, too, at the time when the oatmeal cure was in vogue the usual diets were low carbohydrate, high protein and fat, and now we know that such diets lower tolerance in contrast to carbohydrate, which raises it under limited conditions. The fasting or semi-fasting which follow the oatmeal days may be of very great advantage. It is quite possible that carbohydrates stored for a long period in the body may ultimately be better oxidized than carbohydrates representing more nearly an overflow of the carbohydrate reservoir which escape quickly into the urine. With this in mind it is easy to understand why Blum found small quantities of oatmeal worked better than large amounts in severe diabetics. He also showed it was more successful in mild than in severe cases.

Von Noorden also made another observation which indicates that the oatmeal is simply stored. A patient showed no sugar during the two preliminary vegetable days and the three following oat-

[1] Allen and DuBois: Arch. Int. Med., 1916, **17**, 1010.

meal days, yet in the next three vegetable days 96, 106, and 32 grams of sugar were excreted respectively.

The quantity of protein upon the oatmeal days is extremely slight, although not as low as that advocated by Petrén. Thus, whereas the carelessly treated patient in diabetes ordinarily consumes far more than 100 grams of protein, if he takes even the full quantity of oatmeal, 250 grams, he will receive not over 40 grams. The low quantity of protein is undoubtedly an important factor in the success of the treatment. In his study of the oatmeal treatment, Falta observed that protein added to the oatmeal tended to the excretion of more sugar in the urine than could come theoretically from the added protein, and that meat was especially harmful as compared with vegetable protein. Indeed, some patients were more sensitive to protein than to carbohydrate. Bernstein and Falta[1] have shown that a carbohydrate-fat diet lowers the metabolism, and they explain this as a result of the attendant decreased protein metabolism. A lowering of the metabolism is, therefore, to be expected in the oatmeal treatment. They point out that such a lowering is to be expected only when the carbohydrate is utilized and thereby body protein spared. This lowering of the metabolism in and of itself helps the diabetic.

A gain in weight is usually coincident with the employment of the oatmeal cure. This is not peculiar to oatmeal. It occurs as a result of any carbohydrate day and particularly on changing from a fat to a carbohydrate diet in normal individuals. Each gram of carbohydrate retained causes a like retention of 3 grams of water. (See p. 271.) Contrary to many observers, who have considered it a disadvantage that the patient develops edema, in most cases I think it is distinctly helpful. Patients with edema seldom, if ever, develop diabetic coma. Falta noted a remarkable retention of protein during the oatmeal cure. The significance of this has not been explained, but it is probably in some way connected with the retention of fluids by the body. A second explanation of the gain in weight may be the behavior of the kidneys. Barrenscheen injected human subjects intravenously with 20 cc. of a 10 per cent solution of lactose, and upon each of the following two days he gave 250 grams oatmeal. On the third day he gave a mixed diet, together with a repetition of the injection. Upon the oatmeal days the excretion of the lactose was delayed from one to five hours, which Barrenscheen attributed to slight renal changes, not otherwise demonstrable, caused by the oatmeal. A third reason for the gain in weight may be the high caloric value of an oatmeal day. This is not generally appreciated. It is shown in Table 230.

[1] Bernstein and Falta: Deutsch. Arch. f. klin. Med., 1916, **121**, 95.

TABLE 230.—NUTRITIVE VALUE OF AN OATMEAL DAY.

Substance.	Quantity.	Carbohydrate.	Protein.	Fat.	Alcohol.	Calories.
Oatmeal	240	160	40	16	..	944
Butter	240	...	..	200	..	1800
Whisky	60	...	..	...	30	210
Total		160	40	216	30	2954

A fourth cause of gain in weight upon an oatmeal day is the considerable quantity of salt taken by the patient. For example, in the preparation of 240 grams of oatmeal the usual quantity of salt added by the cook is 10 grams and the patient may take even more. If to the oatmeal an equal amount of butter is added, according to the original advice of von Noorden, the quantity of salt is increased by 6.3 grams, for butter contains on the average 2.51 per cent salt. It would therefore seem quite likely that the edema which is associated with the oatmeal treatment might in great part be explained by the unusual quantity of salt given upon that day, and it is conceivable that along with the salt a considerable quantity of the carbohydrate of the oatmeal might be retained as well.

The apparent success of oatmeal in severe cases rather than in mild is in part attributable to this cause. One should try a salt-free oatmeal day and study the result.

Carbohydrate in only one form is a striking characteristic of the oatmeal treatment and it has been contended that this is one reason for its apparently better assimilation than the same amount of carbohydrate in several forms. There is little sound evidence for this belief. Such a phenomenon might be explained by the simplicity and blandness of such a diet leading to very slight stimulation of the digestive glands in general, and the pancreas in particular. In fact Cohnheim and Klee have noted this peculiarity in oatmeal. This may explain why boiled oatmeal acts better than baked oatmeal. Allen has pointed out that if the external function of the pancreas is relieved of work the internal function may act more vigorously and the diabetic condition be correspondingly benefited. The explanation agrees with facts. Allen[1] cites the work of Cohnheim and Klee, who observed that the foods which caused the greatest activity of the external pancreatic function are the ones which give rise to glycosuria, and the foods which stimulate the external pancreatic function least are the ones which have least tendency to glycosuria. The duodenal tube should furnish information along these lines.

The acidosis frequently decreases or disappears following or

[1] The literature on the oatmeal treatment is given by Allen: Glycosuria and Diabetes, 1913, 441.

during the oatmeal cure. If such a reduction were constant it could be used as an argument in favor of the utilization of oatmeal, but unfortunately it is not. With Cases No. 591 and 707, the acidosis was so severe that the respiratory quotient reached our lowest recorded levels, 0.65 to 0.62.

The employment of oatmeal in the "oatmeal cure" has stimulated its use in smaller quantities, and it is undoubtedly one of the most valuable additions to the strict diet of diabetic patients. It can be given in many different forms, it serves well as a vehicle for butter and cream, and is useful as gruel in the treatment of indigestion or diarrhea. It subjects the patient to less temptation than bread though the carbohydrate value is similar. Oatmeal water gruel and orange juice are the foods best borne by the patient on the verge of coma or before or after operation.

In prescribing oatmeal the dry weight should be the measure employed. Different brands vary enormously in bulk and hence in content of carbohydrate when cooked, because of the water employed. How wide these variations are Table 231 illustrates:

TABLE 231.—WEIGHTS OF DIFFERENT VARIETIES OF OATMEAL UNCOOKED AND COOKED.

Quantity, 1 gill.	Uncooked			Cooked.	
	Weight, grams.	Carbohydrate, content.	No. tablespoonfuls, heaping.	Weight, grams.	No. tablespoonfuls, heaping.
H-O oatmeal	32	19	4	353	3½
Quaker oats	37	22	5	325	4
Scotch oatmeal	81	49	5	851	10
American oatmeal	84	50	3½	690	6½
Irish oatmeal	96	58	5	853	15

F. OTHER CARBOHYDRATE CURES.

1. **Wheat.**—Blum[1] believes wheat flour acts just as efficaciously as oatmeal in a carbohydrate cure, and Csonka[2] has observed no difference between the utilization of starch of wheat and the starch of oatmeal flour by completely phlorizinized dogs. Blum demonstrated that the effect of the oatmeal or wheat was most marked in the mild cases. He noted that patients having a positive carbohydrate balance of 70 to 80 grams could take 200 to 250 grams of oatmeal with a similar quantity of butter and occasionally 3 or 4 eggs or 50 to 75 grams of vegetable albumin, and after living upon the diet for the customary three days, and then having a vegetable day, the last trace of sugar would disappear. Should the diabetes be a little more severe he employed 125 to 150 grams of oatmeal, but the same amount of butter. In still severer forms of

[1] Blum: Semaine médicale, 1913, **33**, 313.
[2] Csonka: Jour. Am. Med. Assn., 1916, **67**, 1114.

diabetes with acid intoxication only 100 grams of oatmeal were allowed for a day or two, then only 75 grams for a few days, and finally a vegetable day. In other words, he was fasting his patient to a moderate degree.

2. **Potatoes.**—A potato diet was advocated years ago by Mossé,[1] and in fact was the first of the carbohydrate cures recommended in diabetes. From what is known now it is easy to understand why a potato diet frequently worked well. (1) The potato diet was an undernutrition diet because no emphasis was laid upon the simultaneous use of fat; (2) there is little protein in a potato; (3) potatoes are a bulky food, and so satisfy the patient's appetite. The claim that considerable quantities of alkali are thus introduced into the system does not rest upon a firm foundation. I have had little experience with potato, but in 2 cases (Nos. 765 and 806) in which it was employed, respiratory quotients gave no evidence that it was assimilated.

In small quantities potato, like oatmeal, is most valuable. It carries butter well, contains only about one-third the quantity of carbohydrate in bread, and is easily measured. A potato the size of an egg weighs about 60 grams, whether cooked or uncooked, and contains 12 grams carbohydrate. With a good many mild cases of diabetes it is advantageous to exclude bread entirely from the diet and to substitute potato, of which the quantity need be only slightly restricted. One hundred grams of carbohydrate in the form of 160 grams bread are quickly eaten, but it is not so easy to take the same 100 grams carbohydrate in 500 grams of potato.

Little potatoes, carefully cleaned, when baked are often eaten with the skins by patients with much relish, and with relief to their constipation as well.

3. **Bananas.**—Bananas have been advocated by von Noorden as a substitute for oatmeal. Like potatoes they contain about 20 per cent carbohydrate. Most of the carbohydrate is in the form of starch, but when the banana thoroughly softens and ripens this changes to sugar. Bananas are usually eaten in the starch stage. The average weight of 12 whole bananas was 141 grams, the range 119 to 167 grams. When peeled these same bananas weighed on the average 87 grams, the range 73 to 101 grams. The carbohydrate in 1 banana is about 20 grams and this partial standardization makes them superior to potatoes.

4. **The Milk Cure.**—Milk was advocated as an exclusive diet for diabetic patients by Donkin[2] some years ago, and attention has been again called to it by Williamson.[3] It has not come

[1] Mossé: Rev. de méd., 1902, **22**, 107, 279, 371, 620. Cited by Naunyn.
[2] Donkin: British Med. Jour., 1874, **1**, 838.
[3] Williamson: British Med. Jour., 1915, i, 456.

into favor. It was not intended by the original promoters of the milk cure that other foods should be simultaneously eaten, but, as so often happens, the original directions have been overlooked. More harmful than the indiscriminate use of milk is that of buttermilk. Buttermilk contains all the carbohydrate which is in ordinary milk, but the fat which contains so much nutriment for the diabetic has been removed.

Case No. 17, is the only one in my series who suggested an apparent tolerance for milk. Male, teacher, onset of diabetes at the age of fifty-five years; came under my observation in August, 1900, at the age of sixty years, having lost 27 pounds, 16 per cent of his highest weight. Upon a diet of 3000 cc. milk, containing 150 grams carbohydrate, which he had employed with only trifling additions for a period of six weeks, the sugar in the urine was only 13 grams. During this period weight fell 1 kilo. I endeavored to make him sugar-free, and lowered the carbohydrates in the diet to 25 grams, but the sugar in the urine fell only to 9 grams. I well remember having greatly increased the protein and fat in the diet when the milk was omitted. Undoubtedly the secret of the favorable course of the patient upon the milk diet was the comparatively small number of calories which he obtained and, conversely, the harmful effect of the rigid protein-fat diet was due to the large number of calories it contained as well as to the acidosis which my records of twenty-three years ago show it brought on. How plain the explanation of this case is today, but for a long time it was a puzzle.

5. **Levulose, Its Clinical Use.**—(Howard F. Root, Elliott P. Joslin.) Levulose behaves differently from the other sugars, both in normals and diabetics. Külz[1] and Minkowski[2] noted this peculiarity. Writers generally have recognized an unusual utilization of levulose by diabetics, but, like von Noorden and Naunyn, saw that this vanished when the levulose was given continuously. Folin and Berglund observed only a trifling increase in the blood sugar of normal individuals when levulose was administered and it was followed by a fall of blood sugar below the initial level at the end of three or four hours. In diseases of the liver, the blood-sugar curve after the ingestion of 45 grams of levulose was high and sustained in 43 cases reported by King.[3] It has been demonstrated by Cori and Cori[4] that glucose is absorbed twice as fast as levulose but both are on a par as glycogen formers. Reinhold and Karr[5]

[1] Külz: Beitr. zur. Path. und Ther. des Diab., 1874, p. 130.
[2] Minkowski: Ueber Diab. Mel., 1893, p. 80.
[3] King: Lancet, 1927, i, 385.
[4] Cori and Cori: Jour. Biol. Chem., 1926, **70**, 577.
[5] Reinhold and Karr: Jour. Biol. Chem., 1927, **72**, 345.

noted that levulose reduced the hyperglycemia resulting from a successive dose of glucose. They also found that if a rabbit was fasted for four days his tolerance for all sugars was reduced, but that levulose produced the least degree of hyperglycemia of all six sugars tested. Cori and Cori[1] found that rats absorb and oxidize less levulose after a forty-eight-hour fast than after twenty-four hours of fasting. Levulose is less effective than glucose in relieving hypoglycemic convulsions after insulin, or in relieving the hypoglycemia which follows hepatectomy according to Mann.[2] Wierzuchowski[3] found that when levulose and glucose were injected intravenously in dogs at a constant rate, the excretion of levulose in the urine was not affected by insulin as was that of glucose and concluded that levulose does not act in the normal metabolism as does glucose. Snapper *et al.*[4] found in a case of levulosuria with normal tolerance for dextrose that insulin had no influence upon the levulosuria.

Steinberg and Elberg[5] observed levulosuria in two sisters and a brother. The glucose tolerance was good; injection of epinephrine produced neither glycosuria nor levulosuria; injection of phlorizin only glycosuria. They believe that the main disturbance is in the formation of glycogen from levulose in the liver. Students of respiratory metabolism, likewise, have perceived the peculiarities of levulose. In experiments at the Carnegie Laboratory, the unusual degree to which levulose raised the respiratory quotient in normals as compared with other sugars was demonstrated by Benedict and Carpenter,[6] and in our experiments this same power was proved to hold with diabetics. See pages 352 and 353. When given rectally, however, Carpenter[7] found not only that levulose raised the respiratory quotient less than dextrose, but that the effect was less marked than when levulose was given by mouth. He points out that in experiments with rectal feeding the absorption of substances may occur by way of the portal system through the liver without any stimulation of the hormones which is brought about by the ingestion of food by mouth. Lundsgaard and Holboell[8] found that fresh muscle tissue, when incubated with insulin, converted glucose into a different form which he called neo-glucose. A similar experiment with levulose showed no change whatsoever. This would seem to indicate a specific relation between glucose and insulin such as Wierzuchowski postulates. Levulose probably does

[1] Cori and Cori: Jour. Biol. Chem., 1927, **73**, 555.
[2] Mann: Jour. Am. Med. Assn., 1925, **85**, 1472.
[3] Wierzuchowski: Jour. Biol. Chem., 1926, **68**, 631.
[4] Snapper, Grünbaum, and Creveld: Arch. f. Verdaunugskrank., 1926, **38**, 1.
[5] Steinberg and Elberg: Klin. Wchnschr., 1925, **4**, 2399.
[6] Benedict and Carpenter: Carnegie Inst. Washington, Pub. No. 261, 1918.
[7] Carpenter: Carnegie Inst. of Washington, Pub. No. 369, 1925, p. 197.
[8] Lundsgaard and Holboell: Comptes Rend., 1926, **95**, 50.

not change into glucose but the levulose metabolism is dependent on glucose and indirectly on insulin through a glycogen phase.

Desgrez[1] and his co-workers have reported favorable results when they prescribed levulose for patients in two eight-day periods each month combined with vitamin B and calcium phosphate. They believe that levulose wards off certain metabolic disturbances. Labbé,[2] on the contrary, doubts the advantage of levulose over other carbohydrates, and regards the absence of protein and fat as more effective in combatting diabetic acidosis than levulose or any carbohydrate. Linossier[3] recommends infusions sweetened with levulose during fasting. Davidoff[4] observed that his Russian patients took honey with improvement of glycosuria. An interesting point in this connection is that the amount of levulose in different kinds of honey varies according to the food of the bees. Recently a new method for extracting levulose from artichoke tubers has been devised by Jackson, Silsbee, and Proffit[5] which may enable the manufacture of levulose on a commercial basis and the substitution of levulose for glucose in ordinary diets. (See also an article by Shoemaker.[6])

From the observations at the Nutrition Laboratory, both with normals and with diabetics, the conclusion seemed justified that levulose instead of being burned wholly as carbohydrate was in many cases, particularly in the diabetic, to a greater or less extent first transformed into fat.

During the last four years an attempt has been made clinically to utilize levulose and inulin, its precursor, with our patients at the New England Deaconess Hospital. Insulin, however, complicated a problem, already intricate, and impressions, therefore, rather than conclusions must be drawn from the work. The levulose used was especially prepared and purified by Mr. Bean in the laboratory of Prof. Otto Folin in order to prevent the diarrhea which had frequently occurred according to the testimony of past workers. The levulose was administered in several different ways. The first method consisted in giving 1.5 grams levulose per kilogram body weight in water by mouth to a patient in the postabsorptive state and then recording the changes in the metabolism which took place during the next six hours. Analyses of blood and urine were made during this period and in many instances during the twenty-four hours before and after the test. A second method adopted was to give to certain cases small amounts of levulose daily for

[1] Desgrez et al.: Bull. Acad. de Méd., Paris, 1922, **88**, 167 and 1923, **89**, 25.
[2] Labbé: Bull. Acad. de Méd., Paris, 1922, **88**, 189.
[3] Linossier: Paris Médicale, 1922, **12**, 265.
[4] Davidoff: Russki Vrach, 1915, **26**, 601.
[5] Jackson, Silsbee, and Proffit: Scientific Papers of the Bureau of Standards, No. 519, Washington, D. C., 1926.
[6] Shoemaker: United States Depart. of Agric., Tech. Bull. No. 33, 1927.

periods of days or weeks. To one patient, and this represented a third method, a large quantity of levulose was given daily for three consecutive days.

Inulin was administered as artichokes to a considerable group of patients, over a still more extended period. The artichokes were supplied for this purpose through the courtesy of the late Hon. Joseph C. Sibley, of Franklin, Pennsylvania. Two studies of the respiratory and energy metabolism with inulin have been carried out at the New England Deaconess Hospital.

(*a*) **The Effect of the Administration of Levulose in a Single Large Dose.**—Ten patients whose age varied from sixteen years to fifty years received a single large dose of levulose and the respiratory metabolism was at once determined. In some cases two or even three series of experiments were carried out with the same patient.

A summary of a series of observations of the metabolism after a single dose of levulose in 1 normal and 8 diabetics is given in Table 232. In this series as in the 51 experiments of the Carnegie Series earlier reported, p. 347, the respiratory quotients, both maxima and average, were highest in the normal, next highest in the mild, and least in the severe cases. On the other hand, the increase in heat production was greatest in the severe cases, less in the mild, and least in the normal control. In the Carnegie Series, see p. 347, there was an average increase in the metabolism of 17 per cent with a maximum increase of 32 per cent in contrast to an increase of 9 per cent for normals under similar conditions. This increase was chiefly in the first two hours. In the present series shown in Table 232 the increase in the metabolism of the normal subject at no time rose above 15 per cent, of the mild diabetics not over 12 per cent, but in 2 of the 9 diabetics reached 29 per cent and more.

(*b*) **Significant Features of Clinical Tests with Levulose.**—1. The respiratory quotient returned to the basal level within two hours in only 3 cases, Case Nos. 632, 2476 and 2801. With Case No. 2801 no rise occurred, and this patient died of coma August 18, 1923, four months after having left our observation, while taking daily over 45 units of insulin. Case No. 2476 showed 7.04 per cent fat in the blood thirteen days before the levulose test, yet the quotient rose from 0.74 to 0.85 within one hour, and Case No. 632 was a diabetic who had lived on a low carbohydrate diet, 25 grams, for many years. His quotient rose in different experiments 0.03 to 0.13.

2. The respiratory quotient did not return to the basal level even at the end of six hours with Cases Nos. 2296, 2548 and the first experiment with Case No. 3001, all of whom were comparatively mild cases, but it did with the subjects Case Nos. 2448, 2729 and in the second experiment with Case No. 3001. The first two of these

TABLE. 232—THE EFFECT OF LEVULOSE UPON THE METABOLISM OF 1 NORMAL INDIVIDUAL AND 8 DIABETICS.

Case No.	Severity[1]	Weight, per cent of standard.	Metab. H and B[2] ±, per cent.		Basal.	Time in half hours. 1	2	3	4	5	6	7	8	9	10	11	12
Normal	....	−10	−8	R.Q.	0.76	0.85	1.01	0.94	....	0.90	....	....	....	0.80	....	....	0.76
				Cals.	1246	1398	1361	1438	....	1361	....	....	....	1303	....	....	1233
				% Deviation	....	+12	+9	+15	....	+9	....	....	....	+5	....	....	−1
2548	Mi.	−22	+3	R.Q.	0.78	0.80	0.96	....	0.91	....	0.89	....	....	0.80	....	....	0.79
				Cals.	1259	1350	1408	....	1383	....	1344	....	....	1269	....	....	1306
				% Deviation	....	+7	+12	....	+10	....	+7	....	....	+1	....	....	+4
3001	Mi.	−21	−14	R.Q.	0.79	0.86	0.88	....	0.85	....	0.83	....	....	....	0.85	....	0.78
				Cals.	1076	1182	1116	....	1085	....	1069	....	....	....	1125	....	1058
				% Deviation	....	+10	+4	....	+1	....	−1	....	....	....	+5	....	−2
3001	....	−21	−14	R.Q.	0.80	0.90	0.95	....	0.89	....	0.93	....	....	....	0.86	....	0.84
				Cals.	1078	1164	1128	....	1115	....	1132	....	....	....	1115	....	1094
				% Deviation	....	+8	+5	....	+3	....	+5	....	....	....	+3	....	+2
2448	Mod.	−19	−15	R.Q.	0.78	0.82	0.85	0.87	....	0.84	....	....	....	0.87	....	....	0.89
				Cals.	1243	1279	1446	1430	....	1397	....	....	....	1356	....	....	1414
				% Deviation	....	+3	+16	+15	....	+12	....	....	....	+9	....	....	+14
2476	Mod.	−22	−18	R.Q.	0.74	0.84	0.85	....	0.67	....	0.72	....	....	0.73	....	....	0.73
				Cals.	1334	1628	1754	....	1732	....	1485	....	....	1292	....	....	1407
				% Deviation	....	+22	+32	....	+30	....	+11	....	....	−3	....	....	+5
2687	Mod.	−27	±0	R.Q.	0.83	0.94	0.90	....	....	....	0.88	....	....	0.82	....	....	0.83
				Cals.	1240	1450	1479	....	....	....	1404	....	....	1229	....	....	1293
				% Deviation	....	+17	+19	....	....	....	+13	....	....	−1	....	....	+4
2729	Mod.	−26	−36	R.Q.	0.77	0.98	....	0.90	....	0.80	....	....	0.82	....	....	0.78	
				Cals.	954	1083	....	1063	....	982	....	....	966	....	....	975	
				% Deviation	....	+13	....	+11	....	+3	....	....	+1	....	....	+2	
2296	Mod.	−21	−3	R.Q.	0.74	0.79	0.79	....	0.77	....	0.78	....	....	....	0.76	....	0.72
				Cals.	1293	1482	1535	....	1556	....	1505	....	....	....	1393	....	1345
				% Deviation	....	+15	+19	....	+20	....	+16	....	....	....	+8	....	+4
632	S.	−31	−18	R.Q.	0.76	0.78	0.79	....	0.73	....	0.71	....	....	....	0.76	....	
				Cals.	1115	1424	1444	....	1425	....	1242	....	....	....	1155	....	
				% Deviation	....	+27	+29	....	+28	....	+11	....	....	....	+4	....	
2801	S.	−25	+5	R.Q.	0.75	0.73	0.76	0.72	....	....	0.74	....	....	0.72	....	....	0.72
				Cals.	1338	1437	1442	1456	....	....	1362	....	....	1289	....	....	1250
				% Deviation	....	+7	+8	+9	....	....	+2	....	....	−4	....	....	−7

[1] Mi = Mild; Mod. = Moderate; S. = Severe.
[2] Per cent ± variation from Harris and Benedict standard.

patients, Case Nos. 2448, 2729, were at the time of the test moderately severe and Case No. 3001 was on the borderline between moderate and mild. Thus the severest cases showed the least rise for the shortest period. The remainder of the cases were not so easily classified, but it is significant that Case No. 3001 showed a greater and more prolonged rise in quotient in the second experiment when she had been receiving more carbohydrate.

3. The heat productions were at or below the basal level at the end of six hours in two instances, Case Nos. 3001 and 2801. The greatest increases in heat production occurred with Case Nos. 632 and 2476, both severe. The persistence of high quotients and high metabolism is all the more significant when one takes into account that in the control experiment with Case No. 866 both quotient and metabolism had fallen definitely below the initial level at the end of six hours.

The above results confirm the impression that here we are dealing with a different type of metabolism than takes place with the mere oxidation of carbohydrate. This could be explained upon the theory that part of the levulose was being transformed into and being burned as fat in certain of the cases, but that in the severest cases, such as Case No. 2801, even this transformation failed. Another possibility exists, that the stimulating effect of levulose upon insulin production differs from that of glucose.

(*c*) **Levulose and Blood Sugar.**—The influence of levulose upon the percentage of sugar in the blood in normal individuals, mild diabetics, and severe diabetics, both with and without insulin, is shown in Table 233. To each patient the quantity of levulose given was 1.5 grams per kilogram body weight.

TABLE 233.—THE EFFECT OF LEVULOSE ON BLOOD SUGAR WITH AND WITHOUT INSULIN.

	No. of cases.	Levulose, grams.	Blood sugar, fasting.	After levulose.					
				1 hour.	2 hours.	3 hours.	4 hours.	6 hours.	24 hours
Normal	1	85	0.08	0.11	0.10	....	0.08	0.10	
Mild diabetes	1	77	0.10	0.16	....	....	....	0.08	0.10
Moderate and severe diabetes	9	73	0.21	0.29	0.30	0.26	....	0.22	0.24[1]
Moderate and severe diabetes	4	74 and 11 units insulin	0.21	0.24	0.21	....	0.17	0.13	0.19

The mild diabetics showed a higher rise, and the moderate and severe diabetics a much higher rise than the normal control and the

[1] Average of only 4 analyses

hyperglycemia was more prolonged. It should be said that the twenty-four-hour value was obtained in the fasting state. When insulin was given at the same time as the levulose there was a much less rise of blood sugar at the end of one hour and a steady fall thereafter to the lowest point at the end of six hours. Three patients, 1 mild and 2 severe, received both levulose and dextrose. In each case dextrose raised the blood sugar to a higher point than did levulose.

The urinary sugar excreted averaged 5.7 grams when three patients took 74 grams levulose in six hours, but when the same quantity of levulose was preceded in these patients by 10 units of insulin, the sugar excreted was 0.4 grams. With 3 cases after 71.6 grams levulose the sugar excreted in six hours amounted to 6.5 grams, but with the same patients after 69 grams dextrose to 21.3 grams.

Thus levulose produced less marked hyperglycemia and glycosuria than did dextrose. Insulin counteracted the hyperglycemia produced by levulose just as it does with dextrose. Wierzuchowski, on the other hand, found that in normal dogs insulin did not diminish the excretion of levulose in the urine during constant intravenous injection although it did lower the blood sugar.

(*d*) **Levulose and Its Relation to Acidosis.**—The criteria by which the effect of levulose upon acidosis was estimated in the different subjects were derived from analyses of the plasma CO_2 combining power and of the acetone in the blood and from the urinary ammonia as well as the NH_3 N : total N ratio. At the beginning of the experiments 4 of the patients showed acidosis and 5 did not. As a result of the administration of levulose there was a definite increase in acidosis as shown by a fall in the plasma CO_2 combining power during the first and second hours after the levulose was taken, but a decrease in acidosis as shown by a fall in the NH_3 N:N ratio. Various interpretations may be placed upon these two opposing results. It is possible that the lowering of the plasma CO_2 was the result of a dilution of the blood rather than a true acidosis because in our experiments the levulose was given in a highly concentrated solution, the average dose of 75.1 grams being dissolved in 50 to 55 cc. water. At any rate the CO_2 value returned to about its initial level at the end of the six hours, so if acidosis was increased during the first and second hours it had disappeared by the end of the period. Likewise an explanation may be offered for the fall in the NH_3 N : total N ratio in that this may have been caused by the increased excretion of nitrogen. At all events, the excretion of NH_3 nitrogen per hour remained essentially uniform.

The development of an acidosis after levulose may have been due in part to the withdrawal of insulin on the days of experiments, but

this factor does not explain its disappearance in six hours. It must be remembered that the ingestion of 60 to 70 grams levulose immediately makes available calories in excess of metabolic needs. On *a priori* grounds one might expect in severe cases acidosis from such over-feeding. That some abnormality of fat metabolism occurred in 2 of these cases after the levulose seems clear, because the blood acetone increased. However, this increase was not consistent since in 4 of the cases showing acidosis at the beginning of the experiment there was a lowering of the blood acetone at its conclusion. Two of these had lipemia. What relation this lipemia bears to the acetone it is impossible to say. From this confusing picture at least this conclusion appears justifiable, namely, that it is preferable to give levulose in small rather than in large doses.

The patients without acidosis who received levulose with a single exception, did not develop acetonemia, although the plasma CO_2 during the first two hours fell as in the cases with acidosis. The one exception was Case No. 3001 who exhibited a marked acetonemia on the third day without insulin and with 72.5 grams levulose daily. Here again the withdrawal of insulin and overfeeding with carbohydrate may be the explanation.

The analyses of plasma lipoids under various experimental conditions are presented in Table 234, and for these we are indebted to Prof. W. R. Bloor.

TABLE 234.—PLASMA LIPOIDS AFTER INGESTION OF LEVULOSE WITH AND WITHOUT INSULIN. (BLOOR.)

	Levulose without insulin.				Levulose and 10 units insulin.		
Case Nos. . .	3001	3001	2296	2476	3194	2296	3001
Date, 1923 . .	Feb. 15	Feb. 17	Feb. 7	Apr. 4	Mar. 14	Feb. 13	Feb. 22
Levulose, grams	72.5	72.5	75.6	90.0	71.5	75.6	73.2
Fasting:							
Cholesterol	132	115	375	465	92	340	142
Fatty acids	292	282	825	830	325	900	325
Lecithin	250	242	440	720	...	528	260
One Hour Later:							
Cholesterol	...	...	415	220	97	390	132
Fatty acids	...	...	750	850	400	750	325
Lecithin	...	...	438	800	280	560	236
Two Hours Later:							
Cholesterol	132	115	367	450	125	500	102
Fatty acids	277	282	650	830	300	700	300
Lecithin	224	236	472	400	300	484	260
Six Hours Later:							
Cholesterol	140	187	340	415	102	450	102
Fatty acids	600	370	625	1250	300	800	300
Lecithin	260	300	390	720	360	484	256

(*e*) **Levulose and Blood Lipids.**—We present data on 7 experiments, 3 of which are in one patient and 2 on another. Visible lipemia was present in Case Nos. 2296 and 2476, and in all cases an abnormally high lecithin : cholesterol ratio was present. The most interesting question with regard to these figures relates to the rise in fatty acids six hours after the taking of levulose, because the highest point in the curve of blood lipoids after eating fat also occurs at six hours. Only Case No. 2296 failed to show this rise. He was an unusual patient in that he had such an extraordinarily low blood sugar renal threshold that for some time he was suspected of being a renal glycosuric. Possibly he should not be included in this group. However, the results of the other 3 experiments raise for discussion the possibility as to whether the rise in lipids, especially fatty acids, is due to withdrawal of stored fat or to the metabolism of fat formed from levulose.

In 16 experiments with inulin, levulose and artichokes, including normals as well as diabetics, Root and Baker noted that the tendency for an increase in the plasma cholesterol to occur after ingestion of carbohydrates was less in patients of lower body weight and who showed the greatest increase in respiratory quotient. In general the fatty acids of the plasma paralleled the cholesterol. In the 3 cases who had levulose and insulin a pronounced drop in the fatty acids in the plasma occurred during the first hour. A slight rise followed at the end of six hours without, however, reaching the initial level. Thus the reaction of the plasma lipids was quite different when insulin was taken with the levulose. Possibly insulin induced oxidation of the levulose as carbohydrate or storage as glycogen and thus prevented its transformation into fat. Possibly insulin affects fat metabolism directly.

In 2 cases[1] levulose was given by mouth at the rate of 10 and 12 grams per hour for five and six hours respectively. The blood sugar was unaffected during the first, but rose during the second hour. The respiratory quotients showed scarcely any rise until the sixth hour.

The daily administration of levulose in small quantities for prolonged periods was studied in 4 patients. The levulose was well borne at first, but later hyperglycemia and glycosuria followed. One wonders whether one of the differences between levulose and glucose may not be its greater specific stimulating effect upon the secretion of insulin. That glucose taken by mouth stimulates the secretion of insulin is suggested by the fact that in the normal a glucose-tolerance test results in a blood sugar below the original level four hours after a meal. If levulose when taken by mouth possessed

[1] Root and Baker: Arch. Int. Med., 1925, **36**, 136.

the power of stimulating insulin production more promptly and more vigorously than glucose one can understand why the increase of the sugar in the blood of the diabetic is less with the levulose and why practically no increase in blood sugar occurs in the normal. Furthermore, if insulin has the power of checking the formation of sugar from protein and fat in the liver, levulose would result in an inhibition of this process with its lowering effect on the respiratory quotient and at the same time an increased supply of sugar would be available for combustion in the tissues so that the two influences might give a high respiratory quotient. Furthermore, the lessened effect of levulose when given rectally would be explained by the fact that the stimulation of insulin production is brought about when the substances are taken by mouth or introduced into the duodenum. A point about levulose, however, remains to be explained and that is the respiratory quotients above 1 after its ingestion. Here is a stumbling block in the path of any explanation except that of fat formation from levulose.

6. **Dihydroxyacetone** CH_2OH
$|$
$C=O$
$|$
CH_2OH—This ketone triose, one of three trioses considered to be products of normal carbohydrate metabolism seems to affect the metabolism somewhat as does levulose. After administering dihydroxyacetone Isaac and Adler[1] found in rats and mice a greater proportion of glycogen in the liver than after glucose. Ringer and Frankel[2] found in normal animals that the blood sugar was lowered after taking 60 grams of dihydroxyacetone. Rabinowitch[3] gave to the same subjects dihydroxyacetone one day and glucose on another day. He found that the curve of blood sugar during six hours after the test showed less elevation in the case of the dihydroxyacetone and that less sugar was excreted in the urine than after the glucose. The respiratory quotient also rose with an increase in the heat production and he was able to replace small amounts of insulin with dihydroxyacetone. He also reports the treatment of a case of diabetic coma with dihydroxyacetone. Acidosis diminished within one hour and no increase in blood sugar occurred although 18 grams of the drug were given. At the end of twelve hours, when 68 grams of dihydroxyacetone had been given great improvement had occurred although the excretion of sugar had decreased but slightly and the ferric chloride

[1] Isaac and Adler: Klin. Wchnschr., 1924, **3**, 1208.
[2] Ringer and Frankel: Jour. Biol. Chem., 1914, **18**, 233.
[3] Rabinowitch: Jour. Biol. Chem., 1925, **65**, 55.

reaction was still positive.[1] Mason[2] observed both a greater and a more suddenly attained rise in respiratory quotient and total heat production with dihydroxyacetone than was produced when glucose was taken. Neither by the excretion of glucose nor by calculation based on possible transformation in the tissues could he demonstrate that the dihydroxyacetone was converted into glucose as stated by Lusk.[3] Mason also found that the increase in blood sugar was not so great in diabetics after ingestion of dihydroxyacetone as after a like amount of glucose. On the other hand, Campbell, Fletcher, Hepburn, and Markowitz[4] as well as Hewitt and Reeves,[5] found that in an animal the intravenous injection of dihydroxyacetone cured insulin convulsions and from this observation concluded that glucose must be formed from the dihydroxyacetone. Markowitz and Campbell[6] believe that the transformation into glucose occurs in the liver, and concluded that it had no greater clinical value than glycerol or any other substance slowly converted into glucose. Campbell and Markowitz[7] found in a depancreatized dog no difference in utilization of dextrose, levulose, or inulin. In the absence of the pancreas differences in stimulating effect on pancreatic secretion of various substances would disappear.

(7) **Inulin and Jerusalem Artichokes.**—Inulin, the chief carbohydrate constituent of artichokes gives levulose by hydrolysis. Other polysaccharides, including polymers of levulose more readily hydrolyzable than inulin, as well as small amounts of sucrose were also found in artichokes by Jackson, *et al.*[8] the average ratio in 14 specimens from River Ridge Farm, Franklin, Pa., of levulose to total reducing sugars being 0.767.

Apparently inulin is not hydrolyzed and absorbed under all conditions, although Goudberg[9] was convinced of its utilization by observing a pronounced rise in the respiratory quotient and metabolism after its administration and Okey[10] recovered from the stool an inulase and observed hydrolysis of inulin by the hydrochloric acid of the stomach. Root and Baker obtained slight or no change in the respiratory quotient after giving pure inulin, but in 6 dia-

[1] Rabinowitch: Canadian Med. Assn. Jour., 1925, **15**, 374.
[2] Mason: Jour. Clin. Invest., 1926, **2**, 521, 533; Canadian Med. Assn. Jour., 1926, **16**, 367.
[3] Lusk: The Science of Nutrition, 3d edition, 1917.
[4] Campbell, Fletcher, Hepburn, and Markowitz: Jour. Biol. Chem., 1926, **67**, lvii.
[5] Hewitt and Reeves: Lancet, 1926, ii, 703.
[6] Markowitz and Campbell: Am. Jour. Physiol., 1927, **80**, 548.
[7] Campbell and Markowitz: Jour. Clin. Invest., 1927, **4**, 93.
[8] Jackson, Silsbee, and Proffit: Scientific Papers of the Bureau of Standards, No. 519, 1926, Washington, D. C., p. 595.
[9] Goudberg: Ztschr. f. exper. Path. u. Therap., 1913, **13**, 310.
[10] Okey: Jour. Biol. Chem., 1919, **38**, 33; 1919, **39**, 149.

betics found that the respiratory quotient as well as the blood sugar rose after eating Jerusalem artichokes. The absorption of some carbohydrate was clearly proved, but further demonstration of the utilization of large quantities of carbohydrate derived from artichokes was made possible through the coöperation of Dr. Thorne Carpenter of the Nutrition Laboratory of the Carnegie Institution and Professor B., Case No. 1500, aged fifty-two years, who had used dried artichokes for a period of three years. He had eaten as much as the equivalent of 2 pounds, undried, daily and found by his own tests that he was unable to substitute even a smaller amount of any other form of carbohydrate without the appearance of glycosuria.[1]

In order to carry out further observations Professor B. spent a week at the New England Deaconess Hospital where he consumed his usual resting diet of carbohydrate 29 grams, protein 46 grams, and fat 63 grams, with the addition of 100 grams of carbohydrate in the form of dried Jerusalem artichokes, and food substitutes such as broth, bran, Irish moss and mineral oil. Duplicates of all food ingested as well as all urine and stools were analyzed and a balance of food and energy obtained. Metabolism experiments were carried out at the Carnegie Nutrition Laboratory and it was clearly shown that the patient absorbed fully 100 grams of carbohydrate from the artichokes. Furthermore, when an equivalent amount of carbohydrate in the form of potato was substituted for artichokes glycosuria and hyperglycemia appeared within two hours and disappeared only after the potato was discontinued and artichokes resumed!

During the last three years Jerusalem artichokes have been used freely in the diet of patients both in the Deaconess Hospital and at Mrs. Leatherbee's diabetic cottage. In Table 235 are summarized the records of 17 patients.

Usually it is possible to substitute 15 grams in this form for 5 grams of carbohydrate in the form of 5 per cent vegetables. At times it has been possible to render the urine sugar-free by substituting carbohydrate in the form of artichokes for carbohydrate in some other form.

The Jerusalem artichokes tuber may be prepared for use as food in a variety of ways, such as boiling, baking or frying. It must be remembered, however, that if the tuber is boiled, a large part of the inulin will be lost in the water. Baking is the best method of cooking. If baked in their skins they resemble baked potatoes but have a sweet taste. Eaten raw, they taste like chestnuts and may be used in salads. First, however, they should stand overnight

[1] Carpenter and Root: To be published.

in cold water. Mrs. Leatherbee recommends the following recipe: The artichokes should be washed in cold water and sliced like cucumbers, then baked in a small casserole until soft. No water should be added, but mineral oil may be used.

TABLE 235.—AVERAGE DIET, INSULIN AND WEIGHT OF DIABETIC PATIENTS TAKING ARTICHOKES.

Number of cases	17	
Carbohydrate added as artichokes	19	gm.
Times	6	months
Diet at beginning:		
Carbohydrate	51	gm.
Protein	51	gm.
Fat	105	gm.
Calories	1353	
Diet[1] at end:		
Carbohydrate	59	gm.
Protein	53	gm.
Fat	117	gm.
Calories	1501	
Insulin:		
Beginning	18	units
End	21	units
Weight:		
Beginning	36.3	kg.
End	42.4	kg.

Case No. 1500 secured a supply of artichokes all the year round by drying them over a radiator in the form of chips.

SUMMARY.—Tentatively we are inclined to the opinion that levulose can be used with advantage in the diabetic diet in very small amounts daily for intermittent periods. It will raise the respiratory quotient in a diabetic more than dextrose and the heat production as well. Levulose seems to cause a different type of metabolism from dextrose, possibly due to the conversion of levulose in part into fat by the diabetic or to a more active stimulation of insulin production. Similarly inulin and lower polymers of levulose in the form of Jerusalem artichokes have been used by our patients with pleasure and benefit.

8. **Rectal Injections of Sugar.**—The experiments of Arnheim in 1904 showed that glycosuria in diabetic patients was not increased after enemata of solutions of sugar. Simultaneously, acetonuria diminished, and this appeared to be good proof that the sugar was absorbed and oxidized. This favorable action was attributed to the slow absorption of the rectal injection. Since this time others have studied the problem, notably Bingel, Reach, Balint, Lüthje, Jahnson-Blohm and Petitti.[2]

The subject is, however, by no means settled. In the first place, it is questionable whether in former experiments one sufficiently

[1] Exclusive of artichokes.

[2] See Allen: Glycosuria and Diabetes, W. M. Leonard, Boston, 1913, p. 59.

considered the effect of fasting, and secondly, the possibility of carbohydrate storage following fasting. Finally, today the respiratory exchange is far more generally employed, and this is really the ultimate test. Experiments dealing with rectal alimentation of normal individuals have been made by T. M. Carpenter[1] of the Nutrition Laboratory. He has studied the effect upon metabolism of solutions of glucose and levulose administered by rectum. The increase in metabolism is less than when these are given by mouth, but this may be explained by the smaller quantities of materials used. Likewise the rise in respiratory quotient is less, although in one case with levulose it was quite considerable. Carpenter suggests that the type of metabolism which follows the introduction of food by rectum may be different from the type when given by mouth. He does not believe this is due to the commonly accepted idea that by rectum these foods during their absorption avoid the liver, because his observations tend to show that the absorption takes place not alone from the lower hemorrhoidal veins, but also through the tributaries of the portal venous system.

Lüthje[2] repeatedly witnessed the disappearance of acidosis during the treatment of patients with enemata of sugar. As evidence of the absorption of sugar, he observed an increase of the percentage of sugar in the blood, and controlled the observation by noting no such increase following the administration of salt solution. The slow absorption of the sugar did not account for its better utilization when given by the rectum, because when the sugar was introduced into the body at the same rate by being slowly sipped, the difference in favor of rectal alimentation persisted. Lüthje found that with good technique patients may absorb 1 or 2 liters of solutions of sugar containing 5.4 per cent, and thus may get 50 to 100 grams a day. Ten patients were treated by him by this method.

Bergmark also showed that after the enemata of dextrose there was an increase in the carbon dioxide production, and that the experimental acidosis diminished as well. Jahnson-Blohm found that with healthy subjects the instantaneous as well as repeated doses by mouth gave inside of the first three and one-fourth hours a strong increase in the glycemia, which rapidly sank in several cases so far that hypoglycemia took place. Dextrose injected by rectum gave blood-sugar values which lay very near to those at the beginning, and inside the limits of error of the method. The experiments with the diabetic subjects showed a strong rise of the blood-sugar curve with ingestion of dextrose by mouth. As with the normal subjects, the rectal experiments gave no increase in the percentage of blood

[1] Carpenter: Human Metabolism with Enemata of Alcohol. Dextrose and Levulose. Carnegie Inst. of Washington, Pub. No. 369, 1925.

[2] Lüthje: Therapie der Gegenwart, 1913, **54**, 193.

sugar. An increase in the urinary sugar did not occur either with healthy or diabetic subjects after the rectal feeding. This work shows well the unsettled state in which the question now rests.

9. **Insulin Refractory Diabetics.**—It is hard for me to believe that an insulin refractory diabetes exists, if by that term it is meant that true, uncomplicated diabetes is uninfluenced by insulin. Marcel Labbé[1] takes the same view. Nearly all the cases requiring unexpected amounts of insulin that I have seen could be classified under the following headings:

(1) Cases of renal glycosuria are not true diabetes and can be dismissed at once from the discussion, and so can allied conditions in pregnancy. (2) Abnormalities in the pituitary, thyroid, and adrenals as well as castration interfere with the action of insulin, but the blame rests upon them when they complicate diabetes (3) Infections,[2] whether chronic or acute, lower the potency of insulin either directly or through the agencies of the ductless glands, the thyroid and adrenal, as Lawrence[3] believes, but anyone can demonstrate that insulin is working to a greater or less extent by varying the carbohydrate in the diet or the dose of insulin. (4) In diseases of the kidney, functional or organic, or in disability from an incompetent heart,[4] especially with edema, insulin does not act as well as when the diabetes is uncomplicated or as well as when the patient has regained his compensation, but the insulin still acts. So too with high renal thresholds insulin may not depress the percentage of sugar in the blood to any considerable degree, but it will reduce the sugar in the urine either to zero or to so trifling an amount that it demonstrates it has provided for the utilization of carbohydrate. Perhaps in this group should be included diabetics with cirrhosis of the liver, and those cases also referred to by Labbé as hepatic glycosuria. (5) In certain lesions of the skin the tolerance for carbohydrate drops and insulin must be increased to prevent glycosuria. The so-called pruritus of old age is one. A clearer example I think is a severe and extensive sunburn. The skin is more actively concerned in metabolism than has been thought and the readiness with which it responds to an increase in the sugar in the blood in contrast to other tissues is evidence of it. (6). Acidosis damages the kidney we know; it also neutralizes in part the force of insulin. (7) One of the most unjustifiable attacks upon the efficacy of insulin arises because insulin, when given, is not absorbed. I have seen the tissues cut and refuse to bleed, so moribund was

[1] Labbé: Med. Jour., 1927, i, 530.

[2] Tisdall, Drakeand Brown: Am. Jour. Dis. Child., 1926, **32**, 854; Sweeney and Lackey: Arch. Int. Med., 1928, **41**, 257.

[3] Lawrence and Buckley: Brit. Jour. Exp. Path., 1927, **8**, 58.

[4] Escudero: Revista de la Soc. de med. int., Buenos Aires, 1925, **6**, 312.

the patient, and not very rarely are patients seen with areas of skin and subcutaneous tissues so indurated that insulin when injected is inert. Introduce the insulin into the blood, if it can be made to flow, or change the location of the injection and insulin's action is disclosed. (8) Cancer of the pancreas is often associated with glycosuria and rarely cancer of the pancreas develops in a diabetic, but neither of these states is true diabetes. If the cancer is of the islands of Langerhans the reverse of diabetes might take place if the clinical course followed that of Wilder's non-diabetic patient who developed that condition. Just as with tuberculosis, so with cancer in a diabetic, diabetic laws have seemed awry, until the autopsy showed the real truth. (9) Lack of muscle tone and of exercise, such as occurs in bed-ridden patients complicated by rheumatism, distinctly reduces the effectiveness of diabetic treatment and of insulin as well. (10) Finally, one must not forget that sometimes diabetics are not reliable and it may take a long while to find out where the deceit lies. Insulin is always active in the treatment of true diabetes, but there are tricks of technique.

Lawrence,[1] commenting upon Labbé's negation of any true diabetic being refractory writes, "I should have agreed with Professor Labbé two months ago, but since then I have had under close observation a lad of nineteen years who is extraordinarily resistant to insulin." This patient was upon a diet of carbohydrate 50 grams, protein 80 grams, fat 150 grams, and insulin. Two hundred and twenty units a day failed to reduce his blood sugar to normal and to keep him sugar-free. For this purpose he required 400 units. When insulin was omitted, he developed coma within a week, and was rescued only by large doses of insulin.

Falta[2] had a diabetic patient apparently resistant to insulin, but later the same patient was found by Basch[3] to be amenable to treatment when placed upon the Petrén regime.[4,5]

Taussig[6] had such a case with urticaria after injections of insulin. She received very large doses without becoming sugar-free and upward of 1100 units of insulin in one day during coma. Eventually the insulin was reduced to 104 units daily.

The one outstanding case of an insulin refractory diabetic in my series was a physician, Case No. 6247. He came to me in August, 1927, with 2.3 per cent of glycosuria, while taking 60 units of insulin, and a history of cirrhosis of the liver, and a nodule the size of a walnut in the head of the pancreas having been found in 1923. Upon a diet of 30 calories per kilogram, carbohydrate 78 grams,

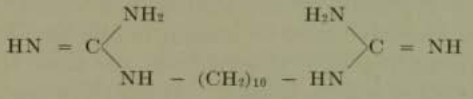
[1] Lawrence: Brit. Med. Jour., 1927, i, 595.
[2] Falta: Klin. Wchnschr., 1924, **3**, 1315.
[3] Basch: Klin. Wchnschr., 1924, **3**, 1861.
[4] Falta: Wien. Arch. f. inn. Med., 1924, **8**, 13.
[5] Radoslav: Ibid., p. 395.
[6] Taussig: Jour. Am. Med. Assn., 1927, **89**, 149.

protein 60 grams and fat 122 grams and 100 units of insulin he excreted 70 grams of sugar with slight acidosis. Physical examination was essentially negative, save for a slightly enlarged liver, blood-pressure 98/62, Wassermann reaction repeatedly negative, spinal fluid Wassermann negative, bilirubin 0.4 mg. per 100 cc., blood sugar 0.23 to 0.30 per cent, non-protein nitrogen 33.0 mg. per 100 cc., sodium chloride in urine 7.2 grams, nitrogen in urine 8.9 grams; gastric contents no free hydrochloric acid, total acidity 13. He went home and eventually required 850 units day after day and two days before his death in coma on October 30, 1927, 1600 units daily. He never showed hypoglycemia or gave evidence of an insulin reaction. "The postmortem showed nothing relative to his diabetes except a moderate fibrosis of the pancreas and atrophic cirrhosis of the liver. The postmortem was very thorough and complete. There was no sign of carcinoma or of any neoplasm anywhere, and no evidence of infection." I understand that the autopsy was performed by a most competent pathologist, and I hope that the patient's physician and he will report the case in detail.

For a theoretical discussion and experimental investigation of the subject consult Hausler and Högler.[1] They conclude that the cells of the insulin refractory diabetic are unable to respond to the action of insulin. Extensive literature can be found in connection with the articles cited in this section.

G. OTHER METHODS OF TREATMENT.

Synthalin.—Synthalin, when given by mouth to a diabetic patient, materially reduces the sugar in the blood and urine and is remarkable in that it is the first drug known to have this power. It was discovered by E. Frank, M. Nothmann and A. Wagner in 1926 and already the literature has become extensive. Professor Frank has told me that it is a dekamethylendiguanidin, the graphic formula of which is:



Under its use a diabetic patient can secure a tolerance for an additional 40 to 45 grams carbohydrate. The usual dose is from 10 to 25 mgms. twice a day for two days in succession, followed by a pause for one or two days. Unfortunately it may give rise to nausea, but this is far less apt to occur with the more recent neosynthalin which contains more methyl groups and is now being investigated. Indeed the chemical compound similar to synthalin which has but 8 methyl groups is very productive of nausea.

[1] Hausler and Högler: Klin. Wchnschr., 1927, **6**, 541.

Synthalin acts slowly and for this reason is contraindicated in coma. It will, however, reduce the acidosis and revive fasting phlorizinized dogs which are comatose from severe acidosis. With the help of synthalin the respiratory quotient can be raised to 0.97, and depancreatized dogs have been kept alive for a period of six weeks with this product. Aside from the temporary digestive disturbances which may arise following its use I have known, in my limited experience, no harm to result from it. Professor Frank told me that no more urobilin or urobilinogen than is normal was found in the urines of patients who had taken synthalin for a year, although Morawitz observed that urobilinuria frequently appeared. Traces of bilirubin in the blood may even disappear with synthalin. Professor Frank has seen but 2 cases of jaundice among 500 patients treated with synthalin, and these patients had taken an unusual amount of synthalin over a long period of time including some three weeks of definite indigestion. As he quite justly points out tests with synthalin should be made with therapeutic, not with toxic doses.

Only one compound of guanidin in nature has so far been recognized—galegin, but it is possible that it may be a component part or at least closely related to insulin. Likewise it may be present in various proprietary preparations or extracts of plants.

The method of administration of neo-synthalin, kindly furnished me by Professor Frank and the Eli Lilly Company, is to give 10 mgms. three times a day for four or five days or 40 mgms. for three or four days. The drug is then omitted for an interval of two days. After a period of some three weeks neo-synthalin is omitted for eight or ten days, during which time either the diet is reduced or more insulin is administered. Neither synthalin nor neo-synthalin should be given constantly.

If diarrhea should occur, calcium carbonate or phosphate, subgallate of bismuth or certain biliary salts may be used to advantage in overcoming it.

The action of synthalin or neo-synthalin is similar to insulin in that just as an excessive dose of insulin is followed by the almost complete disappearance of glycogen from the liver the same phenomenon takes place with synthalin. It will, however, in moderate doses store glycogen in the liver, but to a far less extent than does insulin. Synthalin appears to act upon glucose in such a manner that it makes it utilizable in the metabolism of the cell.

The blood sugar is reduced after synthalin and may fall to normal or nearly normal. Coincident with this, acidosis, if present, decreases. Gain in weight is less frequent than during treatment with insulin; in fact the weight may fall as in my Case No. 4306 and Duncan noted loss in weight when symptoms from excessive dosage were

present. The glucose equivalent of 1 mgm. synthalin is about 1 gm. glucose, and in certain cases which have appeared refractory to insulin it has been reported as effective. But were these cases truly insulin refractive?

Synthalin and neo-synthalin act very slowly and consequently the organism can mobilize epinephrine to counteract the effects. The effect of synthalin seems to become stronger with successive cycles of use.

I have tried synthalin or neo-synthalin with a moderate number of cases and am convinced that it will lower the sugar both in the blood and urine. Few cases have continued it, partly because of the nausea resulting from its use and partly because of improvement in the diabetes. One old lady, Case No. 6490, a school teacher, who lost her right arm in childhood seemed an especially favorable case and when her diabetes in the course of six weeks grew milder and her insulin had been reduced from 30 units to 10 units, 30 mgms. of synthalin were substituted. For a time she needed to continue her insulin, but eventually it was entirely omitted and she is now sugar-free with synthalin alone. Should she omit that too, and continue sugar-free, one cannot help wondering whether her improvement was due to the medication or to persistence in both dietetic and medical treatment. However, synthalin was of real assistance because it allowed her to give up insulin at an earlier stage than she otherwise would have done.

With Case No. 4306 the insulin has been reduced from 28 units daily to 16 units daily during the course of five months and the carbohydrate, protein and fat in the diet maintained at their previous levels. I have tried to omit 6 more units, the evening dose, but as yet without success as glycosuria appears. With another patient, Case No. 5900, insulin 13 units has been totally replaced with synthalin and in an interval of two weeks the patient's blood sugar has fallen nearly to normal. To the former patient 50 mgms. synthalin were given daily for two days and then as a rule omitted for one or two days and the cycle repeated: to the latter 30 mgms. synthalin were given daily for three days and then omitted for a day and then repeated. None of my other cases are as convincing. Still another patient, Case No. 5974, became sugar-free with diet and insulin; the insulin was then omitted and he too remained sugar-free with synthalin, but he was a case of recent onset and might have done so anyway. One patient, Case No. 3483, with hyperthyroidism did better after operation with synthalin replacing insulin, then one would have expected without insulin. This observation is of significance because I have experience, thanks to F. H. Lahey, with 75 cases of diabetes complicated by hyperthyroidism. One patient, Case No. 5608, disliked synthalin; 2 others, also old ladies, Case Nos. 1494 and 3751, with a few grams of sugar in the

urine appeared to be more nearly sugar-free and more consistently sugar-free when synthalin was used.

Priesel and Wagner, in contrast to Hirsch-Kauffmann, have reported unfavorably upon the use of synthalin in children. Ringer *et al.* report favorably upon its use.

I wish to acknowledge my indebtedness to Professor E. Frank of Breslau and to the Messrs. Kahlbaum Company for the privilege of using synthalin. I believe it is worthy of further trial because, with a better knowledge of it, there may be found a group of diabetic cases in whom it can advantageously be employed. More important is the hope that it is the forerunner of other and better preparations which one can give by mouth and that these to a certain extent will replace insulin.

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2. Myrtillin.[1]—When insulin is abundant, it requires a courageous man today to advocate a new remedy in diabetes, and I admire this quality in F. M. Allen and his sincere efforts in seeking to establish the worth of myrtillin by scientific tests before recommending its use to the profession. Dr. Allen has been encouraged by the confirmation of his results of the action of myrtillin with depancreatized dogs in various laboratories, such as E. R. Squibb & Sons and in La Jolla by Sherrill. He has kindly prepared for me the following abstract, and has elsewhere published a report upon myrtillin.

"Because teas or powders of the leaves of plants of the myrtle family were used as a diabetic remedy among the Alpine peasantry, the investigation of their beneficial effects was undertaken by Dr. Richard I. Wagner in Professor Durig's laboratory at the University of Vienna. The substance called myrtillin was thus discovered, and later the leaves of American blueberries were found also to be a favorable source of supply. The myrtillin must be separated from

[1] Allen, F. M.: Jour. Am. Med. Assn., 1927, **89**, 1577.

another substance which raises the blood sugar. Later work has shown that these same two substances are present in variable quantities in all green plants,[1] also yeasts and bacteria. Their nature and composition are unknown, but they are assumed to be anabolic and catabolic factors in the carbohydrate metabolism of plants. It is suspected that myrtillin likewise is present and participates in the metabolism in all living cells, but its demonstration in animal tissue has not been possible, because no means is yet known for separating it from such quantities of protein.

"A few tests of the physiological properties of myrtillin were performed in Vienna in 1925, and animal experiments and clinical trials were then carried out on a wider scale by Dr. Wagner and Dr. F. M. Allen in 1926–1927 at the Physiatric Institute in Morristown, N. J. Myrtillin does not lower the normal blood sugar, and never causes hypoglycemia. It reduces alimentary hyperglycemia in human beings and dogs, but not in rats or rabbits. It prolongs the lives of totally depancreatized dogs to periods ranging from three to seven weeks. When a remnant of one-twentieth or less of the pancreas is left, the dogs if untreated die after a short course of extremely severe diabetes, but with myrtillin they are enabled to thrive indefinitely on mixed diet with sugar-free urine and normal blood sugar.

"For patients, the dosage of myrtillin is three 5 grain (0.3 gm.) tablets per day. One tablet is given one hour before each meal, because a mixture with food interferes with the absorption of myrtillin. No increased benefit is obtained by increasing the dosage above this quantity. The principal advantages of myrtillin are that it is effective when taken by mouth, and that it is entirely harmless even in doses many times larger than the therapeutic dose. The disadvantages are the slow, feeble and uncertain action as compared with insulin. It cannot be recommended for diabetic coma, gangrene or infections, and in cases where myrtillin is acting efficaciously the advent of an infection may create a temporary demand for insulin. The principal action to be expected is a gradual and long-lasting upbuilding of tolerance. For this purpose the patient should be placed in the most favorable position for gaining tolerance. It is a mistake to give myrtillin in the hope of reducing glycosuria in uncontrolled diabetes, for this result is unlikely except in some of the mildest cases. Diet, and if necessary insulin, should first be used to stop glycosuria and to bring the blood sugar to normal. Only then should myrtillin be begun, and the effect should be looked for in a gradual increase of tolerance extending over weeks or months. The success is usually greatest in the mild or moderate cases in later life, and least in the severest forms of diabetes in children and young people. Some youthful cases, however, are decidedly benefited,

[1] Mills reports 7 cases treated with oral adminstration of an alcoholic extract of plants rich in vitamin-B. Glycosuria was reduced. Am. Jour. Med. Sci., 1928, **175**, 376.

while some cases in the elderly show no result. Only actual experience over a period of weeks or months can decide whether a given case will prove a success or a failure. To date the successes have greatly outnumbered the failures.

"One of the benefits often (but not invariably) obtained from myrtillin is a reduction or disappearance of the tendency to violent hypoglycemic symptoms in insulin cases. In a number of juvenile cases especially, the patients or their families have desired to continue the use of myrtillin even when the insulin dosage was not reduced. Another effect noted is that patients sometimes declare that they feel better under myrtillin than under insulin treatment, and there seems to be reason to believe that this result is not imaginary.

"As myrtillin is stored in the body, the effect does not cease promptly when the dosage is discontinued, also the omission of occasional doses does not interfere with the treatment. In some cases sugar gradually returns in one to several weeks after myrtillin is stopped. In other cases the high tolerance seems to continue indefinitely. There are exceptional instances in which the action of myrtillin was so powerful that patients who had been using 40 to 50 units of insulin daily for several years became able to stop insulin altogether. Usually in such severe cases there is only an intermediate degree of success, in the form of a reduction of insulin. But in all favorable cases the most hopeful feature of the myrtillin treatment is the long-lasting improvement of tolerance. Also in all these cases the continued use of myrtillin is advised, in the hope of obtaining the utmost effect of a cumulative or curative character."

In Table 236 I have recorded my data with relation to 3 patients, of whom 1 took myrtillin.

TABLE 236.—THE RESULTS OF TREATMENT OF THREE RELIABLE DIABETICS.

	No myrtillin		Myrtillin		No myrtillin	
Case No.	632		Case No.	3448	Case No.	5738
Age at onset	30 years.		Age at onset	48 years.	Age at onset	42 years.
Year of onset of diabetes	1912		Year of onset of diabetes	1923	Year of onset of diabetes	1917
Succeeding years.	C. P. F. grams.	Insulin, units.	C. P. F. grams.	Insulin, units.	C. P. F. grams.	Insulin, units.
1922	41–72–122	4				
1923	40–74–147	10	70–70–150	24		
1924	38–74–148	14	80–70–140	40		
1925	51–72–148	16	76–65–132	48		
1926	90–79–137	20	76–65–134	60	98–68–134	15
1927	97–76–116	25	100–80–120	48	174–75–125	18
1928	126–73–116	26	100–80–120	40	180–75–105	17

I have tried myrtillin in a considerable number of cases, but I am unable to state whether it has acted favorably. I know it has

been innocuous. To test its action the patient must be aglycosuric and living according to rule. Most patients who can fulfil such conditions with or without the help of insulin improve with time. One is therefore in a quandary to decide whether myrtillin given to such a patient is helpful. Has Case No. 3448, who has taken myrtillin for six months, improved because of myrtillin any more than Case No. 5738 and Case No. 632 who have been without it? In two of the three instances the tolerance for carbohydrate has risen about 75 gms. Two other patients taking myrtillin ascribe their improvement likewise to it, but I remain unconvinced. The patients who have not been sugar-free (and consequently have not fulfilled Dr. Allen's conditions) have not been helped.

3. **Effect of the Feeding of Liver on the Blood Sugar of Diabetic and Non-diabetic Individuals.**—Murphy and Blotner[1] have reported concerning the effect of liver feeding on the blood sugar in diabetic and non-diabetic persons. This study was suggested to them by the fact that the administration of large amounts (200 gms.) of liver to patients with pernicious anemia was followed sometimes by symptoms resembling those due to hypoglycemia. To determine the effect of liver feeding on the blood sugar, patients were first given a control breakfast containing 20 gms. of carbohydrate, 40 gms. of protein, and 35 gms. of fat; the protein being supplied largely by red muscle meat. The blood sugar level was observed at the fasting period and at three hour intervals after the meal for nine hours. On a subsequent day similar observations were made after the administration of a breakfast composed of the same amount of carbohydrate, protein and fat, but in which 180 gms. of raw beef liver pulp replaced the red muscle meat.

In non-diabetic patients the blood sugar nine hours after the control meal was usually at about the same level as before the meal. In diabetics the blood-sugar level, nine hours after the control meal, usually varied from 15 to 50 mgms. below the fasting level. Following the administration of the meal containing liver the blood sugar of both diabetics and non-diabetics was distinctly lower nine hours after the meal than before it. This difference was usually greatest in the diabetic patients in whom the decrease in blood sugar often amounted to as much as from 80 to 120 mgms.

The studies indicate that the ingestion of 180 gms. of liver is as effective in lowering the blood sugar in diabetics as about 10 or 15 units of insulin. Furthermore, patients continuing to take daily about 180 gms. of liver for some days have maintained a distinctly lower fasting blood-sugar level than when their diet contained the same amount of carbohydrate, protein and fat but did not contain liver. This is comparable to what occurs following the daily use of insulin.

[1] Murphy and Blotner: Jour. Clin. Invest., 1927, **4**, 440.

SECTION IX.

THE TREATMENT OF ACID INTOXICATION AND DIABETIC COMA.[1]

Introduction.—Sixty-three instances of coma in 53 patients with 6 fatalities have occurred on the service of the writer and his associates at the Deaconess Hospital.[2] All received insulin, none received alkalis or glucose. As shown by autopsy 1 death, Case No. 3267, was due to acute pancreatitis; 1, Case No. 4525, to a vulval abscess with general peritonitis; 1, Case No. 5176, to pulmonary infarct, empyema and thyroid storm eleven days after recovery from coma; 1, Case No. 5784, to alkalosis and tetany thirteen days after recovery and 2 patients, Cases No. 3021 and 3240, died from inadequate doses of insulin during 1923. Four of the deaths were easily preventable and all of the cases of coma developed needlessly. The death from pancreatitis was unavoidable and the death from alkalosis with tetany is still not satisfactorily explained.

The quantity of insulin given on the first day averaged 132 units in the first 33 cases and 166 in the second series, range 20 to 300 units among those that recovered, upon the second day 66 units in the first series and 60 in the second, range 10 to 210 units, and upon the third day 56 and 49 units respectively, range 12 to 175 units. Glucose was not given during the coma, but was administered later to 1 patient on account of hypoglycemia. There had been many punctures of the vein for therapeutic tests. We have all wondered whether the later appearing pulmonary embolism with subsequent empyema might have originated in this manner. Alkalis have not been given to my patients since 1916, and even before the discovery of insulin there were 15 recoveries with acidosis as severe as that represented by plasma CO_2 combining power of 18 volumes per cent, by CO_2 tension in the alveolar air of 18 mm. mercury or

[1] Joslin, Root and White: Med. Clin. North America, 1925, **8**, 1873; 1927, **10**, 1281. See also for reports of series of cases: Violin: Wien. klin. Wchnschr., 1926, **39**, 1304. Leake: California and West. Med., 1927, **26**, 475. Faber and Holst: Acta Med. Scand., 1927, **65**, 461. Frissell and Hajek: Jour. Am. Med. Assn., 1926, **86**, 1903. Petrén: Verdauungs. u. Stoffwechsel-Krankh., 2d ed., 1927, vol. **8**, Heft 5. Odin: Acta Med. Scand., 1927, Supp. 18.

[2] These cases occurred between April 1923, and March 1, 1927, but up to March 31, 1928 there have been 26 others, of whom 1 died of septicemia six days after recovery from coma and another within six hours of entrance, showing pneumonia at autopsy.

less. But I cheerfully acknowledge that the normal salt solution, of which I have made great use, given subcutaneously, has probably acted as an alkali although I believe in a better way than sodium bicarbonate given by the intravenous method or by mouth.

A. **Frequency of Coma.**—Coma as a cause of death is uncommon today in my practice or among my former patients. Six cases only out of 1138 diabetics treated died of it in the year ending July 1926, and there was no death from coma among 1241 traced, representing 93 per cent of the 1329 seen in the next twelve months. Cancer was as common as fatal coma in the former year and still more so in the latter. Non-fatal coma, however, is by no means unusual, and among those who have it come first of all the children. Forty-five children of the 200 or more living children have already had it altogether 53 times, although not one child under fifteen years of age died of it during the above two years. In fact, coma led to the discovery of diabetes in children in 9 instances.

The explanation of the frequency of coma today is easy. As long as a diabetic patient does not overeat he will not contract coma, will not die of coma, though he may die of inanition. He can overeat of food carelessly or overeat of his own body innocently, because in fever or in hyperthyroidism he does not realize his metabolism is raised and he is overeating. However, overeating for a diabetic is a very different proposition from overeating for a healthy man. The calories which constitute even a normal diet for a man in health represent overeating, an excessive diet, for the patient with diabetes. The only way the severest diabetics can exist is by undereating, by living on a lowered plane of metabolism. Insulin, it is true, allows the intake of a normal quantity of food, but every insulin-taking diabetic is overeating so far as his own resources are concerned, and if he omits his insulin and continues his food he will pay the penalty of the reckless and disobedient diabetic, and if a severe case will develop coma. Furthermore, even if he stops eating and gives up insulin he may develop coma, because he no longer is the thin diabetic with a low metabolism, who can oxidize the little carbohydrate, protein, and fat which his emaciated body requires; today he is so well nourished that his own tissues are capable of furnishing him many hearty meals which he cannot utilize without insulin. He is the fat and not the thin depancreatized diabetic dog. Therefore, every insulin diabetic is overeating, and since overeating leads to coma, every insulin diabetic is a potential coma case, and should be treated accordingly.

In Hyperthyroidism.—If there is an interrelationship of glands of internal secretion in diabetes one would expect to find evidence of this during such a diabetic crisis as coma. Three cases, Cases No. 4289, 4306, 5176, did, as a matter of fact, show thyroid activation near the period of the coma. This appears like a considerable pro-

portion, but it can hardly be regarded as such, because we have had, up to February, 1927, 75 cases of true diabetes associated with thyroid disease, of whom all have been operated upon and yet only 1 has had coma. It is difficult to say which condition antedated the other in the 3 cases which showed increased thyroid activity near the period of coma. The thyroid activation was recognized in all 3 before the impending acidosis and the cases were seen in consultation by Dr. F. H. Lahey. All 3 recovered from coma more quickly than is usual, and none had insulin shock.

Of these 3 cases of hyperthyroidism with coma 2 were fatal. Case No. 5176 in this series recovered from both coma and thyroid storm to die seven days after the coma from multiple pulmonary emboli and empyema. Patients with diabetes and thyroid disease change their status with surprising rapidity. The ordinary diabetic goes to bed at night mild and wakes up in the morning severe for want of insulin, but the thyroid diabetic's metamorphosis is far more rapid. He changes his status like a flash and one must be on the *qui vive* for acidosis, hypoglycemia, and hyperthyroidism. This patient went through all of these states with a suddenness which was surprising to nurses and doctors who have been in close contact with both thyroid cases and diabetic cases for years. A good many punctures of the veins were made and we cannot help thinking that some one of these may have led to the emboli in the lungs which appeared to lead to a general pulmonary infection, empyema, and death. Possibly the emboli arose in the heart, as auricular fibrillation was present, the pulse-rate reaching 270, and the blood-pressure taken three times varied between 55 and 132. Since our experience with pulmonary embolism in this case we have curtailed the number of venepunctures in the course of coma and now depend for many of our estimations of the blood sugar upon micro methods. It would not be surprising if pulmonary embolism should occur more frequently in patients treated with intravenous injections of glucose and sodium bicarbonate than with patients not receiving such injections. It is for this reason that we report this case. We notice that Foster[1] and Bowen and Beck[2] warn against the dangers of intravenous therapy in coma, though without prohibiting it or, as a matter of fact, mentioning thrombosis, which existed in our case.

B. **The Usual Causes of Coma are Preventable.**—If an insulin-treated diabetic omits his insulin, he should be taught that he is in danger of coma when sugar appears in his urine, even though he curtails or omits his diet. He must be made to realize that he can overeat his own tissues and that he always requires insulin as long as sugar shows.

[1] Foster: Jour. Am. Med. Assn., 1925, **84**, 719.
[2] Bowen and Beck: Bull. Buffalo Gen. Hosp., 1925, **3**, 13.

It pays to prevent coma rather than to treat it. Diabetic coma wastes a hospital bed, because it means that the previous instruction of the patient was inadequate.

Irregularities of diet exceed by far any other cause of coma. The little son of my Case No. 4501 cries if he sees his mother break her diet because he is afraid he will lose her. Clawson and Harrop[1] report an eleven-year-old girl treated for coma twelve times and dietary excess was the cause on ten occasions. A history of broken diet was obtained in 70 per cent of our series. The girl whose first attack was precipitated by "banana royal and hot dogs"[2] when she returned in her second experience had peanuts washed out of her stomach, to the edification and we hope to the future salvation of the other patients in the ward. Nausea and vomiting were actually present in 76 per cent of the last 30 coma admissions. Though it is true the diabetic is not exempt from the conditions causing nausea and vomiting other than acidosis, such as indigestion, duodenal ulcer, acute appendicitis, gall stones, coronary thrombosis, acute infectious diseases, any one of these conditions can and will precipitate coma. One state passes quickly into the other, each masking the other and making the end-result more serious. Unable to take food, the uneducated, unprepared diabetic patient omits his insulin and coma follows. We have been forced to conclude that in diabetes vomiting is an evil omen and unless heeded leads to death.

The number of cases of coma precipitated by infections has increased. Of the 30 admissions for coma since May, 1925, 60 per cent had a temperature above 99.6° F. The infections for the most part were not severe in type with the exception of two instances, an acute pancreatitis with fat necrosis and a carbuncle which was followed by peritonitis and septicemia. In the remainder the infections were of an upper respiratory nature, tonsillitis, and otitis media. In not a single case had the patient been adhering both to a regular schedule of diet and insulin.

Four of the cases had been untreated, and 1 had been fasted prior to the onset of his coma.

The slow onset of coma allows time to check it. In this series the symptoms preceded the onset by more than twenty-four hours in every instance, notwithstanding the presence of an overwhelming infection in 2 of the cases and in 1 case a thyroid storm.

C. **Patients Prone to Coma.**—Coma attacks the young diabetic and the diabetic who is in the first few years of his disease. Thirty of our 63 cases of coma treated recently were below twenty years of age. Twenty-eight of these were between ten and twenty years of

[1] Clawson and Harrop: Jour. Am. Med. Assn., 1927, **89**, 23.

[2] Banana with three kinds of ice cream and three syrups plus nuts and cherries, together with hot Frankfurt sausages in a buttered roll.

age. The adolescent is coma's shining mark. These figures apply to the cases treated in the hospital. The distribution according to the age of the 122 fatal cases of coma among the 609 deaths in diabetes since the introduction of insulin is shown in Table 237.

TABLE 237.—AGE DISTRIBUTION OF ALL REPORTED DEATHS FROM COMA IN AUTHOR'S SERIES, AUGUST, 1922, TO JULY, 1926.

Age at death decades.	Coma.	
	Cases.	Per cent.
0– 9	7	5.7
10–19	20	16.4
20–29	19	15.6
30–39	17	13.9
40–49	11	9.0
50–59	22	18.1
60–69	17	13.9
70–79	9	7.4
	122	100.0

Coma has been no respector of age, so far as our total statistics go, because the number of deaths was almost the same in the first and eighth decades, the percentage in each of these decades to total coma deaths, August, 1922, to July, 1926, was 5.7 and 7.4 per cent.

A better realization of the far greater frequency of coma in the early years of life is obtained by comparing these high percentages with the low percentages of diabetics whose disease begins under forty years. (See Table 50.) The high percentage of deaths from coma in the sixth decade is explained by the years fifty and fifty-one, which are the peak years for onset of diabetes in women and men respectively.

TABLE 238.—DURATION OF DIABETES AND ITS RELATION TO REPORTED DEATHS FROM COMA SINCE THE ADVENT OF INSULIN.

Duration of diabetes, yrs.	Coma.	
	Cases.	Per cent.
0– 1	8	6.6
1– 2	20	16.4
2– 3	24	19.7
3– 4	16	13.1
4– 5	7	5.7
5– 6	6	5.0
6– 7	3	2.5
7– 8	10	8.2
8– 9	8	6.6
9–10	3	2.5
10–11	5	4.1
11–12	1	0.8
12–13	2	1.6
13–14	2	1.6
14–15	2	1.6
15–16	1	0.8
17–18	1	0.8
19–20	2	1.6
20–21	1	0.8

Will one-half of all the deaths from coma take place during the first four years of the disease? This is the period, therefore, upon which all should concentrate their efforts in attempting to overcome coma. Coma is exceptional after ten years of diabetes. Among the 63 hospital cases there was 1 over this duration and among the 122 fatal coma cases since insulin there were reported but 12 cases in whom diabetes had been present for over ten years. This represents but 10 per cent of the total deaths from coma. In none of Petrén's[1] series of 28 comas in 25 patients was the duration of the disease over four years, and, in fact, all but 8 of his cases were under one year's duration.

The first four years of diabetes and the second decade of life are the best hunting grounds for lowering mortality in diabetes, because here coma is most frequent and coma is the most easily preventable of all the causes of death in diabetes. Consider, in contrast, the difficulty of making headway against that still more common cause of death in diabetes, namely, arteriosclerosis.

The mild diabetic is not immune to coma. One man who had an amputation of a leg at the hospital at sixty-two years of age, Case No. 5126, left with a diet of carbohydrate 113 grams and no insulin. One month after discharge we learned that he had died of true diabetic coma. Eighty per cent of our coma cases treated in the hospital since 1925 have been relatively mild diabetics.

Six of the 53 hospital patients, whose attacks of coma numbered 63 in all, died in the hospital, and we have traced and learned of 6 other deaths among this group since discharge, 1 each from coma, pneumonia, pulmonary tuberculosis, myocarditis, gangrene, and septicemia. The remaining 41 cases are alive at varying periods from four years to a few months since the outbreak of coma.

It is still the poorer class of patients in whom the incidence of coma is highest.

Influence of Weight.—The weight of but 1 coma case at the time of coma exceeded 140 pounds, and the weights of but 4 coma patients were as much as 130 pounds. Another patient was not weighed, but probably was in excess of 130 pounds. This low average weight represented the result of the ravages of diabetes but the loss was not extreme, because approximately only 15, or 43 per cent, were fat at any previous time in contrast to 75 per cent for 1000 diabetics of our series. The fat diabetic can get coma, but it takes gross mismanagement to produce it. It would be of great interest, and of importance, too, to determine the changes in weight in coma.

Case No. 3129 developed ascites during his convalescence from coma, but he, too, had received 1 liter of salt solution.

[1] Petrén: Ergebn. d. inn. Med. u. Kinderh., 1925, **28**, 92.

D. **Symptoms and Signs in Coma.**—The symptoms of diabetic coma are notoriously vague and even to a doctor the diagnosis often proves elusive. The spectre of threatening diabetic coma should always haunt the physician, particularly when the patient is first seen. It is astonishing how insidiously coma steals over a patient, and I have given up expecting nurses, unless they have had great experience with diabetic patients, to recognize its approach. It is better to treat any symptom out of the ordinary as premonitory of coma and better for patients when they feel sick to begin coma precautions than to run the risk of beginning treatment too late. Despite the only too large number of cases of diabetic coma which I have seen myself, more than once I have been chagrined at having failed to realize its onset. Any occurrence out of the ordinary should arouse suspicion, and one should instantly investigate any of the following symptoms: anorexia, nausea, vomiting, restlessness, unusual fatigue, excitement, vertigo, tinnitus aurium, drowsiness, listlessness, discomfort, painful or deep breathing. In the presence of fever always be on the alert for coma.

Rules for the prevention of coma consequently are taught to all of my patients to be followed whenever they feel indisposed from any cause whatsoever. These measures can do no harm under any conditions and by their adoption in the early stages of acidosis will avert it in all but the most desperate cases. They are as follows: (1) Go to bed whenever indisposed; (2) call the doctor; (3) drink a glass of liquid each hour—such as coffee, tea, broths, diluted orange juice, water oatmeal gruel; (4) secure a nurse or at least someone to wait upon you and save your strength; (5) move the bowels by enema, and, if liquids have not been retained by mouth, follow the enema by an injection of 1 pint luke warm water containing a teaspoonful of salt; (6) keep warm; (7) never omit insulin when the urine contains sugar.

Nausea, vomiting, hyperpnea, drowsiness (or coma), hyperglycemia, and ketonuria and ketonemia are the cardinal symptoms and signs of diabetic coma. Added to these are vague pains in any part of the body, and useful in diagnosis is the history of irregularity in diet or insulin, of an infection or of an increase in metabolism.

The frequency of nausea and vomiting we have already stressed. Their significance we cannot overemphasize. Hyperpnea usually follows the vomiting. Küssmaul breathing is the most significant clinical finding. It was constant in 60 of the 63 cases. One exceptional patient had a blood CO_2 under 20 volumes per cent without Küssmaul respiration or acetonuria. The absence of acetonuria might be explained on the ground of renal pathology, a perinephric abscess and a chronic nephritis.

Coma, complete unconsciousness, was present in 12 cases. The

others could be roused in spite of the fact that the CO_2 was 20 volumes per cent or below in all but 10, and 15 volumes per cent or below in one-half of the cases.

The soft eyeball in diabetic coma is a sign of considerable value. It was originally described by Krause[1] and subsequently its importance emphasized by Riesman.[2] It is not due to blood-pressure changes, or is it agonal, for it is not present in persons dying from other causes. Krause observed it in 22 cases of coma. I have repeatedly observed it in coma and have noted its absence in coma of non-diabetic origin. In our series of 50 cases in which it was especially observed it was present in 29.

Glycosuria as pointed out by Dr. H. F. Root was not excessive. One case had a nearly sugar-free specimen on admission, due to the fact that she was a repeated offender and had taken large doses of insulin just prior to admission. Usually there are several patients in the hospital who have shown at the time of their entrance 6 to 10 per cent of sugar in the urine. These are not the patients whom one sees in coma. Fifty-three of the patients had a glycosuria which was less than 5 per cent.

The concentration of salt and nitrogen in the urine is also low in coma and rises with recovery. The urinary nitrogen is not a guide to the protein metabolism, because of the state of the kidneys. This was noted years ago by Magnus Levy and Joslin. Bulger and Peters[3] found that the blood, on the other hand, was concentrated by dehydration in coma, but became more diluted with recovery.

The demonstration of acetone or diacetic acid is almost a requisite for a diagnosis. However, it was not present in 2 of these cases. One has already been described. In the other no specimen of urine was obtained until the patient had received vigorous treatment for several hours.

The urine may contain acetone and diacetic acid and yet the patient be well over the serious stage of acidosis. In this instance one is dealing with urine which was secreted hours before, but retained in the bladder. The possibility of retained urine must always be borne in mind.

The alterations in the blood, in the alimentary, circulatory, renal, glandular and respiratory systems are so profound that each merits a special discussion.

1. **The Blood in Coma.**—(*a*) *Blood Sugar.*—The sugar in the blood in coma is high. This is in contrast to the comparatively low percentage of sugar in the urine, though doubtless this too is high

[1] Krause: Verhandl. d. XXI Kong. f. inn. Med., 1904, p. 439.
[2] Riesman: Jour. Am. Med. Assn., 1916, **66**, 85.
[3] Bulger and Peters: Arch. Int. Med., 1925, **36**, 857.

in the prodromal stage. When the patient is overeating, the excretion of sugar is large, but when nausea and vomiting set in, the sugar in the urine quickly falls, because there is comparatively little source for urinary sugar save from meager glycogen stores, catabolized body protein, and that in the blood, which in this state may be considerable, reaching 1.62 per cent in Case No. 4099 who recovered in October, 1927.[1] Any antiketogenic effect which the diabetic may derive from his carbohydrate debauch is fleeting, but the harmful ketogenic effect of his orgies in protein and fat is "oft interred with his bones." During 1923 and 1924 no case of coma showed a percentage of sugar in the blood above 0.73 per cent, but 2 later cases have reached 0.90 per cent and 1.62 per cent. Attention has been called to the patient with a blood-sugar percentage of 1.37, and Olmsted and Kahn[2] have recorded a similar case. Dehydration and nephritis apparently accounted in large measure for each of these figures. The blood sugar of our 1923 cases averaged 0.39 per cent; our 1924 cases 0.43 per cent, and in 1925 the percentage of sugar was 0.52. As insulin has often been given before the blood has been taken for a test for sugar, the percentage of sugar has undoubtedly been higher than these figures would indicate.

How high the percentage of sugar in the blood can rise without the development of acidosis we do no remember to have seen stated. We can say, however, that using as a measure of acidosis the ferric chloride test we have found acidosis absent and a blood-sugar value of 1.37 per cent. (Case No. 1015.)

The height of the percentage of sugar in the blood above normal bears little relation to the consciousness of the patient. The patient with the blood-sugar value of 1.37 per cent could be roused, the patient with a blood sugar of 0.90 per cent was responsive, as was our recent imminent coma case, Case No. 3877, with 0.78 per cent. The high blood-sugar value of Case No. 3877 is all the more notable because the patient had already received, three hours before coming to the hospital, 60 units of insulin. The common cause for unconsciouness in diabetic coma, therefore, must be sought elsewhere than in the percentage of sugar in the blood. This much, however, can be said—we have seen no patient at the time of an attack of diabetic coma who was unconscious when the percentage of sugar in the blood was below 0.49. Of course cases of hypoglycemia are excluded.

The average fall in the percentage of sugar in the blood from the first day to the second and third days was as follows: First day, 0.47; second day, 0.23; third day, 0.26.

Argy[3] reports a colored male, aged thirty-three years, who entered the hospital in profound coma with diabetes of six months' duration.

[1] Curtis and Dixson: Iour. Am. Med. Assn. 1928, **90**, 1115.
[2] Olmsted and Kahn: Jour. Am. Med. Assn., 1923, **80**, 1903.
[3] Argy: Boston Med. and Surg. Jour., 1925, **193**, 1236.

Five days previously he was seized with nausea, vomiting, and severe epigastric pain. Under a low-carbohydrate diet and high-fluid regime he improved. Two days before admittance he made a lemonade, sweetening it with 1 pound of sugar and drank it all in one draught. A few hours later he developed complete coma. Sugar was present in the urine but no acetone or diacetic acid or could they be found upon repeated examination. White blood count 10,000, non-protein nitrogen 152 mg. per 100 cc. and blood sugar 1.714 per cent. Gradually the blood sugar fell to 0.582 at the end of thirty-six hours. The postmortem was made by the Pathological Unit of the Army Medical Museum in Washington and showed a chronic parenchymatous and diffuse nephritis; a focal necrosis of the liver with fatty degeneration; a cerebral edema and a chronic interstitial fibrosis of the pancreas.

The pancreas was enlarged, 33 cm. in length, was firm on palpation, fibrous and markedly lobulated. Histological section revealed a dense fibrosis which amounted to conspicuous scars in numerous areas. In its distribution, the fibrosis tended to isolate many of the acini and the new tissue formed heavy capsules about the islands of Langerhans. The latter were deficient in number and presented a fibrous invasion. The cells were cloudy but the cytoplasm was apparently intact. Stains failed to demonstrate lipids to any extent.

In the kidneys there was an advanced fatty degeneration and necrosis throughout, involving mainly the high type of epithelial cells. Only the epithelium of the collecting tubules was normal. The glomeruli were swollen, with little cell infiltration, but marked degeneration.

(*b*) *Carbon Dioxide in the Blood.*[1]—The lowest value for the plasma CO_2 combining power in volumes per cent in our cases was 5. This was below the scale and therefore estimated to be 5; in a few hours it rose to 8 and later to 14 volumes per cent. How much lower the CO_2 can fall and yet be compatible with life we do not know. The CO_2 remained under 20 volumes per cent for five days

TABLE 239.—PERSISTENT LOW PLASMA CO_2 COMBINING POWER IN COMA WITH RECOVERY.

Case No.	Days.				
	1	2	3	4	5
3129	8.0	18.5	19.5	13.6	18.0
4171	14.0	20.0	25.0		
4232	10.9	22.0	20.0	26.0	

in Case No. 3129. (See Table 239.) In these cases the blood sugar had not been brought to normal, and upon studying the protocols of their treatment it is evident too little insulin was given.

[1] All figures for CO_2 in the blood mean the CO_2 combining power of the plasma saturated at normal alveolar tension expressed in volumes per cent.

During the days these patients remained with a low CO_2 value in the plasma they appeared to be in a state of exhaustion rather than suffering from acidosis *per se*. They had not regained their ability to eat. Very likely, however, the exhaustion in reality was a symptom of their acidosis.

The average value for the CO_2 in the plasma for the 63 cases was 16. Certain of these values represent an analysis after the first dose of insulin. On the second day of the coma period the CO_2 had risen to 32.8 volumes per cent, and on the third day averaged 31.8 volumes per cent. Undoubtedly these values are low because they represent averages based upon those coma cases convalescing slowly rather than rapidly. These evidences of persisting acidosis correspond with the clinical relapses toward the coma state which patients are prone to show as a result of lack of alertness in treatment.

As yet I have seen no confirmation of the enhancement of the growth of certain bacteria in the blood of children in coma or precoma as observed by Hirsch-Kauffmann and Heimann-Trosien.[1] They did not attribute this phenomenon to glucose, the ketone bodies or lipids.

(*c*) *Leukocytosis.*—A leukocytosis is the rule in coma. Leukocyte counts were made in 19 cases of the last 30 and in but 3, Case Nos. 4710, 4740, 5121, were the number of corpuscles 10,000 per cm. or less. The 4 cases with severe infections showed a range in the white count from 20,550 to 31,450. In 5 cases the stomach upon lavage showed blood. Four of these cases were without the history of an infection and the highest count of all, 81,400, was noted in this group. The range of the count in the 5 cases who were without any apparent infection or hemorrhage from the stomach was 15,000—44,100. Allan[2] has recently reported a leukocytosis ranging from 16,000 to 60,000 in 5 cases none of whom gave definite evidences of infection.

2. **Discrepancies Between Clinical and Chemical Data.**—The discrepancy between coma (unconsciousness) Küssmaul respiration, and the plasma CO_2 and sugar we have already recorded, but in 2 of our coma cases it especially attracted our attention. A boy, Case No. 3129, entered the hospital in a wheel chair with CO_2 in the plasma of 8 volumes per cent and yet conscious, and his improvement with a single dose of 40 units of insulin was spectacular. In Case No. 2786 the content of sugar in the blood after the patient had received 70 units of insulin was 0.59 per cent, and even after three and a half hours when 70 more units were given was essentially the same, 0.58 per cent; yet two hours before this second blood sample was taken it was perfectly evident to onlookers that the

[1] Hirsch-Kauffmann and Heimann-Trosien: Klin. Wchnschr., 1926, **5**, 1922.
[2] Allan, F. N.: Am. Jour. Med. Sci., 1927, **174**, 506.

patient was clinically improving. During this interval the change in CO_2 content was from 13 volumes per cent to 15 volumes per cent. Administration of insulin was stopped not because of the slight changes in the blood, but because of the clinical improvement of the patient. As Dr. Christian remarked the next day when he happened to visit the hospital: "Here is an illustration of recovery in the ward and death in the laboratory in contrast to the more frequent experience of a clinical death and a laboratory cure." He offered the further suggestion that the condition of the blood was not an index of the condition of the tissues. This may be the correct explanation of those cases of coma who die despite the fact that the blood alkalinity has returned to normal.

3. **Gastro-intestinal.**—Gastric symptoms are constant. Abdominal findings are frequent. Four patients, Cases No. 3129, 3224, 4710, 5630, were seen by surgical consultants because of abdominal tenderness and muscular spasm with abdominal pain, nausea, and vomiting. Warfield believes in some cases this may be related to a pancreatitis. Case No. 2982 had an abdominal operation, with negative abdominal findings. Case No. 4740 was a problem for several days. The diagnosis of acute gall-bladder disease was made when coma was impending. With recovery from coma his signs and symptoms disappeared entirely. As all these patients had fever and leukocytosis a differential diagnosis was extremely difficult. In spite of our findings, however, we believe that even though coma is present, if a surgeon feels reasonably sure that the patient has an acute lesion in the abdomen, operation is the safer procedure, because an acute abdominal infection may not only precipitate coma in the diabetic but prolong it as well.

Explanation of the gastro-intestinal symptoms is difficult. Dilated stomachs, even with evidence of hemorrhage, would not give just the picture one so commonly encounters. Moreover, a dilated stomach was absent in some of this group in whom abdominal symptoms were present. Pancreatitis should be considered because of the occurrence of pain in the upper left quadrant of the abdomen. But there is little clinically to suggest it. These cases do not have pancreatic stools. It is true that 1 of the 4 cases which came to autopsy showed an acute pancreatitis. We feel confident, however, that this was the predisposing cause rather than the result of the coma.

Large quantities of old blood in the vomitus late in diabetic coma and in the contents of the stomach after death are frequently found. The presence of so much blood is positive proof of the susceptible state of the stomach in diabetic coma and emphasizes every rule given for its protection. The hemorrhage is not like that from an ulcer, but it is the hemorrhage such as one sees in

various toxic conditions. At autopsy the walls of the stomach have appeared pale and very thin. The rugæ are entirely flattened out and the lining membrane shows small petechial hemorrhages. Dr. Lawrence Smith points out that the dilation of the stomach stretches its walls with the result that the muscle-fibers are separated.[1] The walls of the capillaries are so stretched that the blood probably escapes not so much by rupture of their walls as by diapedesis. This is also favored by circulatory stasis.

Hematemesis in coma is furthermore important, because it represents an additional depletion of circulating fluid. There may be an anemia during coma which the concentration of the blood conceals.

Ehrmann and Jacoby[2] observed hemorrhages especially in the brain and lungs in 12 cases of coma. In 5 of these cases spasms of face or extremities had been present.

A leukocytosis may furnish evidence of hemorrhage in coma. Often the leukocytosis in coma can be explained by the presence of an infection, but this is by no means an invariable rule. The leukocytosis may in part be explained by the hemorrhage itself.

4. **Circulatory.**—A poor peripheral circulation characterizes nearly all advanced cases. Low blood-pressure and tachycardia were common. In 65 per cent of the last 30 patients the pulse-rate was 130 or above.

(*a*) *Pulse-rate.*—The pulse-rate in our series varied greatly. With Case No. 3877 before the stomach was emptied it was 212, but afterward it fell quickly to 160. Of 35 cases in which the pulse was especially observed, only in 3 was it below 100, in 20 it was between 100 and 120 and in 12 above 120. One can hardly relate the pulse to the basal metabolism, because it was so feeble. Indeed, it would appear always desirable to combine blood-pressure estimations with the pulse-rate when endeavoring to correlate the pulse-rate and basal metabolism. The rapidity of the pulse may be out of proportion to the intensity of coma, and when its cause from a dilated stomach was found and remedied in Case No. 3877 it fell from 212 to 160 beats in a few moments. Case No. 3240 we believe died largely because the stomach was not emptied earlier. The patient is so far *in extremis* that it takes but a slight additional burden upon the heart to cause death.

There is some evidence of disorderly heart action. Auricular flutter occurred in Case No. 4306, age at coma thirty-six years; auricular fibrillation in Case No. 5176, age at coma forty-three years; heart-block in severe acidosis, not quite coma, in Case No. 1794, at thirty-three years; and alternation in Case 4157, age at coma fifty-four years.

[1] In Case No. 6729 in March, 1928 2050 cc. of tarry contents were removed at entrance to the hospital in coma. Six hours later 1000 cc. of similar fluid were removed.

[2] Ehrmann and Jacoby: Klin. Wchnschr., 1925, **4**, 2151.

Clinical signs of dilatation such as temporary extension of the borders beyond normal limits with murmurs and irregularities were not infrequent.

(*b*) *Blood-pressure.*—The systolic pressure could not be read in 2 cases, was below 100 in 9 others, varied between 100 and 120 in 17 more, and between 120 and 160 in the remaining 17 patients. The systolic blood-pressure in coma under present methods of treatment is therefore not so low as often reported, or in fact as we ourselves have thought. Case No. 3382 recovered when the blood-pressure was 78/60 mm. Hg., but Case No. 3021 died when his blood-pressure was 70/30. Case No. 6729 recovered on March 10, 1928, with a blood-pressure of 60 mm.

5. **Renal.**—The role played by the kidney is important in coma both during the actual attack and also during the days immediately following it. Casts, red cells, traces of albumin, are nearly constant, oliguria frequent, and anuria occasionally occurs as it did in 3 of our cases. Snapper[1] finds a peculiar insufficiency of the kidneys in coma characterized by retention of nitrogen and inability to oxidize β-oxybutyric acid and diacetic acid, which are rapidly destroyed by the normal kidney. Odin[2] also found evidence of renal injury practically constant in coma and increasing with the lowering of the CO_2. This happened with eventual recovery in Case No. 4232 who received four injections of normal saline subcutaneously. She developed edema, a rare condition in the coma case, but here undoubtedly due to renal block as is shown by her non-protein nitrogen of 53, 69, and 139 mg. per 100 cc. blood on the three successive days of coma. This patient had been given insulin without a diabetic diet, had taken insulin regularly, always injecting it in the same spot until an abscess formed; following this she came to the hospital in coma.

Already attention has been called to the dangers of catheterization of the bladder, but these should be emphasized, because at the time this is done the patients are especially feeble and their kidneys vulnerable. One should get rid of an "in-dwelling" catheter as soon as possible.

Warburg,[3] in an admirable historical description of coma, includes cases without diacetic acid in which the renal deficiency brought on by acidosis was the chief factor. He noted that insulin treatment diminished the renal irritation. These cases of coma without diacetic acid[4] in the urine may have outlived their acidosis, though we recognize that this is not the usual and more probable explana-

[1] Snapper: Med. Klin., 1927, **23**, 897.
[2] Odin: Acta med. Scandin., Supp. 18, 1927, **18**, 520.
[3] Warburg: Acta med. Scandin., 1924, **61**, 301. Also Hospitalistidende, 1924, **67**, 809.
[4] Starr and Fitz: Arch. Int. Med., 1924, **33**, 97. Appel and Cooper: Am. Jour. Med. Sci., 1927, **173**, 201

tion. Anuria developed not infrequently. I first observed it with Case No. 1015, see p. 213.

The non-protein nitrogen may be normal in coma and it may range as high as 138 mg. per 100 cc. blood. The average for the first day was 46.3 mg., and for the second 44.1 mg.

The correlation of the high non-protein nitrogen values with diabetic coma does not appear difficult to explain. Large quantities of acid and salts are excreted by the kidney and these probably result in impaired efficiency. A rise above 40 mg. occurred in 14 out of 25 cases. The non-protein nitrogen did not always fall in proportion to the degree of recovery from coma. High values persisted on the second and even on the third day. Case No. 4978 had symptoms of uremia on the third day. In general the severer the case and the more prolonged the coma, the higher the non-protein nitrogen.

Then, too, in these patients with a late developing high non-protein nitrogen in the blood the values for CO_2 in the plasma are low and remain low for a longer period than usual. One must certainly bear in mind, therefore, the possibility of other acid factors being present as emphasized by Starr and Fitz and by Arlie Bock. Improvement in these cases, however, is not dependent exclusively on the administration of alkalies.

Another explanation of the renal block must be considered which is not dependent primarily upon the renal block, but is associated with the large doses of insulin which patients are given in diabetic coma. Upon an analysis of these 63 cases it appears that in general the more insulin they received the higher the non-protein nitrogen values. Thus Mary M., Case No. 4232, received 300 units on her first day and her non-protein nitrogen values rose daily as follows: 53, 69, 139 mg. per 100 cc. I. J., Case No. 4987, received 350 units upon the first day and her non-protein nitrogen rose on successive days also as follows: 41 and 55 (first twenty-four-fours), 72, 106, 115 mg. per 100 cc. If we compare the insulin dosage and the non-protein nitrogens in the coma cases it appears that of 17 cases receiving 200 units of insulin during the first twenty-four hours, 14 had a non-protein nitrogen over 40 mg., on the first or second day, whereas of 19 cases receiving less than 125 units there were but 3 with a value above that level.

If one examines the 3 cases of diabetic coma associated with "acute nephritis" reported by Bowen and Beck,[1] one obtains further evidence pointing in this direction.

Their cases are tabulated below.

Suggestive evidence is also afforded in a case report of John.[2] His patient received a large quantity of insulin and later, on the

[1] Bowen and Beck: Bull. Buffalo Gen. Hosp., 1925, **3**, 131.
[2] John: Jour. Am. Med. Assn., 1925, **84**, 1400.

third day, the urea nitrogen rose to 162 mg. and still later to 255 mg. per 100 cc., but before it had reached this maximum the insulin has been greatly decreased, which is obviously out of harmony with insulin being a factor.

TABLE 240.—THE RELATION OF LARGE DOSES OF INSULIN TO LARGE QUANTITIES OF NON-PROTEIN NITROGEN IN THE BLOOD IN COMA. (BOWEN AND BECK.)

Case.	Insulin, units (first day of coma).	Blood- urea-nitrogen, mg. per 100 cc.; day.			
		1	2	3	4
I	350	14	80	102	87
II	265	40	70	70	80
III	190+	30	51		

In our cases we attributed the return of the urinary secretion simply to the forcing of liquids of all kinds, salt solution, broths, orange juice, water. Bowen employed in addition to the above sodium bicarbonate and magnesium sulphate, and John used Fisher's solution. It would seem to be evident that the liquids were the important factor.

All of these cases recovered. All had normal kidneys before coma and normal kidneys after coma and recovery was so rapid and complete one can hardly ascribe the temporary disorder to an acute nephritis. Is it possible that the anuria was a manifestation of extreme edema?

A renal function test with phenolsulphonephthalein was unfortunately not made in any of the cases during coma, but 8 tests, made within ten days of recovery, averaged 33 per cent excretion in two hours, and later tests upon the same patients averaged 55 per cent. The damage to the kidneys was evidently temporary.

6. **Edema.**—Edema was observed in 3 of these patients just mentioned, not noted in 2 and recorded absent in 1 case. Very likely it could have been demonstrated in all if the weights of the patients had been taken daily. For the relation of salt to edema, see p. 273.

Edema is as common an occurrence in the use of insulin as it is uncommon in coma. The more severe the case of diabetes, the more apt is it to appear. This may be explained in part by the sudden retention of water, 3 grams for each gram of glycogen, stored both in the muscles and liver. The retention may be overdone with the sudden reduction of the large quantities of sugar in the blood and possibly to a lesser extent of fat.[1]

Edema develops, according to Odin,[2] when the CO_2 rises above normal. This is his explanation of insulin edema.

[1] For a discussion of edema after use of insulin, see references in von Noorden and Isaac, Die Zuckerkrankheit., 8th ed., Berlin, Springer, 1927, p. 535, and for a case of insulin edema, see Leifer: Jour. Am. Med. Assn., 1928, **90**, 610. See also P. Govaerts for a study of physico-chemical properties of proteins as a cause of edema, 19th French Medical Congress, 1927, p. 61.

[2] Odin: Loc. cit., p. 521.

7. **Respiratory.**—*Air Hunger.*—Küssmaul respiration is usually present, but may be absent. Several years ago it was found absent in a woman, Case No. 1070, when the acidosis had reached a stage 12 to 15 mm. Hg. in the alveolar air. Root explains this disappearance of the hyperpnea in the comatose patient by the increasing exhaustion. Thus in 2 cases observed before insulin the period of excitement—active Küssmaul respiration with great use of the accessory muscles of respiration, bounding rapid pulse—was gradually succeeded by a period in which the rapid pulse became feebler, the respirations shallow, and the patient exhausted. In this period the abolition of reflexes with incontinence of urine, divergent pupils and other evidence of damage to the nervous system were most evident. It would appear that the subsidence of the Küssmaul respiration, which occurs in spite of persistent acidosis and high blood sugar, may be interpreted as a result of toxic effects on the respiratory center, so that it no longer responds to the stimulation of low bicarbonate and non-volatile acids in the blood.

Aside from causation of the coma and confusion in diagnosis respiratory symptoms were not prominent save for one remarkable instance, Case No. 3739, who had first an exudate simulating diphtheria of the larynx and later edema of the same. This patient twice required intubation and was saved through the prompt coöperation of the Boston City Hospital and its Director, Dr. Place, and of Dr. A. A. Hornor. Edema of the lungs with rales and dullness led us to make a tentative diagnosis of pneumonia in 5 cases of the 63. All these diagnoses save 1 were refuted by Roentgen-ray. Pneumonia is by no means as frequent as one would be led to believe by reading certificates of death and coma case reports.

The low body temperature in coma is probably due to the loss of vaporized water through the lungs and consequent loss of body heat. This may be extreme. In Case No. 3382 a two-hour chart of the rectal temperatures shows a steady rise in body temperature from 95° to 102.8° under the influence of insulin, fluids by mouth and rectum, and heat applied to the body. Foster's[1] article has a remarkable chart illustrating this rise of temperature. Similarly a rise in blood-pressure occurs. It reminds one of the recovery of a patient from a profound surgical shock, except that the skin is dry in coma and moist in shock.

E. **Treatment.**—Picture to yourself the patient in coma. He is really a patient in shock. Here is an individual who has been struggling against odds for hours or days and perhaps for weeks or months. If his disease has been undiagnosed it is probable that, Sisyphus-like, he has tried in vain to replace the 2000 calories, more or less,

[1] Foster: Jour. Am. Med. Assn., 1925, **84**, 719.

lost in the urine as sugar and β-oxybutyric acid, by eating more food, yet, because of his high metabolism, which the food has caused, he is stimulated like the toxic thyroid patient to greater and greater exertion until he finally collapses and is forced to bed, and then not to rest, but there to be tortured with a gruelling combat for breath. The food he has hitherto eaten, nausea forces him to expel; the liquids he has taken he vomits. In his restlessness he throws off the clothes. Finally, beaten in this struggle for life, he falls back helpless, unconscious, with rapid pulse and labored respiration, with a body temperature rapidly falling below normal, with so little liquid in the body that his muscles melt away before the touch, the eyes soft as jellyfish, the skin parchment dry, the cheeks, which so recently wore the hectic flush of an increased metabolism, now showing slow recovery of the circulation to pressure, and with the blood-pressure so low and the flow of blood so feeble that to get a specimen one may be forced to puncture the jugular, which in contrast to the other veins is large. In the brief space of hours the body has seemingly gone through months of the ravages of cancer, and death appears at hand.

Ketosis[1] is associated with a reduced functional activity of the pancreas, and consequently a reduced capacity of the tissues to oxidize glucose.

The principle underlying the treatment of these cases is the treatment of the disease diabetes and not the symptom acidosis. No alkalis have been used; no glucose has been given to protect (!) the insulin or to offset future possible reactions. Carbohydrate has been given by mouth, usually to the amount of 50 grams in twenty-four hours, so soon as the patients could swallow. When the blood sugar has fallen nearly to normal and vomiting has prevented retention of food, it has been administered as glucose, but in these cases we have found it necessary to give it intravenously but six times.

All the routine measures, therefore, which are employed in the treatment of shock from whatever cause should be utilized, because in doing so there will be a far better opportunity for the insulin to act.

1. **Insulin.**—Insulin is, of course, the chief weapon by which coma is fought. The initial dose depends upon the depth of coma, the general appearance of the patient, and the blood-sugar level. The first four doses have usually been given at thirty-minute intervals. The amount of the succeeding doses is based on the increase or decrease in hyperpnea, and the rise or fall of the blood sugar and urinary tests. The insulin has been administered subcutaneously in all 63 instances of coma, save for one or two doses in 2 cases. In

[1] Cori and Cori: Jour. Biol. Chem., 1927, **72**, 615.

these 2 patients the patient was so far *in extremis* and the circulation so feeble that we feared insulin given locally would be too slowly absorbed. We believe that whenever insulin is given intravenously it is desirable to give it subcutaneously as well. The action by the former method is more transitory and probably less active unit for unit under ordinary conditions. In general insulin in moderate doses of 20 units, more or less, every fifteen, thirty, or sixty minutes seems preferable to double, treble, or quadruple the dose at greater intervals, because it appears to act more powerfully in this manner and one can more readily avoid overdosage.

The quantity of insulin administered on the first day averaged 132 units in the first series of 33 coma cases and 166 in the second; on the second day 66 units in the first series and 60 in the second, while upon the third day the units were respectively 56 and 49.

We never intend that a patient at the New England Deaconess Hospital shall come up to within two hours of death from coma without having received at least 150 units of insulin in the preceding hour.

In our cases with recovery the dosage of insulin varied between 20 units and 300 units[1] in the first twenty-four hours. Case No. 3877 recovered from her first attack of impending coma, taking 30 units the first day, but in her second attack a few weeks later she received 270 units. At the beginning of the second attack of coma she was given *outside* the hospital the juice of 22 oranges. This was the patient whose pulse fell from 212 to 160 after gastric lavage. Case No. 4279 received but 20 units of insulin the first day, but evidently needed more, because on the second day she was given 100 units. Case No. 4271 came in twice in a precoma state with air hunger and urine loaded with casts, yet he recovered with 25 units. It is because of these recoveries of certain cases with a small amount of insulin that we are conservative in its use and advise its administration in 20- or 40-unit doses at hourly, half-hourly, or quarter-hourly intervals. This keeps the doctor near the bedside, it is true, but we believe that in no other way will patients in diabetic coma be saved.

The danger of hypoglycemia is slight with insulin given in the above manner. A single one of our cases had an insulin reaction, though the blood sugar fell below normal on several occasions. So soon as the symptoms of coma lessen and the sugar in the urine and blood is nearing normal limits, the interval between doses is increased and the size of the individual dose of insulin is decreased. One must be on the watch, however, for a relapse with a sudden rise of blood sugar and a return of the coma state.

In the treatment of a coma case remember that just as Page[2]

[1] Case No. 6729 received 350 units in March, 1928, and recovered.

[2] Page: Am. Jour. Physiol., 1923, **66**, 1.

showed, acid diets render rabbits more resistant to insulin than basic diets, so the coma patient is more resistant with his acidosis. So soon as that has passed, lower the insulin. Insulin acts indirectly as a powerful alkali by checking the formation of acetone bodies, and so setting free alkalies formerly used in neutralizing them. (Fitz.[1])

Insulin injected intravenously and slowly acts more strongly than when injected rapidly. Holm[2] proved this by comparing the effect of 33 units in 600 cc. salt solution given during six hours with the same quantity at a single dose. I thought our coma cases would recover with less insulin if we gave it every fifteen or thirty minutes instead of every hour or two hours, but my supposition proved to be wrong.

2. **Accessory Measures in Treatment.**—Without a special nurse a patient will get out of bed, will either take no nourishment or take it irregularly, will keep uncovered. Coma is a combat with death and the patient needs every help in the fight. Insulin has made the treatment more complicated. As yet orders for the nurse of a patient in coma cannot be written more than one or two hours in advance.

(*a*) *Warmth.*—Patient after patient with coma has entered the hospital with a rectal temperature below 96° F. It is common sense to conserve every atom of energy. Hence the urgency for keeping a patient warm from the inception of acidosis until recovery from it, whether in the ambulance or in the hospital.

(*b*) *Liquids.*—Desiccation of the tissues is an almost invariable accompaniment of the onset of coma.[3] Blum[4] determined the chlorine and sodium content of the tissue of a woman dead from coma and found an increased chlorine content. This suggests that insulin should be combined with sodium in the form of sodium bicarbonate or sodium chloride. No matter what else is done, the patient must receive sufficient liquids to counteract desiccation and to enable him to void considerable quantities of urine. Fluids are given to replace the loss caused by polyuria and the increased pulmonary ventilation. All of the famous cases of recovery from coma in the pre-insulin days passed large quantities of urine, and though recovery takes place with the excretion of less urine today than formerly, partly because alkalis are not allowed and partly because of insulin, the necessity for a liberal supply of liquid remains. Foster has recently emphasized this point.

Salt solution should be given subcutaneously if the case is in the

[1] Fitz: Northwest Med., 1925, **24**, 368.
[2] Holm: Klin. Wchnschr., 1926, **5**, 2157.
[3] Ehrström: Cited in Jour. Am. Med. Assn., 1922, **79**, 173.
[4] Blum: Compt. rend. Soc. de biol., 1927, **96**, 643.

slightest degree urgent, because more can be accomplished for the case threatened with coma in the first hour of treatment than in the following twenty-three hours. With modern aseptic precautions no instance of abscess following a subcutaneous injection of salt solution in a diabetic in the hospital has come to my attention.

Liquids given a diabetic patient with threatened coma should be hot or at least not ice cold. The latter are agreeable but in the end lead to vomiting. The liquids may take the form most agreeable to the patient, tea, coffee, broths, orange juice, or water oatmeal gruel. A glassful of liquid an hour is about as much as any diabetic can take continuously, save perhaps for the first one or two hours. Rather than run the chance of vomiting with the subsequent impossibility of giving liquids further by mouth, I depend upon the coincident administration of salt solution by rectum or subcutaneously. In operations upon diabetics it is almost always the rule for the surgeons to give salt solution to the patients before they leave the table and there should be always an endeavor to fill the patients with liquids before the operation.

The subpectoral administration of saline is preferred to the intravenous, because of the danger of thrombosis, because absorption is more gradual, and because it is far more simply administered with these patients whose blood-pressures are low.

Peters[1] *et al.* state that "if chloride can aid in maintenance of the blood reaction by yielding base for neutralization of ketone acids . . . the administration of sodium chloride would seem to be a rational procedure."

Foster[2] has reported 2 deaths during intravenous injection of saline and points out the vulnerability of the heart in cases of coma. He also recommends the intraperitoneal method.

The need for fluids was especially exemplified by the case of Mary T., Case No. 3739, already cited, who developed an acute laryngeal obstruction during the course of coma treatment. She was given diphtheria antitoxin during the night as a precautionary measure. The laryngeal obstruction proved not to be due to diphtheria, but to be a dry membranous laryngeal exudate caused by pneumococcus infection and dehydration.

(*c*) *Gastric Lavage.*—Lavage of the stomach is now done in every diabetic admission when the CO_2 is below 20 volumes per cent, even without the history of nausea or vomiting. Almost during the lavage which produces evidence of a dilated and full stomach the patient shows clinical improvement. We take no chances with a dilated stomach or even a stomach partially filled with food. The death in one of the cases assigned to deficient insulin may have

[1] Peters, Bulger, Eisaman and Lee: Jour. Clin. Invest., 1925, **2**, 167.
[2] Foster: Jour. Am. Med. Assn., 1925, **84**, 719.

occurred because the patient did not have lavage of her stomach early enough. A word of warning is here needed, however, because it has been called to my attention by a visitor at the hospital that he once saw a diabetic patient in the early stages of coma die suddenly during the rather strenuous manipulation involved in washing out the stomach. Burgess[1] also reports such a case. This only goes to show how cautiously, delicately, and tenderly one must treat the coma patient. The life of a diabetic in acidosis hangs by a thread.

Gastric hemorrhage is comparable with the blood found in the feces of dogs in diabetic coma according to F. M. Allen.[2]

(*d*) *Circulatory Stimulation.*—In coma the heart is in jeopardy. The work involved in hyperpnea alone is considerable and the heart has difficulty in withstanding the demands made upon it. It must be protected and not imperilled by the treatment adopted. A diabetic of ten years' duration without coronary sclerosis is the exception which proves the rule. Whatever manipulation of the patient is undertaken must be with this in mind. Therefore, we have made it a rule to use caffein in the form of caffein sodio-benzoate freely. The usual subcutaneous dose is 0.3 to 0.5 gram every two hours, but usually less than 2.3 grams have been given in any twenty-four hours. In order to safeguard the heart, fluids are given by rectum and subcutaneously, cautiously by the mouth, and seldom intravenously. I have not yet used the intraperitoneal method, but it has Foster's[3] recommendation.

Adrenalin is recommended by von Neergaard[4] as helpful to the circulation in coma. I shall certainly test its action soon, because it appears rational, despite any contraindication on the ground of its antagonistic action to insulin. Ephedrine has the advantage that insulin does not counteract its effect on the blood-pressure according to Csépai.[5] Its action is somewhat slower than that of epinephrin, but continues at a higher level for a longer period of time. Case No. 6511 in profound coma received 50 mg. ephedrine subcutaneously and within thirty minutes her blood-pressure rose from 80/56 to 104/—. Strauss[6] observed during the World War that many diabetic patients died in coma from failure of the circulation rather than from the coma itself.

(*e*) *Alkalis.*—The danger of the alkali treatment of diabetic coma is now supported by clinical evidence in the *occurrence of alkalosis following recovery from coma in one of our patients to whom no alkalis were given.* If one patient without receiving alkalis develops alka-

[1] Burgess: Rhode Island Med. Jour., 1925, **8**, 38.
[2] Allen: Jour. Metab. Research, 1923, **4**, 189.
[3] Foster: Jour. Am. Med. Assn., 1925, **84**, 719.
[4] von Neergaard: Klin. Wchnschr., 1926, **5**, 2148.
[5] Csépai and Pinter-Kovâts: München. med. Wchnschr., 1927, **74**, 1011.
[6] Strauss; Klin. Wchnschr., 1927, **6**, 296.

losis, how many there must be who after taking alkalis develop it. This case substantiates our belief in the danger of the alkaline treatment of diabetic coma. Mrs. C., Case No. 5784, with onset of diabetes two months previously, at the age of fifty-four years, was admitted to the New England Deaconess Hospital January 14, 1927, in diabetic coma brought on by fasting and a badly abscessed tooth. She received routine coma treatment. Insulin 80 units in twenty-four hours; gastric lavage; enema; no salt solution. She took carbohydrate 54 grams by mouth. The following day she was out of coma and the abscessed tooth was extracted. During the ensuing week the daily diet ranged as follows: carbohydrate 60 to 83 grams, protein 34 to 48 grams, fat 47 to 84 grams. On the eighth day after coma she became disoriented. Two days later she had typical tetanoid convulsions with carpopedal spasm. Examination of her blood showed blood sugar 0.18 per cent, CO_2 80 volumes per cent, calcium 9.6 mg., and the next day 9.2 mg. per 100 cc. She was immediately given salt solution subcutaneously. The CO_2 fell to 67 volumes per cent and remained between 43 and 55 per cent at subsequent observations. The blood sugar never fell below 0.18 per cent, or rose above 0.48 per cent. The following day she was comatose. She was again given salt solution. On January 27th, from 7.45 A.M. to 8.55 P.M. she had convulsions every few minutes which were general in character. The fundi, ears, spinal fluids, and blood culture were negative. White blood count, 15,000. She was afebrile until moribund, when her temperature rose to 105° F. The autopsy revealed no abnormalities to account for death save multiple, scattered, fine punctate cerebral hemorrhages.

This patient without alkalis developed alkalosis. The insulin which she received, plus her own supply of insulin, set free an excess of basic elements and alkalosis resulted.

For consent to insert the report of another case of alkalosis developing as a result of alkalis administered during coma I am most grateful, and all the more so, because I do not feel quite at liberty to credit the well-known laboratory from which it emanated.

"She was again admitted to the hospital October 11, 1923, bordering on coma. The laboratory findings before treatment was begun were as follows: CO_2 10 volumes per cent; pH 7.05; blood sugar, 0.220 per cent. The urine gave a strong diacetic acid reaction.

"Her chief complaint on this admission was difficulty in breathing. Because of her respiratory distress 50 grams of bicarbonate of soda, that amount which according to the formula of Palmer and van Slyke should raise her CO_2 to 50 volumes per cent were given over a period of eighteen hours. Ninety units of insulin were given during that time.

"The following gives the effect on the CO_2 and pH:

Date 1923.	Blood sugar.	CO_2 content.	pH.	Insulin.	Remarks.
Oct. 11 . .	0.22	10	7.05	..	Urine—diacetic acid ++++.
	Administration of 50 gms. sodium bicarbonate over period of 18 hours.				
Oct. 12 . .	....	92	7.59	90	
Oct. 13 . .	....	110	7.60	50	
Oct. 14 . .	....	99	7.65	35	
	Administration of 0.1N HCl				
Oct. 15 . .	....	53	7.53	40	
Oct. 29 . .	Discharged				

"During the three days following the soda therapy the alkalosis was maintained in spite of no additional soda. The drop on the third day was due to the ingestion of 0.1 N HCL which was given because of the fear of tetany. There was no edema at any time. She was discharged October 29, 1923, in good condition and receiving 45 units of insulin.

"Concerning the use of bicarbonate of soda, we learned early in our studies on the use of insulin that we could dispense with its use. The cases which Dr. ———— and I reported in our article on the shift of the acid base equilibrium did not receive soda except the case cited above. Nor was any effort made to force sodium chloride.

"Although I believe soda is not indicated in most cases, I have advised its use in small doses in those cases with marked respiratory distress.

"Dr. ———— working in the Department of Research Medicine in this University, and others have shown that the chlorides are low in many cases of diabetes, which, together with the recent publication of Peters and his colleagues, proves the rationale of giving sodium chloride solution to cases of diabetes with acidosis. The reason, most probably being, as you suggested, to make available more sodium ions."

Blum was one of the first to describe convulsions after the use of alkalis during treatment of diabetic coma. We are sure these occur far more often than is reported and we know that this is not always due to failure to recognize them. We advise doctors to leave alkalis alone in diabetic coma, save as salt solution. Recently[1] a report on intravenous therapy countenanced the administration of 1000 cc. of a 5 per cent solution of sodium bicarbonate in coma. If anyone has had a case so treated with recovery since January, 1927, I should appreciate a note about it, because I do not know of a clinic in the world in which so large a quantity is now advised.

If interested in the harmful effects of akalis in coma as well as in other conditions one should consult articles by Harrop,[2] Grant,[3]

[1] Hunt, *et al.*: Jour. Am. Med. Assn., 1927, **88**, 1798.
[2] Harrop: Bull. Johns Hopkins Hosp., 1919, **30**, 63.
[3] Grant: Arch. Int. Med., 1922, **30**, 355.

Hardt and Rivers,[1] Binger, Hastings and Neill,[2] Addis, MacKay and MacKay[3], Kast, Myers and Schmitz.[4]

All concede the doses of alkalis given formerly were excessive and harmful, and, as Blum said, occasionally led to convulsions. Then, too, with the giving of alkalis more acid appeared to be liberalized. Haldane, Wigglesworth, and Woodrow[5] have proved this to be the case even in a normal subject and have gone so far as to conclude that the administration of alkalis interfered also with the combustion of carbohydrate.

I had given alkalis very freely up to 1917, but then stopped their use save perhaps quite fortunately in the form of normal saline.

The constant use of an alkali appears to promote the constant excretion of acid bodies. I have known a moderate acidosis of months' duration to vanish with the omission of soda. A very small quantity of alkali may cause the appearance of a positive ferric chloride reaction in the urine. Patients have observed this after a Seidlitz powder, and one patient, Case No. 942, thought it followed the use of a brand of saccharin which was combined with sodium bicarbonate. In other words, the administration of an alkali may give a false idea as to the severity of the case if one is guided by the urine alone. This shows how necessary it is to study the blood. Van Slyke in the discussion of a paper by Fitz at the Association of American Physicians in May, 1917, pointed out that not only acids remaining in the body might do harm but also those excreted in the urine by removing bases. It is by no means, therefore, an unmixed blessing to favor the removal of acids from the body by the use of alkalis.

Even when the alkalinity of the blood of a patient is brought back to normal by the administration of alkalis coma may persist. This applies not only to a patient but to the dog in diabetic coma. Allen in his Harvey Lecture said: "Aside from a possible, very brief rise in blood-pressure, sodium bicarbonate intravenously or otherwise brings no visible benefit to the dog dying of acidosis."

Alkalis are apt to upset the stomach, and this constitutes another reason for not giving such an irritant in coma. Should the stomach be disturbed then medication and food must be given intravenously or subcutaneously. In a hospital where such methods are commonly in use the risk is not great, but in general practice the delays and dangers involved by such methods are considerable.

Still another reason against alkalis is that when they are given to a patient with acidosis the quantity of β-oxybutyric acid and its

[1] Hardt and Rivers: Arch. Int. Med., 1923, **31**, 171.
[2] Binger, Hastings and Neill: Arch. Int. Med., 1923, **31**, 145.
[3] Addis, MacKay and MacKay: Jour. Biol. Chem., 1926, **71**, 157.
[4] Kast, Myers and Schmitz: Jour. Am. Med. Assn., 1924, **82**, 1858.
[5] Haldane, Wigglesworth and Woodrow: Proc. Royal Soc., London, 1924, **B, 96**, 15.

derivatives removed through the kidneys is increased[1] and the volume of urine as well, because these acids are not excreted in concentrated form. With young individuals this is less important, but with adults it is serious because the acid is an irritant and their more vulnerable kidneys may be incapacitated thereby. Mrs. L., Case No. 2595, excreted 70 per cent of the phenolphthalein in a two-hour test and had a non-protein nitrogen value of 36 mg. per 100 cc. in the blood three days before coma. During coma the non-protein nitrogen rose to 60 mg. and very little ammonia was excreted. Whether the anuria which formerly was seen so frequently in coma was due in part to alkalis is not improbable.

I have great respect for the therapeutic results in coma which excellent clinicians, however in dwindling number, obtain with alkalis. But Petrén, the Minkowski School, Falta, Priesel and Wagner, Newburgh and Marsh, Bertnard Smith, and many others have given up alkalis.

Extraordinary Tolerance of the Body to Variations in Blood CO_2 Content.—Alkalis were given up originally by us in the treatment of acidosis because the patients vomited and subsequently died. In earlier days we did not feel as free to replace fluids by the mouth with salt solution under the skin. The decrease in the formation of ammonia, the body's means to combat acidosis, was less than one would expect after alkaline medication. Again alkalis were given up, because, although the acidosis of the patient was relieved and the normal alkalinity of the blood restored, the coma progressed. It has been claimed that this is no argument against the use of alkalis, because the tissues of the patient at this stage of the coma period have been so saturated with acids and so injured that their recuperation is impossible. In the following paragraph evidence is presented against this view.

The human body is tolerant to an extraordinary degree to extreme alterations in the CO_2 content of the blood. A young man, Case No. 3129, lay for five days in the hospital with the volume of CO_2 varying between 8 and 19.5; an old woman, Case No. 4271, presented no clinical symptoms to cause worry in the three days during which her CO_2 volumes per cent was between 14 and 25. Case No. 3877 appeared to be clinically *in extremis*, although not quite unconscious, when her CO_2 volume per cent was as high as 22. In contrast to these examples of exposure of the body for days to severe acidosis should be mentioned the exposure to extreme acidosis for shorter periods, also with recovery. Thus the CO_2 volume per cent fell to 8 in Case No. 3129. Bock and his confreres record values as low as 8.5 per cent, again with recovery; Foster,

[1] Mosenthal, Killian and Myers: Jour. Am. Med. Assn., 1922, **78**, 1751.

as low as 3.0; Olmsted, 1.10 volume per cent; and Allen, 10.9. At the other end of the scale is Mrs. H., a non-diabetic with cirrhosis of the liver and extreme anemia following gastric hemorrhage, with an alkalosis of 91 volume per cent CO_2, who was unconscious for four days and then became rational. These examples illustrate the body's tolerance for acidosis for days and for extreme acidosis for hours. This was also shown by Case No. 344, who tolerated acidosis for a year. (See p. 747.)

Closer clinical observations and micro-blood-sugars are replacing frequent venous blood sugar and CO_2 determinations. Frequent venipuncture is not without an element of danger as shown by Case No. 5176. It does no harm even if I do exaggerate its danger. My associates and I have had so few deaths in coma that we do not wish to take a chance of doing any harm to any patient. A micro-blood-sugar test in coma can replace with advantage several of the tests from the vein. As in our former series, the clinical picture may show vast improvement, while the laboratory still shows the patient to be in deep coma.

(*f*) *The Diet in Coma.*—The choice of nourishment to be given during coma admits of little discussion. Fat is unnecessary in this twenty-four-hour struggle between life and death. It is hard to conceive of any patient so reduced that he has not enough fat available to furnish body needs for twenty-four hours. Patients so emaciated that such a quantity of fat is unavailable may die from inanition, but if they die from coma, it is due to the ingestion of too much rather than too little exogenous fat. Similarly protein is not required in this twenty-four-hour period. The metabolism is stimulated quite enough, and here again, if death is imminent from inanition, coma will not appear. Carbohydrate, therefore, is the only food whose administration must be considered. I confess that I was not, in pre-insulin days, in the habit of giving much carbohydrate to a diabetic at the beginning of coma. Already the blood sugar is elevated enough and it is not logical to increase the percentage of sugar in the blood just before threatened death when in all the years of life one has tried in every way possible to decrease the sugar in the blood. Furthermore, I believe it probable that an increase of the already high percentage of sugar in the blood in these patients may work deleteriously toward their recovery. Petrén has the same idea and there is a general undercurrent in the literature pointing in the same direction.

The administration of comparatively small quantities of carbohydrate, given in small doses, is allowable today because insulin will be given simultaneously to the patient and the carbohydrate furnishes material upon which the insulin may act. Yet the insulin should be utilized to burn up the surplus carbohydrate in

the body first. Fear, usually a sign of ignorance, is the excuse for giving additional carbohydrate on the ground that there is not enough carbohydrate in the body, when burned, to offset the acidosis. In giving carbohydrates one may be helping a symptom, acidosis, but one is hurting the disease, diabetes, and thus breaking one of the fundamental rules of therapeutics. An improvement in the tolerance for carbohydrate is a cardinal principle in diabetes. Some years ago Lüthje remarked, with much truth, that one need not worry about acidosis when sugar is absent from the urine. Treat the diabetes and the acid poisoning will take care of itself.

From the total metabolism can be deduced the grams of glucose which must be oxidized to offset the catabolizing protein and fat. Take for example a man weighing 55 kilograms, height 176 cm., age twenty-two years. His basal metabolism by the Harris and Benedict scale is 1555 calories. Add to this 30 per cent for restlessness and acidosis and the total metabolism becomes 2022 calories. Assume the nitrogen excretion to be 12 grams. Deducting from the total calories as per Shaffer's formula, see p. 523.

$$\frac{\text{Total metabolism (urinary nitrogen in grams} \times 100)}{50} = G,$$

we have

$$2022-1200 = \frac{822}{50} = 16 \text{ grams glucose.}$$

Multiplying this by 2, as Shaffer suggests, for safety's sake, we have $16 \times 2 = 32$ grams of glucose required to be oxidized to offset the fat metabolism. The body in coma contains about 100 grams[1] of B-oxybutyric acid or its derivatives, so that we might add 40 grams more of carbohydrate. This would make necessary the oxidation of about 70 grams of carbohydrate. There is little glycogen in the liver in coma, but in the blood there is glucose available, and allowing 5 liters of blood with 0.5 per cent of sugar there would be, deducting 0.1 per cent for the normal blood sugar, 20 grams of carbohydrate. This would leave a requirement of only (70—20) 50 grams, or about 2 grams of carbohydrate per hour, demanded in addition to that in the blood to offset acidosis in twenty-four hours, even providing the sugar in the blood was not replenished. The amount of acid formed depends upon the protein and fat metabolized. There is obviously, therefore, little need for much additional carbohydrate food during coma, and, in fact, there is need for none at all until the sugar in the blood is normal. The only evidence we recall in the other direction is Macleod's experiment on depancreatized dogs, which showed that with more carbohydrate available, more glucose per unit insulin is oxidized, but in the presence of a high blood sugar it is a question whether this rule would hold. Therefore, we feel justified in giving little carbohydrate to our patients in coma.

[1] See p. 366.

F. **Length of Coma Not a Measure of Its Severity.**—The length of the coma is by no means a perfect measure of its severity. In other words, the patient is not necessarily being steadily and progressively poisoned from acidosis. On the contrary, it is quite possible that the acidosis is decreasing and that death ensues during recovery from the acidosis and coma and is due to exhaustion and cardiac weakness rather than to acidosis. Coma and acidosis are not one and the same. One might almost say the longer the patient can be kept alive in coma, the more chance of recovery, because the effect of food and other extraneous causes which brought on the coma are steadily passing off and are being replaced by undernutrition which, if not too extreme, is helpful. Undernutrition lowers the metabolism and thus reduces the need for combustion of glucose to offset the combustion of fat. Therefore, never be discouraged by the length of the coma alone. Anyone who takes many diabetic histories encounters now and then the story of a spontaneous recovery from diabetic coma. This is not surprising if one considers the metabolism.

G. **The Differential Diagnosis of Diabetic Coma.**—Granted the patient has diabetic coma, do not forget that simultaneously he may have appendicitis, diphtheria, meningitis, or some other condition which, if untreated, kills. Second, acidosis often occurs in a diabetic, but it may be far removed from the degree of intensity which is characteristic of coma. Hence, because of a positive ferric chloride reaction, do not consider the diagnosis complete. Third, acidosis and coma always have a cause. What is it? Has the patient been overeating exogenously or endogenously? Discover the cause and more than half the battle is won.[1]

Real danger exists in the confusion of coma with hypoglycemia. When Eleanor had acidotic coma in college, it followed measles; when she had hypoglycemic coma in the summer it came after tennis, and she received 20 units of insulin. She owes her life to two alert and modest doctors: the one who diagnosed the coma of acidosis and the other who, never having seen her before, diagnosed her unconsciousness as due to hypoglycemia, made critical by her mother's administration of an additional dose of insulin, because she supposed the coma to be due to acidosis.

Uremia may develop in the course of coma. Cerebral hemorrhage in a diabetic who may have a little acidosis is not uncommon. Meningitis from a mastoid has caused confusion. Coronary thrombosis, appendicitis, drugs, body injuries, and abdominal emergencies are always to be excluded and, as above related, alkalosis.

Table 241 is an attempt to lessen two of the diagnostic difficulties.

[1] See Murphy (Med. Clin. North America, 1925, **8**, 1517) for an instructive group of cases of coma discussed from point of view of differential diagnosis.

TABLE 241.—THE DIFFERENTIAL DIAGNOSIS OF THREE TYPES OF COMA OCCURRING IN THE SAME PATIENT.

	Coma of diabetic acidosis.	Coma of hypoglycemia.	Coma of nitrogen retention.
Type of onset	Gradual, days	Rapid, minutes	Slow, days or weeks.
Causes	Overeating Omission of insulin Infection Hyperthyroidism	Omission of food Too much insulin Unusual or excessive exercise	Suppression of urine due to: (*a*) Nephritis. (*b*) Toxic effects of infections, drugs or acidosis. (*c*) Retention of water. (*d*) Obstruction in urinary tract.
Symptoms	Indigestion: Nausea Vomiting Pain in abdomen Dim vision Constipation Dyspnea	Hunger Weakness Tingling Trembling Sweating Double vision	Apathy. Headache, occipital. Nausea. Vomiting. Vision blurred. Spots before eyes.
Clinical signs	Air hunger Kussmaul respiration	Shallow respiration	Stertorous respiration often of the Cheyne-Stokes type and rarely of Kussmaul type.
	Skin, dry Heart of normal size	Skin, cold, moist	Skin, dry. Hypertrophy of the heart.
	Pulse rapid, 130+	Pulse-rate normal, occasionally irregular	Full and bounding pulse.
	Coma incomplete at first and progressive	Coma profound	Lucid intervals.
	Blood-pressure, low or normal Soft eyeballs		Blood-pressure usually elevated.
	Acetone odor of the breath Reflexes normal or absent	Drooling from the mouth	Uremic odor.
	No convulsions	Convulsions (in late stage)	Muscular twitching (face and hands) or convulsions.
	Normal eye grounds	Normal eye grounds	Eye grounds may show hemorrhage or retinitis (albuminuric).
		Resistive and antagonistic Mumbling speech	

TABLE 241.—THE DIFFERENTIAL DIAGNOSIS OF THREE TYPES OF COMA OCCURRING IN THE SAME PATIENT.—(*Continued..*)

	Coma of diabetic acidosis.	Coma of hypoglycemia.	Coma of nitrogen retention.
	Sugar present	Sugar usually absent; second of two specimens sugar-free	Sugar-free.
	Acetone ++	Acetone 0	Acetone 0.
	Diacetic acid ++	Diacetic acid 0	Diacetic acid 0.
	Albumin trace +		Albumin trace +.
	Casts in showers, a single type predominating	Casts, few or none	Casts cellular and fatty, usually granular, with red blood cells.
	Volume increased	Volume normal	Anuria.
Blood	Sugar above 0.35 per cent	Sugar low 0.06 per per cent or below	Sugar normal occasionally as high as 0.2 per cent.
	Plasma CO_2 combining power below 20 vol. per cent	Plasma CO_2 combining power normal or high	Plasma CO_2 combining power reduced, not often below 25 vol. per cent.
	Non-protein nitrogen normal at onset, but tends to increase	Non-protein nitrogen normal	Non-protein nitrogen high, 120 mg. per 100 cc. or above.
Response to treatment	Insulin causes rapid progressive improvement within twelve hours	Response immediate to glucose (given intravenously, by mouth, or by rectum) within ten minutes; insulin makes worse	If cause is progressive chronic nephritis prognosis is bad.
			If due to acute nephritis improvement may be definite though gradual.
			If due to toxins, infections or water retention, removal of cause may result in rapid improvement.

but the three preceding paragraphs are worth more in general differentiation than the schematic diagnostic points. One case may be cited. With Ida J., Case No. 4978—a girl with double cataracts now happily operated upon—frequent blood-sugar tests were permitted only when her condition seemed to warrant it, which was some fourteen hours after her admission in coma of acidosis. Orders for insulin were based upon urinary specimens. In the following seventeen hours the urine contained but a slight trace of sugar and was acid-free, yet in spite of this the patient became again unconscious with breathing of the Küssmaul type, and she presented the

typical picture of acidosis. This diagnosis was also confirmed by the blood CO_2 combining power which was 14 volumes per cent. The output of urine was scanty, and it was due to its suppression that it was not representative of her true state. With a large dose of insulin she was conscious within two hours, but twelve hours later, at midnight, she presented another picture quite new to us. For the third time in the course of two days she was again unconscious. Upon this occasion the respiration was shallow and quite unlike that of diabetic acidosis. The skin was dry and hot, not moist as in an insulin reaction. Her pulse was full and bounding, she was combative, quite the opposite of the usual flaccidity of insulin shock, though occasionally we have known patients in that to be combative too. The blood sugar by the micro test was 0.08 per cent. Although this was a nearly normal value we thought the probable cause of her coma was a rapidly falling blood sugar. Consequently, she was treated for hypoglycemia, but she failed to improve with increased carbohydrate intake. By the following day, September 14th, the riddle was solved for the patient showed the earmarks of nitrogen retention, such as a rising blood-pressure, from 120 on September 12th to 150, non-protein nitrogen of 106 mg., a large trace of albumin in the urine, a diminished urinary output in spite of an intake of between 2000 and 3000 cc., of fluid per twenty-four hours.

The cause of the nitrogen retention, presumably brought about by renal blocking, is still unknown. Prior to insulin this occurred not infrequently and we attributed it to the excessive quantity of acid amounting in one case, Case No. 4, to 437 grams of hydroxybutyric acid which passed through the kidneys in three days. In those days unless large quantities of urine were voided the patients died after a few hours of coma. With the use of insulin no such amounts of acid are excreted, and yet the same condition occurs. At the beginning of her coma she did not show the usual extensive renal involvement in diabetic coma so frequently manifested by showers of granular casts. As soon as this condition of deficient elimination was recognized fluids were increased, subcutaneously and intravenously as salt solution, despite her previously liberal supply. She improved both clinically and by the laboratory tests in proportion to her increasing urinary output. Her subsequent course was uneventful.

Snapper[1] attributes the especial seriousness of the prognosis in these cases of coma with renal involvement to the interference of the function of the kidney, also probably present in the muscle and perhaps bones too, of destroying the ketone acids. Clinically, however, my cases with the greatest evidence of renal blocking, Cases No. 4232, 4099, have recovered.

[1] Snapper: Med. Klin., 1927, **23**, 897.

SECTION X.

ARTERIOSCLEROSIS.[1]

THE diabetic lives and dies in the arteriosclerotic zone. Lives in it, because two-thirds of the 4592 true diabetics in the present series originated after thirty-nine years of age; dies in it, because although the average age at death of 339 cases in the Naunyn Period was 44.8 years, the average age at death of the 607 fatal cases in the present Banting Epoch is 54.2 years, and for the last year's 60 fatal cases was fifty-nine years. During 1925 of all the diabetics who died in Massachusetts 86 per cent were above the age of fifty years. This is the year of age in which diabetes develops most frequently in women, and fifty-one years is the year most frequent for men, the most common quinquennium for both sexes being between forty-nine and fifty-three years.

Exposure of the patient to the influence of diabetes was not long enough in Naunyn's time to show whether it would result in arteriosclerosis. The average duration of the disease was then only 4.7 years and the few diabetics who exceeded this limit were the mild, old cases who already presented at the onset of diabetes the vascular changes which were due to their age.

The length of exposure was greater in the Allen Period, but has become still more evident in the Banting Epoch in the midst of which we now are. Fifty living children who have had diabetes on the average for more than seven years attest this, as well as the average duration of the disease in the last 600 fatal cases[2] of all ages which has become 7.7 years. Finally there are 934 cases living and dead in whom the duration of the disease is more than a decade. It is on account of this change in the duration of diabetes generally, and particularly because of the ten-year cases, that the subject of arteriosclerosis is now of importance to all diabetics.

Indeed as a cause of death of the diabetic, arteriosclerosis has risen three-fold in importance and coma has dropped to one-third

[1] I wish to express my indebtedness to Dr. F. R. Miller for help in the compilation of the data in this section.

[2] Ending July 1, 1926.

of its former incidence. Formerly 61 per cent of the fatalities were due to coma, but since the introduction of insulin coma has decreased to 20 per cent, and in the last year to zero. Coincidentally arteriosclerosis has risen from 15 per cent in the Naunyn Era to 47 per cent in the present Banting Period.

TABLE 242.—THE INCREASING DURATION OF LIFE IN DIABETES BASED UPON FATAL CASES AT DIFFERENT PERIODS.

Duration, years.	Naunyn.		Allen.		Banting.	
	Cases.	Per cent.	Cases.	Per cent.	Cases.	Per cent.
0 to 1	61	18.1	70	8.7	32	5.3
1 to 2	51	15.1	105	13.0	61	10.2
2 to 3	54	15.9	110	13.6	60	10.0
3 to 4	31	9.2	92	11.4	60	10.0
4 to 5	22	6.5	70	8.7	55	9.0
5 to 6	21	6.2	49	6.1	31	5.0
6 to 7	12	3.6	41	5.1	23	3.8
7 to 8	10	2.9	48	6.0	34	5.7
8 to 9	12	3.5	42	5.2	28	4.7
9 to 10	13	3.8	22	2.7	28	4.7
10 to 11	8	2.4	24	3.0	26	4.3
11 to 12	12	3.5	18	2.2	29	4.8
12 to 13	9	2.7	26	3.2	22	3.7
13 to 14	5	1.5	12	1.5	19	3.2
14 to 15	1	0.3	12	1.5	17	2.8
15 to 16	6	1.8	12	1.5	16	2.7
16 to 17	2	0.6	16	2.0	13	2.2
17 to 18	2	0.6	2	0.2	13	2.2
18 to 19	2	0.6	3	0.4	7	1.2
19 to 20	0	0	6	0.8	5	0.8
20 on	4	1.2	26	3.2	22	3.7
Totals	338		806		600	
Average duration, years	4.7		5.4		7.7	
Average age at death	339* cases 44.8 years				607[1] cases 54.2 years	

A. CRITERIA FOR THE INCIDENCE OF ARTERIOSCLEROSIS IN DIABETES.

The best criteria are furnished by autopsies, next I should say by the causes of death found on the death certificates of diabetics, although here certain instances would escape detection. The third source is the evidence obtained from clinical and physical

[1] In certain cases the age at death, and not the duration of the disease, was known, or vice versa.

examination plus the help of the roentgen-ray. Of autopsies there are 52; of fatal cases among the total of 934 diabetics whose disease lasted more than a decade there are 349 and the causes of death are known in 344. The remaining living cases have been investigated with increasing care in the last few years for signs of arteriosclerosis. Attention has been paid to the peripheral arteries and by no means has been limited to the radials, because, thanks to Dr. L. B. Morrison, roentgen-rays of the lower extremities have been made in 324 instances. For some time the radial arteries of my patients have been classified as normal or as showing sclerosis of four grades. Beginning July 1, 1927, Pratt's[1] classification will be adopted for abnormal vessels: (1) Palpable; (2) roll under finger; (3) tortuous; (4) beaded or pipe-stem.

Too rarely has proof been sought in the eyes. There are also clinical data which allow inference to be drawn upon the existence of arteriosclerosis in the brain, heart, and kidneys. Conclusions upon the presence of arteriosclerosis in the living cases of this series, however, will err on the side of too low a per cent.

1. **Evidence from Autopsies.**—The criteria upon which arteriosclerosis was recorded as a result of the postmortem examinations were as follows:

A. (1) Calcification with or without bone formation, either medial or intimal. (2) Fibrous thickening of intima: Hyaline degeneration of intima. Arbitrarily based on a thickness of intima approximately twice or more the normal. These criteria will be considered indisputable evidence by all.

B. Other cases were included, as arteriosclerosis of the atheromatous type, if they presented in addition to the fatty change (*a*) either proliferative or atrophic changes of a local character in the elastic laminæ, (*b*) cellular necrosis.

The above type may be differentiated from the so-called fatty "streaking," similar to that of marasmus, etc., and from atherosclerosis of puberty, etc., both of which show the following points: (*a*) Lack of actual cell necrosis, (*b*) lack of calcification, (*c*) cellular activity—fatty products chiefly intracellular, (*d*) apparent restriction to aorta.

In 33 autopsies upon diabetic patients whose disease had lasted less than five years, 70 per cent showed arteriosclerosis. All the 19 cases with a duration over five years had sclerotic arteries. In the cases under five years' duration arteriosclerosis was the cause of death in 18 per cent, and for those with a longer duration it was the cause in 68 per cent (Table 243).

[1] Bushnell and Pratt: Physical Diagnosis of Diseases of the Chest, Philadelphia, Saunders, 1925, p. 345.

TABLE 243.—INCIDENCE OF ARTERIOSCLEROSIS AND ITS PRESENCE AS A CAUSE OF DEATH IN 52 AUTOPSIES UPON DIABETIC PATIENTS, ACCORDING TO DURATION OF DIABETES.

Duration of diabetes, years.	Total cases.	Arteriosclerosis.	
		Incidence, per cent.	Cause of death, per cent.
0 to 4	33	70	18
5 to 9	7	100	71
10 to 14	7	100	71
15 to 19	2	100	50
20 on	3	100	67

If one now examines the decades of onset of diabetes and their relation to arteriosclerosis, it will be found that the only decade of onset in which arteriosclerosis did not present gross manifestations at autopsy was the first. In the second decade there was but 1 positive case in 5, 20 per cent, but there were 4 out of 7, 59 per cent, in the third, and from thirty years upward all cases showed atheromatous arteries. Even in the cases in the third decade it was the cause of death in 29 per cent of the cases and it rose to 70 per cent in the seventh decade. Special mention should be made of a boy, Case No. 1305, whose diabetes began at 10.5 years and ended 5.5 years later. The atheromatous plaques in his aorta were plainly evident and not at all to be confused with the minor alterations which occur normally at puberty. The first decade of life thus far, therefore, is the only decade in diabetes immune to arteriosclerosis.

TABLE 244.—INCIDENCE OF ARTERIOSCLEROSIS AND ITS PRESENCE AS A CAUSE OF DEATH IN 53 AUTOPSIES UPON DIABETIC PATIENTS, ACCORDING TO AGE OF ONSET OF DIABETES.

Decade of onset, years.	Total cases.	Arteriosclerosis.	
		Incidence, per cent.	Cause of death, per cent.
4 to 9	4	0	0
10 to 19	5	20	0
20 to 29	7	59	29
30 to 39	6	100	50
40 to 49	7	100	0
50 to 59	11	100	45
60 to 69	13	100	70

A considerable proportion of the cases with postmortems upon which Tables 243 and 244 are based have been described by Warren and Root.[1]

2. **Evidence from Fatal Cases.**—Seventeen hundred and fifty-six of my true diabetics have died. These have been classified in three groups, the Naunyn, 1898 to 1914, the Allen, 1914 to 1922, and the

[1] Warren and Root: Am. Jour. Pathol., 1925, **1**, 415, and 1926, **2**, 69; Boston Med. and Surg. Jour., 1926, **194**, 45. Warren: Jour. Am. Med. Assn., 1927, **88**, 99.

Banting, 1922 to 1926 July, groups. (See p. 375.) Analysis of the causes of death of these patients in order to detemine the part played by arteriosclerosis as a cause of death has been made upon the following basis: The term arteriosclerosis has been taken to include all deaths under the headings (*a*) arteriosclerosis and gangrene, because the latter disease is presumptive evidence of arteriosclerosis of the vessels of the lower extremities, and incidentally, as Wilder[1] has shown, of the coronary arteries as well in an overwhelming percentage of the cases. (*b*) The term also includes deaths reported upon death certificates as apoplexy or its synonyms. Acute disease of the heart and kidney are for all practical purposes in such a compilation absent and consequently all (*c*) cardiac and (*d*) nephritic deaths are included in the arteriosclerotic group. Table 245 is compiled in this manner and indicates the increasing frequency of arteriosclerosis on the death certificate, rising as it does from 15 per cent in the Naunyn Era to 47 per cent in the Banting Era. The table also shows the increasing duration of the disease from 4.7 to 7.7 years and that diabetics are growing old, because the average age at death in the Naunyn Era was in the early forties, and in the Banting Era in the early fifties.

TABLE 245.—INFLUENCE OF PERIOD OF TREATMENT UPON PERCENTAGE OF TOTAL DEATHS FROM DIABETES DUE TO ARTERIOSCLEROSIS AND DIABETIC COMA.

Epoch.	Average duration of diabetes, yrs.	Deaths, total.	Coma, per cent.	Arterio-sclerosis,[1] per cent.	Average age at death, yrs.
Naunyn:					
1894, to June, 1914	4.7[2]	342	61	15	44.8[5]
Allen:					
June, 1914, to Aug., 1922	5.4[3]	805	42	26	
Banting:					
Aug., 1922, to July, 1926	7.7[4]	609	20	47	54.2[6]

[1] Arteriosclerosis includes causes of death on death certificates as follows:
Cardiac deaths, chronic.
Nephritic deaths, chronic.
Apoplexy, cerebral hemorrhage, thrombosis and embolism, hemiplegia.
Arteriosclerosis.
Gangrene and sepsis (extremities).

[2] Based upon 338 cases, instead of 342.

[3] Based upon 806 cases. (Evidently 1 of these cases belonged in another era.—E. P. J.)

[4] Based upon 600 cases, instead of 609.

[5] Based upon 339 cases, instead of 342.

[6] Based upon 607 cases, instead of 609.

In order to secure figures from the population at large for comparison with the diabetic, Miss Angeline Hamblen has furnished

[1] Wilder: Southern Med. Jour., 1926, **19**, 241.

me as nearly analogous data as we could select for Massachusetts for the year 1925. If one compares these data with my own fatal cases, classified in similar age groups, Table 246, it becomes apparent that the percentages of deaths from arteriosclerosis in Massachusetts and in the diabetic in the first five decades correspond closely, but after the fiftieth year the frequency of arteriosclerotic deaths in Massachusetts for the seventh decade corresponds with the diabetics for the sixth, and the State's eighth decade with the diabetics' seventh. It would therefore seem that, hitherto, diabetics became prematurely old.

TABLE 246.—SIX HUNDRED AND FOUR ARTERIOSCLEROTIC DEATHS IN DIABETICS BY CAUSE AND AGE (BANTING ERA) COMPARED WITH ARTERIOSCLEROTIC DEATHS IN MASSACHUSETTS.

Age at death, yrs.	Total deaths.	Types of arteriosclerotic deaths.				Total arteriosclerotic deaths.		Arteriosclerotic deaths in Massachusetts.
		Apoplexy.	Arterio-sclerosis, gangrene.	Cardiac angina pectoris.	Nephritis.	No.	Per cent.	Per cent.
Under 30	77	..	3	4	..	7	9.0	4.5
30 to 39	35	..	3	2	..	5	14.3	16.3
40 to 49	49	1	4	5	3	13	26.5	27.4
50 to 59	149	7	17	35	15	74	49.6	39.0
60 to 69	203	18	39	57	11	125	61.5	51.6
70 to 79	79	8	21	15	3	47	59.5	61.5
80 to 89	12	2	2	5	..	9	75.0	67.3
90	..	..	..	..	..	..	..	65.9
Totals	604	36	89	123	32	280	46.3	36.7
Per cent	..	5.9	14.7	20.4	5.3			
Massachusetts		9.4	3.6	18.2	5.6	..	36.7	

The influence of the duration of diabetes upon the percentage of total deaths from diabetes due to arteriosclerosis has been studied and is shown in Table 247. When the duration was five to nine years, the percentage of total deaths from arteriosclerosis was 36 per cent, when ten to fourteen years it was 49 per cent, when fifteen to nineteen years it was 67 per cent and from twenty years onward, 58 per cent (the decrease in the last period possibly being due to the unusually large number of death certificates in this period bearing the term "diabetes" only). It is true that the long cases formerely were toward middle life and so an increasing duration brought all these patients into the realm of arteriosclerosis, but this could hardly account for the steady increase which the table shows.

TABLE 247.—INFLUENCE OF DURATION OF DIABETES UPON PERCENTAGE OF TOTAL DEATHS FROM DIABETES DUE TO ARTERIOSCLEROSIS.

Duration of diabetes, years.	Total cases.	Percentage of total deaths due to arteriosclerosis.
5 to 9	393	36
10 to 14	201	49
15 to 19	90	67
20 to 35	53	58[1]

In confirmation is Table 248 which bears this out because the cases of ten years' duration are subdivided into eight decades. This

TABLE 248.—FATAL CASES OF DIABETES OF TEN OR MORE YEARS' DURATION CLASSIFIED ACCORDING TO AGE AT ONSET AND ARTERIOSCLEROSIS.

Duration of diabetes, years.	Decade of onset of diabetes.								
	0 to 9.	10 to 19.	20 to 29.	30 to 39.	40 to 49.	50 to 59.	60 to 69.	70 to 79.	Total
10 *to* 14:									
Total cases	0	1	4	9	60	65	25	3	167
Number arteriosclerotic	0	1	2	4	47	62	25	3	144
Per cent		**100.0**	**50.0**	**44.4**	**78.3**	**93.8**	**100.0**	**100.0**	**86.2**
15 *to* 19:									
Total cases	1	0	1	16	40	22	8	0	88
Number arteriosclerotic	0	0	0	14	34	22	7	0	77
Per cent	**0**	**0**	**0**	**87.5**	**85.0**	**100.0**	**87.5**		**85.2**
20 *and over:*									
Total cases	0	0	5	12	22	6	1	1	47
Number arteriosclerotic	0	0	5	9	21	6	1	1	43
Per cent	**0**	**0**	**100.0**	**75.0**	**95.4**	**100.0**	**100.0**	**100.0**	**91.5**
Total cases	1	1	10	37	122	93	34	4	302
Total arteriosclerotic cases									
Number	0	1	7	27	102	90	33	4	264
Per cent	**0**	**100.0**	**70.0**	**81.6**	**83.6**	**96.8**	**97.0**	**100.0**	**87.4**

table includes fatal cases showing arteriosclerosis even though this was not the cause of death. The first two decades can be disregarded because of lack of cases. The third decade shows 70 per cent arteriosclerosis, the fourth decade shows 82 per cent and above this arteriosclerosis was practically universal.

The living cases of diabetes of ten or more years' duration are considerably behind the dead in their percentage of arteriosclerosis. (See Table 249.) The first two decades can be disregarded because of paucity of cases save that 2 cases with onset under twenty years of age are notable for showing arteriosclerosis. The third decade

[1] There were 7 deaths in this group reported as "diabetes" in contrast to 3 deaths in the third group and 11 in the second.

shows 19 per cent, the fourth decade 49 per cent, the fifth decade 70 per cent, the sixth decade 80 per cent and from here onward arteriosclerosis becomes essentially universal just as it did two decades earlier with the fatal cases. However, it is cheerful to record that Dr. J. R. Williams of Rochester, New York has a child with diabetes of ten years' duration without demonstrable sclerosis even by roentgen-ray, and so have Dr. Woodyatt of Chicago, Dr. Geyelin of New York and Dr. Burgess of Providence. I have one with it and another undoubtedly without it.

TABLE 249.—LIVING CASES OF DIABETES OF TEN OR MORE YEARS' DURATION CLASSIFIED ACCORDING TO AGE AT ONSET AND ARTERIOSCLEROSIS.

Duration of diabetes, years.	Decade of onset of diabetes.								
	0 to 9.	10 to 19.	20 to 29.	30 to 39.	40 to 49.	50 to 59.	60 to 69.	70 to 79.	Total.
10 *to* 14:									
Total cases	2	3	9	39	85	80	14	1	233
Number arteriosclerotic	0	2	2	17	57	60	13	1	152
Per cent	**0**	**66.6**	**22.2**	**43.5**	**67.0**	**75.0**	**92.0**	**100.0**	**65.2**
15 *to* 19:									
Total cases	0	1	5	24	44	27	7	0	108
Number arteriosclerotic	0	0	0	10	29	23	5	0	67
Per cent	**0**	**0**	**0**	**41.6**	**65.9**	**85.1**	**71.4**	**0**	**62.0**
20 *and over:*									
Total cases	0	2	13	20	26	10	1	0	72
Number arteriosclerotic	0	0	3	14	23	10	1	0	51
Per cent	**0**	**0**	**23.0**	**70.0**	**88.4**	**100.0**	**100.0**	**0**	**70.8**
Total cases	2	6	27	83	155	117	22	1	413
Total arteriosclerotic cases									
Number	0	2	6	41	109	93	19	1	270
Per cent	**0**	**33.3**	**18.5**	**49.4**	**70.3**	**79.5**	**86.4**	**100.0**	**65.4**

The roentgen-ray has been a great help in the clinical study of arteriosclerosis. Labbé[1] has emphasized this and B. D. Bowen[2] of Buffalo as well. I have been fortunate in having had 324 of my diabetics studied in this manner by Dr. L. B. Morrison and Dr. Bogan.[3] Of course uncalcified arteries do not show by Roentgen-ray and consequently a considerable number of atheromatous cases are overlooked. This makes their positive findings all the more impressive. (Table 250.)

The roentgen-ray confirms data obtained in other ways. It makes evident that 30 per cent of the diabetics whose disease begins

[1] Labbé and Lenfantin: Soc. méd. de hôp., Paris, 1924, **48**, 522.
[2] Bowen: Bull. Buffalo Gen. Hosp., 1924, **2**, 35. Bowen and Koenig: Idem., 1927, **5**, 31.
[3] Morrison and Bogan: Am. Jour. Med. Sci., 1927, **174**, 313.

at twenty to twenty-nine years show arteriosclerosis later, that this holds for 45 per cent of those with onset thirty to thirty-nine years and also practically all diabetics whose disease begins at forty years of age or above. The percentage of total diabetics examined showed arteriosclerosis for successive five-year periods of duration as follows: The first five years, 40 per cent; the second five years, 56 per cent; the third five years, 83 per cent; and 92 per cent from the fourth quinquennium of duration on.

TABLE 250.—INCIDENCE OF ARTERIOSCLEROSIS IN DIABETICS DEMONSTRATED BY ROENTGEN-RAY.

Duration of diabetes, years.	Decade of onset of diabetes.								
	0 to 9.	10 to 19.	20 to 29.	30 to 39.	40 to 49.	50 to 59.	60 to 69.	70 to 79.	Total.
0 *to* 4:									
Cases	33	38	10	19	17	46	29	8	200
Per cent arteriosclerotic	**0**	**0**	**10.0**	**16.0**	**59.0**	**74.0**	**79.0**	**100.0**	**40.0**
5 *to* 9:									
Cases	7	10	5	4	10	17	3	1	57
Per cent arteriosclerotic	**0**	**0**	**20.0**	**50.0**	**90.0**	**100.0**	**67.0**	**100.0**	**56.0**
10 *to* 14:									
Cases	0	4	1	8	13	10	5	1	42
Per cent arteriosclerotic	..	**50.0**	**100.0**	**75.0**	**77.0**	**100.0**	**100.0**	**100.0**	**83.0**
15 *to* 19:									
Cases	0	0	1	1	6	5	0	0	13
Per cent arteriosclerotic	..	..	**0**	**100.0**	**100.0**	**100.0**	**0**	**0**	**92.0**
20 *and over:*									
Cases	0	0	3	6	2	1	0	0	12
Per cent arteriosclerotic	**0**	**0**	**0**	**83.0**	**100.0**	**100.0**	**0**	**0**	**92.0**
Total cases	40	52	20	38	48	79	37	10	324
Total arteriosclerotic (per cent)	**0**	**4.0**	**30.0**	**45.0**	**77.0**	**85.0**	**81.0**	**100.0**	**52.0**

Surely enough has been said to indicate the frequency of arteriosclerosis in the diabetic and its development at an early age.

3. **Arteriosclcerosis in Diabetes Among Jews.**—One hundred and forty-three of my Jewish diabetic patients have died. The mild character of the disease in this race is shown by a reduction in deaths from coma. These amounted to 64 per cent in the Naunyn Epoch, to 38 per cent in the Allen and 11 per cent in the Banting Epoch, the last figure being approximately the same for coma as for all my deaths in the year ending July 1, 1926. Arteriosclerosis was responsible for all the non-coma deaths in the Naunyn Epoch, that is, 36 per cent, but there were only 11 deaths in all in that period. In the Allen Epoch arteriosclerosis caused 25 per cent and in the Banting Epoch 61 per cent of the deaths. Of the 43 arteriosclerotic

deaths in the Banting Epoch deaths were due to lesions in the brain in 19 per cent, in the heart in 44 per cent, in the extremities in 16 per cent, and in the kidneys in 21 per cent.

B. THE ETIOLOGY OF ARTERIOSCLEROSIS IN DIABETES.

1. **Protein.**—Protein is acknowledged to favor rather than prevent the onset of arteriosclerosis. No one today, so far as I am aware, approves of increasing the protein above the usual standard of a gram per kilogram body weight in the diet of an individual who is developing arteriosclerosis. The unrestricted diet of the untreated diabetic contains an excess of all varieties of food, protein, carbohydrate and fat, and only too often in the past the restricted diet of the diabetic has simply meant the lowering of carbohydrate and a free rein for protein of which the diabetic has taken advantage. A protein element in the etiology of arteriosclerosis in diabetics is therefore assumed.

2. **Carbohydrate.**—Does carbohydrate cause arteriosclerosis? Certainly it does if taken in such excess as to produce obesity, but except in this manner no one would attribute any such function to it. It is the food *par excellence* we all give our arteriosclerotics and particularly to those with localization of the disease in the kidney. To a non-diabetic carbohydrate is benign. But with the diabetic the use of carbohydrate introduces other problems and first of a hyperglycemia which develops when the carbohydrate is not burned. Is a persistent hyperglycemia a cause of arteriosclerosis in diabetes? It very likely is a cause, because it is an abnormal condition and any abnormal state would tend to wear out the machine. It is difficult to estimate the noxious influence hyperglycemia might have in producing arteriosclerosis, because the diabetics with the highest hyperglycemia have lived the shortest periods and succumbed chiefly to coma, and those with the lowest hyperglycemia have lived the longest and succumbed largely to arteriosclerosis. I know of no experiments in which a constant hyperglycemia has been artificially produced and its effect upon the bloodvessels observed.

Our diabetic children of today constitute such an experiment and when 100 diabetic children have lived a decade and reports have been published about them, which state the presence or absence of arteriosclerosis in conjunction with the percentage of sugar in the blood, we shall be in a better position to reach such a conclusion. I personally do not believe that a hyperglycemia up to 0.25 per cent is particularly harmful to a diabetic provided the urine is sugar-free, because this is proof that he is not eating carbohydrate uselessly, and carbohydrate is our standard food.

3. **Acidosis.**—Acidosis is adduced as an etiological factor in the arteriosclerosis of diabetics. This may well be the case, if its action extends over a long period. Hitherto the patient with acidosis died too soon to disclose the effect acidosis would produce, and now with the introduction of insulin we are forced to look elsewhere than in diabetes for information. The modern ketogenic diet prescribed for epileptics should settle this point shortly, because here we have a low-grade acidosis existing for long periods. No case of epilepsy should be exposed to such a diet without the most careful examination for arteriosclerosis by clinical means and the Roentgen-ray, so that its possible advent later can be observed.

The acidosis in diabetes may not be exclusively of the ketogenic type, but may in part be related to the diet. Such a disturbance of the acid-base balance, as occurs with heavy protein and other diets, may lead to the development of arteriosclerosis as has been emphasized and experimentally demonstrated by workers in the Potter Memorial Clinic in Santa Barbara.[1, 2, 3]

4. **Alcohol.**—Alcohol is used comparatively little by diabetics in this country and need not be considered in this discussion. I do not prescribe alcohol for diabetics. I know of several diabetics who have given up their moderate use of alcohol upon their own volition and have felt better for it.

5. **Fat.**—Does an excess of fat in the diet lead to arteriosclerosis? The imbibition theory of arteriosclerosis enunciated by Virchow and reaffirmed and amplified recently by Aschoff[4] and others fits the diabetic situation. Virchow found fat in the intima of the larger arteries and concluded that the fat in the form of cholesterol esters was deposited there by imbibition from the blood stream and that the more fat in the blood the more readily it would be deposited. In the later stages calcium salts would be linked with the cholesterol[5] in the lower layers of the intima and calcified arteries would result. I believe the chief cause of premature development of arteriosclerosis in diabetes, save for advancing age, is due to an excess of fat in the body (obesity), in the diet, and in the blood. With an excess of fat diabetes begins and from an excess of fat diabetics die, formerly of coma, recently of arteriosclerosis.

Obesity and its termination in arteriosclerosis is too well-known to admit of discussion, but the possibility of an excess of fat in the diabetic diet leading to arteriosclerosis is a very good subject for discussion, because it is advocated by clinicians, notable for their contributions to diabetes, Petrén and Newburgh and Marsh. They

[1] Nuzum, Osborne, and Sansum: Arch. Int. Med., 1925, **35**, 492.
[2] Sansum, Blatherwick, and Bowden: Jour. Am. Med. Assn., 1926, **86**, 178.
[3] Nuzum, Segal, Garland, and Osborne: Arch. Int. Med., 1926, **37**, 733.
[4] Aschoff: Lectures on Pathology, New York, Hoeber, 1924.
[5] Westphal and Blum: Deut. Arch. f. klin. Med., 1926, **152**, 331.

contend that when the protein in the diet is low and fat high, acidosis, hyperglycemia and excess fat in the blood are avoided.

Large quantities of fat in the diet are often not tolerated by diabetic patients any more than by normal individuals and I know are disliked after a period of years from experience with the high-fat feeding of diabetics between 1898 and 1914, the Naunyn Era. In the latter part of the Allen Epoch, fat was welcomed, because it allowed the thin patients more food. For the older patients fat was advantageous and analysis of Petrén's and my data, see p. 610, shows that his older patients lived longer than mine, but at the same time the analysis proves fat was dangerous, because his younger patients lived for a shorter time than did mine.

When Petrén[1] gave days of exclusively fat diets, occasionally the acidosis increased, occasionally decreased and today one can explain this on the basis of the glycogen reserve in the body being oxidized. The whole point is not to give more fat than can be burned along with the carbohydrate which is available for oxidation (Blix[2]). It is not only the fat burned which is of significance, but the fat which is incompletely burned. To recognize the importance of this, all one needs to do is to observe what happens to diabetics after the omission of insulin.

A high-fat diet is claimed by its advocates not to lead to acidosis, hyperglycemia and excess of fat in the blood. This may be true under the special conditions in which they give it, but one would not have the hardihood to assert this for the 99 diabetics in each 100 who ordinarily lived upon a high-fat diet. As generally practised, save in the milder types of diabetes, it leads to the accumulation in the blood of incompletely oxidized fat, the ketone bodies, and ultimately to death in coma.

The old idea about the worth of a food in diabetes was its effect upon acidosis and glycosuria. This is not so today. Both of these undesirables we can avoid with insulin. What we are after now is the more remote action of the food and especially its relation to arteriosclerosis for this is what is destroying the diabetic.

(*a*) **Blood Fat and Cholesterol.**—The fat in the blood of the diabetic tends to be above normal and has never been reported in a series of cases as below normal, until the group recorded in this book, based upon the analyses of the blood of my patients by Hazel Hunt. The percentage of fat rises with the severity of the disease (Gray,[3] Blix[4]), varies particularly with the extent of the acidosis and is especially related to the quantity of carbohydrate which is being oxidized,

[1] Petrén: Ergebn. d. inn. Med. u. Kinderh., 1925, **28**, 92.
[2] Blix: Studies on Diabetic Lipemia, Lund, 1925, p. 159.
[3] Gray: Am. Jour. Med. Sci., 1924, **168**, 35.
[4] Blix: Loc. cit., p. 159.

rather than to the fat administered. The larger amount of carbohydrate prescribed of late, together with its better utilization and also quite probably the influence of insulin on the fat metabolism would appear to explain the recent reports upon my cases. For discussion of fat in blood, see p. 229.

Cholesterol, one of the substances always associated with blood fat, is also generally increased in the diabetic's blood. It, too, is of bad prognostic significance. It is said by some not to be destroyed or excreted by the body, but I cannot believe this, because one of my patients, Case No. 3194, eats 5 eggs a day and has done so for years. As 1 egg contains 0.38 gm. cholesterol this would amount to a retention of 1.3 pounds cholesterol in a year and this is hardly conceivable with the normal, 0.207 per cent of cholesterol, which Miss Hunt found in her blood. It is more probable that cholesterol is synthesized in the body and the evidence is in favor of this explanation. Labbé and Heitz[1] found the cholesterol increased in the blood of 18 diabetics and 27 patients with endarteritis obliterans, and attributed a close connection between the cholesterol and the arterial disease. In 1910 Windaus[2] reported the cholesterol in a normal aorta as 0.103 to 0.119 per cent, but in a diseased aorta the value was 0.670 to 0.741 per cent. Analyses of aortæ of diabetics, made by Miss Hunt, substantiate these findings. Letulle *et al.*[3] found atheromatous lesions in the peripheral arteries of a diabetic woman, aged fifty-five years, with hypercholesterolemia and retention of cholesterol in the intima of the arteries. Furthermore, the solubility of cholesterol in the blood is slight and there may be difficulty in its excretion. We have, therefore, in the blood of the diabetic the basis for Virchow's theory and Aschoff's more recent elucidation of it. See Westphal and Blum.[4]

The association of gall stones and disease of the gall-bladder with diabetes has been described. In Table 207, the percentage with gall stones for 4003 diabetics at or above twenty years of age was 5 per cent.

Compare these figures with those of Mentzer[5] of the Mayo Clinic who found 21 per cent in 600 consecutive autopsies, also his statement that 90 per cent of the patients weighing over 220 pounds had diseased gall-bladders in contrast to 30 per cent of adults weighing less than 110 pounds. Mentzer also found in 200 determinations of blood cholesterol in cases of gall-bladder disease, compared with gall-bladders proved negative at operation, a relative increase in cholesterol.

[1] Labbé and Heitz: Ann. d. méd., 1925, **18**, 108.
[2] Windaus: Ztschr. f. physiol. Chem.,1910, **67**, 174.
[3] Letulle, Labbé, and Hertz: Arch. d. mal. d. cœur, 1925, **18**, 273.
[4] Westphal and Blum: Loc. cit. p. 331.
[5] Mentzer: Arch. Surg., 1927, **14**, 14.

In xanthoma diabeticorum Goldstein and Harris[1] found the reports of the cholesterol in the blood to be high. Here again we have a disturbance in the metabolism of fat leading to other deposits of cholesterol.

The frequency of disease of the coronary arteries in my patients with gall stones has been commented upon by Warren and Root.

Warfield[2] has also reported the association of arteriosclerosis with nephrosis in which the cholesterol in the blood is high. Often in nephrosis, arteriosclerosis is absent. Have the patients lived long enough to develop it?

If cholesterol is of major importance in the formation of gall stones in diabetics one would expect the incidence to increase with the duration of the disease, but thus far this is not the case. See p. 539. It is also difficult to reconcile the lower values for cholesterol in diabetics of long duration than in those of short duration, because it is the former group who show the sclerosis. It is easy to offer theories in explanation, but what we want are facts.

In this discussion of fat in the blood and in the diet I have omitted with design citation of the work of our chief authority on blood fat, W. R. Bloor, because of the importance of work now in progress which he will eventually publish. Two of his papers should be mentioned.[3]

C. THE PATHOLOGY OF ARTERIOSCLEROSIS.

Provided he has diabetes long enough every diabetic will die of or with arteriosclerosis, just as will any other individual. In seeking information from pathological reports of arteriosclerosis and diabetes one must never forget that the diabetic lives and dies in what may be termed the arteriosclerotic zone. The most frequent years for the development of diabetes are the fiftieth and fifty-first, and this is the time the arteriosclerosis of age is well underway.

The first question, therefore, we as clinicians wish to ask the pathologist is: "Does this diabetic patient show more arteriosclerosis than is normal for age, sex, and weight?" This has already been answered in the affirmative. And the second question we would propose is: "Provided this diabetic shows more arteriosclerosis than is normal for his age, is it the same type of arteriosclerosis which is characteristic for his age?" In other words, is the diabetic simply prematurely old or is there any thing specific about the type of arteriosclerosis which he presents? Surgeons tell me that the prognosis of recovery from local gangrene in a diabetic is more favorable

[1] Goldstein and Harris: Am. Jour. Med. Sci., 1927, **173**, 195.

[2] Murphy and Warfield: Arch. Int. Med., 1926, **38**, 449.

[3] Bloor, W. R.: Biochemistry of the Fats, Chem. Rev., 1925, **2**, 243; The Utilization of Fat in the Animal Body, Jour. Metab. Res., 1923, **4**, 549.

than in a non-diabetic. Gangrene rests upon an arteriosclerotic basis. Is it more favorable in a diabetic because the arteriosclerosis is of a different type, or because in a diabetic gangrene begins at an earlier age than in a non-diabetic and possibly when the artery is less diseased? Surgically there appears to be a difference between gangrene in the diabetic and non-diabetic, and this implies a difference in the arteriosclerosis or in the tissues in which arteriosclerosis develops.

Clinically, arteriosclerosis in diabetes attacks the arteries of the heart and legs in preference to the arteries of the brain. Is cerebral arteriosclerosis more predominantly medial in type, and arteriosclerosis of the coronaries and of the legs more intimal in character in its early stages? If so, this might explain the difference in the clinical predominance of arteriosclerosis of the heart and legs over that of the brain. It is difficult to answer the question, because the fact is that the two types are found hand in hand. In Table 251 an attempt is made to show the changing tendencies in the localization of arteriosclerosis causing death in the 544 diabetics from among the total 1756 fatal cases of diabetes. Evidently the proportion of deaths from arteriosclerosis of the brain and kidneys is decreasing while that from the heart and peripheral vessels is rising.

TABLE 251.—DEATHS FROM ARTERIOSCLEROSIS IN 1756 FATAL DIABETICS. LOCALIZATION OF TERMINAL LESION IN BRAIN, KIDNEYS, HEART OR PERIPHERAL ARTERIES.

Localization of arteriosclerosis causing death.	Incidence of localization to arteriosclerotic deaths.		
	Naunyn epoch, per cent.	Allen epoch, per cent.	Banting epoch, per cent.
Brain	17	18	13
Kidneys	23	14	11
Heart	37	41	45
Peripheral arteries	23	27	31

Virchow's imbibition theory of arteriosclerosis, so named, and modified by Aschoff,[1] may or may not be the correct theory, but it certainly applies to the conditions found in diabetes. Here we have the arteriosclerotic process accelerated and the type modified and, to explain the process, an increased amount of cholesterol in the blood, which Aschoff believes is one of the prerequisites for arteriosclerosis. The atheromatous process can begin in the young as well as in the old. It is unitarian in character. It is easy for this reason to understand why young diabetics can show marked fatty, atheromatous changes. These changes take place first of all where the vessels "are under great physiological strain and therefore suffer a great degree of loosening and imbibition of plasma."

[1] Aschoff: Lectures on Pathology, New York, Hoeber, 1924.

I will quote Aschoff further. It almost seems as if he were writing of our diabetic patients. "There is a second factor that must be present before these atheromatous spots may appear. This, it seems to me, is a sufficient concentration of lipids, especially of cholesterin esters in the plasma. From plasma of low cholesterin content no deposition of lipids will occur, even though mechanical conditions are favorable. The greater the concentration of the cholesterin esters in the plasma, the more surely will the areas of the aorta subject to the greatest mechanical strain show this fatty deposition even macroscopically. . . . This may, however, entirely disappear in malnutrition, especially when there is a deficiency of lipids in the diet. This accounts for the decrease in atheromatosis in the later years of the World War and in the postwar period in Germany. . . . While in youth a reversibility of the process through a reabsorption of the lipid substances is doubtless possible, such an involution of the atheromatous patch in the period of senescence is absolutely excluded. That is why in the senile period the atheromatous process not only reaches an extraordinary degree but undergoes further transformations that are entirely absent in youth. . . . necrosis occurs. In the necrotic tissue there is progressive splitting-up of the lipid elements in particular. The cholesterin ester decomposes, the cholesterin is freed and crystallizes out in the familiar crystals. As has been described by Klotz, the fatty acids form the usual soaps, the most important of which is the calcium soap, since this leads to incrustation and calcification of the atheromatous deposit and the tissue surrounding it. In this way there develops the peculiar impregnation of the atheromatous patches with their plaques of calcareous and bony hardness, which completes the picture of atherosclerosis. . . . The character of the diet remains the most important factor." Aschoff calls attention to the feeding experiments in rabbits by which the administration of cholesterin over long periods of time leads to arteriosclerosis and with its withdrawal the atheromatosis disappears. "Thus, in this instance, it is in fact a reversible process."[1]

D. PREVENTION OF ARTERIOSCLEROSIS IN DIABETES.

With physiological overstrain as a cause of arteriosclerosis the diabetic at present is not concerned. He has too little rather than too much physiological strain save that which may result from obesity. But with the second factor, an excess of cholesterol in the blood, he has the greatest concern for his diet contains a large amount of fat which predisposes to an excess of cholesterol. Yet

[1] Glaser found an excess of cholesterol in the blood after injections of adrenalin. This makes cholesteremia a link in the chain between conditions of excitement in the vegetative nervous system and arteriosclerosis. See Glaser: Klin. Wchnschr., 1927, **6**, 2377.

the diabetic must live largely on fat. How much is it safe for him to take to prevent arteriosclerosis? First of all, the quantity must be so low that body weight eventually will be kept normal or a trifle below normal.

Fat in the tissues as well as in the diet may do harm as Heiberg[1] has recently emphasized. Second, the diabetic who has seemed to me to develop arteriosclerosis at an abnormally early age has been the severe diabetic, kept alive hitherto upon a low-carbohydrate high-fat diet. He would not be alive without this diet so we should not find fault with it. On the other hand it is encouraging to find that faithful diabetics who have lived upon a diet restricted approximately to 100 gm. of carbohydrate show less arteriosclerosis. This was demonstrated for me in one of my patients by Dr. Bowen in Buffalo and it has been observed in Boston as well. For the present, therefore, I am endeavoring during the first few years of diabetes to raise the tolerance of the patient with the help of insulin so that eventually he will take 100 gm. of carbohydrate or even more with a relatively small amount of insulin. Consequently the low percentages of fat found in the blood of my diabetics are encouraging. I realize Sansum[2] has the same purpose in mind. Also, insulin helps marvellously in allowing our diabetics to utilize 100 gm. carbohydrate daily and thus keep the fat relatively low in the diet, but far lower in the blood and presumably still lower in the tissues, just as the sugar is lower in the tissues than in the blood. Recall that extraordinary story of Rabinowitch's patient. Overnight 1 of the 2 pounds of fat in the blood disappeared and it was but a few hours later when the other pound vanished and almost the normal quantity, about 15 gm., 0.5 ounce, remained. Every dose of insulin you give your patient defers the advent of his arteriosclerosis, postpones old age.

In non-diabetic arteritis obliterans insulin is said to have been of distinct benefit. The pain disappeared with injections of 15 units daily which were continued for months. Improvement was noted and the case reported at the end of six months[3] and again after another period of six months.[4] Who can tell how much good the diabetics will indirectly do mankind? As yet I do not favor complete exclusion of foods rich in cholesterol from the diet of the diabetic, although I do limit eggs to 1 daily in patients over fifty years of age. There are too many such foods and cholesterol is too valuable a compound of the body to be treated in this cavalier fashion. Cholesterol exists in nearly every cell of the body and this cannot be without cause. It appears to protect against infections.

[1] Heiberg: Ueber die Behandlung des Diabetes Mellitus, J. F. Bergmann, München, 1927, p. 6.

[2] Sansum, Blatherwick, and Bowden: Jour. Am. Med. Assn., 1926, **86**, 178.

[3] Ambard, Boyer, and Schmidt: Bull. et mém. Soc. méd. d. hôp., 1926, **50**, 1474.

[4] Yacoël and Boyer: Bull. de l'Acad. de méd., 1927, **91**, 429.

We are going far enough in our present imperfect knowledge of the subject if we provide for the complete oxidation of fat.

But perhaps we can prevent its harmful influence by the use of potassium sulphocyanate in 0.1 gram doses thrice daily for one week, twice daily the next, once daily the next and omit the fourth week and then repeat the cycle as advocated by Westphal and Blum[1] and Gager.[2]

E. TREATMENT OF ARTERIOSCLEROSIS AND DIABETES.

If a diabetic has known enough to live ten years, be sure you know enough to make him live another ten years before you tamper with his diet. This was clearly brought out by Woodyatt[3] in 1923. The arteries of the young diabetic are elastic and his diabetes is so pliable and amenable to all types of treatment that you can toss him about in your diabetic salon like a rubber doll. Not so the old diabetic. His arteries are thickened and sometimes hard and his status must be changed as delicately as you would move a choice piece of bric-a-brac. Be guided by my experience in the early part of this century, when with youthful enthusiasm I suddenly reduced the blood sugar of a cherished Commonwealth Avenue diabetic patient, Case No. 11, who at infrequent intervals had mild attacks of angina pectoris. In the early hours of the morning I was called to her untimely death bed. And that other diabetic in 1922, Case No. 705, should be mentioned who also was found dead a few days after I reduced his blood sugar with diet and insulin. Van den Bergh[4] has commented upon this latter case, added 2 others and cited those of Nicely and Edmondson.[5] Van den Bergh's explanation depends on the unusual need of the diseased heart for sugar as described by Büdingen,[6] and the possibility that the sclerotic heart requires a level of sugar in the blood distinctly higher than normal in order to be properly nourished. A sudden lowering of the blood-sugar level even to values still above normal might work disastrously to a heart accustomed for years to work on a much higher blood-sugar plane. Therefore, with diabetic patients having angina pectoris be extremely cautions. Von Noorden and Isaacs[7] take this same view, and so does E. Grafe who writes the section upon the eye in their book. In discussing hemorrhagic retinitis he writes, "Insulin is to be used here with care. Notable changes for the worse can take

[1] Westphal and Blum: Loc. Cit., p. 331.
[2] Gager: Jour. Am. Med. Assn., 1928, **90**, 82.
[3] Woodyatt: Southern Med. Jour., 1924, **17**, 145.
[4] Van den Bergh: Berlin, Julius Springer, 1926, p. 222.
[5] Nicely and Edmondson: Am. Jour. Med. Sci., 1924, **167**, 570.
[6] Büdingen: Zentralbl. f. Herz. u. Gefässkrankh., 1925, Nos. 14, 15.
[7] Von Noorden and Isaacs: Die Zuckerkrankheit, 8th ed., Berlin, 1927, p. 307.

place. The more outspoken the alterations in the vessels the more conservatively ought insulin to be given. And what it is possible to observe with the ophthalmoscope in the retina ought to hold for other vascular areas." It is encouraging also that he notes certain of the ocular lesions in diabetes are reversible with diet and insulin. Let us not forget that sugar (glycogen) is the food and the only food upon which a muscle can live.

Professor Frank of Breslau recently told me that injections of 30 cc. of 30 per cent glucose were commonly used in Germany in the treatment of angina pectoris. Osato, Ohba and Kasai[1] also recommend injections of glucose and insulin in cardiac failure.

O'Hare's[2] observations upon patients with a high blood-pressure, who presented a lowering of sugar tolerance with the glucose tolerance test, may be interpreted on the basis that the hyperglycemia which he found was conservative and compensatory in order to supply the requirements of the heart.

If the blood sugar is increased as a compensatory phenomenon in arteriosclerosis, it is important, because in the arteriosclerosis of the legs and in other parts of the body it would hold as well as for the heart. I am not at all sure about the matter, but I am positive that a high blood sugar in a chronic sclerotic should not be lowered suddenly.

Something similar to this is suggested by Woodyatt in his article cited above. One must not think of hyperglycemia merely from the diabetic standpoint, but from that of the needs of the entire body.

The danger of hypoglycemia in arteriosclerosis needs only mention that it be appreciated and avoided. Excess of exercise, diet or insulin will cause it. Beware!

German writers and recently Moschcowitz,[3] have strongly emphasized the harmfulness of tobacco in coronary disease, both etiologically and during treatment.

Angina pectoris in diabetics, however, reacts more favorably to treatment than with non-diabetics. In this I agree with von Noorden and Isaacs. Furthermore I always feel justified in speaking hopefully to a diabetic with high blood-pressure, because the treatment of the diabetes will act favorably upon both diseases.

Can it be that the prevalence of arteriosclerosis in diabetes is to be attributed to the high-fat diets we have prescribed and more especially to these diets having been rich in cholesterol? I suspect this may be the case. At any rate it is reasonable to maintain the cholesterol in the blood of our patients at a normal level and that I shall strive to do. This may result in the limitation of eggs, each one

[1] Osato, Ohba and Kasai: Japanese Jour. Med. Sci., 1927, **1**, 25.

[2] O'Hare: Am. Jour. Med. Sci., 1920, **160**, 366. See also Marañon: Presión arterial y metabolismo hydrocarbonado. Madrid, 1925.

[3] Moschcowitz: Jour. Am. Med. Assn., 1928, **90**, 733.

of which contains 0.38 grams cholesterol, and even of olive oil containing about 1 per cent and corn oil more nearly 2 per cent. This therapeutic procedure is adaptable to experimental investigation and should not require long for solution.

I am led all the more to this belief because the limitation of the diet of 11 healthy young men[1] to 1400 calories for one week lowered the systolic pressure from 120 to 102 mm. Hg. and the diastolic, from 83 to 69 mm. Hg.

1. **The Blood-pressure.**—The blood-pressure in diabetes is slightly below normal until the age of thirty-five years is reached; it then changes to slightly above normal and the interval between diabetic and normal widens as age advances. The above statements are based upon data secured from diabetics since April 1, 1919. Previously, the blood-pressure of diabetics was a trifle higher. Whereas the average normal blood-pressure based upon 19,339 normals between the ages of fifteen and fifty years according to Fisher[2] average 127, that of diabetics prior to April, 1919 was 139 and in a group between 1919 and 1923, it was 129. (Tables 252, 253.) The blood-pressure in diabetes varies with the fashions of the diet, and may be high, low or normal, and it is more nearly normal today than heretofore.

Janeway's[3] conclusions coincide with my data. He wrote: " . . . it is clear from my own observations and those of Elliott[4] that diabetes itself is without influence on the arterial pressure. Hypertension is therefore presumably an expression of the well-known tendency of diabetes of suitable age to develop arterial disease."

Rosenbloom's[5] experience is also similar because in every case in which the blood-pressure was found high in his diabetic patients there was a complicating nephritis, arteriosclerosis, or aortitis. In the uncomplicated cases of diabetes the blood-pressure was normal or subnormal.

A distinction in the increase in blood-pressure in diabetes has been observed by Kylin.[6] In the 97 cases of diabetes studied by him since 1919, a high blood-pressure of a purely arterial type was found. In this type the blood-pressure drops toward normal during sleep and there is no high capillary blood-pressure. He considers that this special type of blood-pressure and the diabetes

[1] Benedict, Miles, Roth, and Smith: Carnegie Institute, Washington, 1919, Pub. No. 280, p. 373.
[2] Fisher: Jour. Am. Med. Assn., 1914, **43**, 1752.
[3] Janeway: Johns Hopkins Hosp. Bull., 1915, **26**, 341.
[4] Elliott: Jour. Am. Med. Assn., 1907, **49**, 27.
[5] Rosenbloom: Jour. Lab. and Clin. Med., 1922, **7**, 392.
[6] Kylin: Zentralbl. f. inn. Med., 1921, **42**, 873.

TABLE 252.—THE BLOOD-PRESSURE IN DIABETES.

Period.	Age, group, years.	Total cases.	Blood-pressure.									
			100–125		126–150		151–175		176–200		Above 200	
			No. of cases.	Per cent.	No. of cases.	Per cent.	No. of cases.	Per cent.	No. of cases.	Per cent.	No. of cases.	Per cent.
Before April, 1919 .	21–50	448	174	39	191	43	56	12	19	4	8	2
After April, 1919 . .	21–50	356	161	45	147	41	35	10	10	3	3	1
Before April, 1919 .	Over 50	675	172	26	283	42	129	19	62	9	29	4
After April, 1919 .	Over 50	522	119	23	196	37	124	24	53	10	30	6

are the resultant of some common cause. Among my patients, at the New England Deaconess Hospital with diabetes and hypertension Root, Thompson, and White[1] found an average fall in systolic blood-pressure between 5 P.M. and 8 A.M. of 41.4 mm. Hg. The corresponding drop in diastolic pressure was 17.4 mm. Hg. Patients with diabetes and no hypertension showed a slight rise in both systolic and diastolic pressures during this same period. Counts of the red corpuscles in capillary and venous blood showed in the patients with hypertension evidence of capillary stasis in the afternoon and a fall in the capillary count during the night. This finding may be related to the occurrence of gangrene in that it shows stasis in the terminal blood supply when the patient is active.

TABLE 253.—THE AVERAGE BLOOD-PRESSURE OF NORMAL AND DIABETIC INDIVIDUALS.

Age.	Number of individuals.				Average blood-pressure, mm. Hg.			
	Normals, Fisher.	Diabetics, Joslin.			Normals, Fisher.	Diabetics, Joslin.		
		Before April 1, 1919.	After April 1, 1919.	1926 to 1927.		Before April 1, 1919.	After April 1, 1919.	1926 to 1927.
15–20	281	38	50		120	124	117	
21–25	785	33	50	50	123	122	117	111
26–30	791	56	50		124	121	121	
31–35	689	39	50	50	124	120	119	124
36–40	2111	64	50		127	125	126	
41–45	6740	75	50	50	129	139	131	130
46–50	4471	116	50		131	143	135	
51–55	2371	127	50	50	132	154	146	155
56–60	1100	103	50		135	154	153	
Over 60	...	163	50	50	...	156[2]	155[2]	154
	19,339	814	500	..	127	139	129	135

Low blood-pressures are frequently encountered with diabetic patients. It would appear as if the number of such cases had become greater in the period since undernutrition was introduced and prior to treatment with insulin. Thus, 35 cases were found among 500 cases. In 500 cases seen in 1926 to 1927, there were 25 cases.

Another source of information upon the influence of diabetes on blood-pressure can be found by comparing the blood-pressure of a series of diabetics during subsequent stages of the disease. See Table 256.

[1] Root, Thompson, and White: Jour. Lab. and Clin. Med., 1926, **11**, 405.
[2] Not included in average.

TABLE 254.—CASES OF DIABETES WITH BLOOD-PRESSURE OF 100 MG. HG., OR BELOW CLASSIFIED ACCORDING TO AGE AT THE TIME OF READING.

1923.

15–20. years.		21–25. years.		26–30. years.		31–35. years.		36–40. years.		41–45. years.		46–50. years.		51–55. years.		56–60. years.	
Case No.	Dur., yrs.	Case No.	Dur., yrs.	Case No.	Dur., yrs.	Case No.	Dur., yrs.	Case No.	Dur., yrs.	Case No.	Dur., yrs.	Case No.	Dur., yrs.	Case No.	Dur., yrs.	Case No.	Dur., yrs.
		1130*	2.0	1102*	5.3	1005*	0.4	1018	11.3	1066*	2.0	..	..	1101*	1.0		
		1143*	1 da.	1232[1]	10.4	1085*	0.3	1073[1]	Unt.[4]								
2037	6.5	1227*	1.7	..	..	1159*	0.5	1155*	0.1	2200[2]	6.2	..	..	2835	4.8		
2052	6.5	..	..	2156*	0.8	1196*	1.1	1259*	0.8	2513*	0.3						
2220	6.3	2042	Unt.[4]	2391	5.8	1215	5.8										
2684	5.1	2432	5.6	2406	5.8	..	..	2206[1]	Unt.[4]								
2801*	1.1	2516[1]	5.4	2416*	0.9	2079*	0.8	2259[1]	6.0								
		2687	5.1	2808	4.8	2340*	1.1	2360	5.8								
		2696[5]	5.1	2948	4.6	2582	5.4	2476	5.5								
						2611	5.3	2496*	1 da.								
						2656	5.2	2852	4.8								
						2669	5.1	2868	4.8								
						2702	5.1	2909*	2.9								
						2943	4.8										
Av.	5.1	..	2.9	..	4.0	..	3.2	..	4.0	..	1.2	..	..	..	2.9		

1927.

5011	1.5	5397	1.0	5012	1.5	5396	0.9	5079	1.3	..	..	5152	Unt.	5229	1.2	5398	1.0
5413	1.0	..	..	5029	1.5	5632	0.8	5495	0.8	..	..	..	..	5793	0.4	5733	0.6
5653	0.7	..	..	5114	1.3	5673	0.7	5532	0.8								
5707	0.6	..	..	5384	1.0	5839	0.4										
				5390	1.0												
				5520	0.8												
				5713	0.6												
				5796	0.4												
Av.	0.9	..	1.0	..	1.0	..	0.7	..	1.0	..	..	..	..	..	0.8	..	0.8

* Fatal cases.
[1] Unclassified
[2] Renal glycosuria
[3] Potential diabetic
[4] Untraced.
} Not included in final average.

TABLE 255.—CASES OF TRUE DIABETES WITH BLOOD-PRESSURE OF 100 MM. HG. OR BELOW. ALL HAD DIABETES FIVE OR MORE YEARS. CLASSIFIED ACCORDING TO AGE AT TIME OF READING.

15–20 yrs.		21–25 yrs.		26–30 yrs.		31–35 yrs.		36–40 yrs.		41–45 yrs.		46–50 yrs.		51–55 yrs.		56–60 yrs.		61–65 yrs.		70–75 yrs.	
Case No.	Dur., yrs.	Case No.	Dur., yrs.	Case No.	Dur., yrs.	Case No.	Dur., yrs.	Case No.	Dur., yrs.	Case No.	Dur., yrs.	Case No.	Dur., yrs.	Case No.	Dur., yrs.	Case No.	Dur., yrs.	Case No.	Dur., yrs.	Case No.	Dur., yrs.
				503	15.2	331	17.3	1122	6.9	444	15.8	835	5.9	1327	4.7	..	..	352*	7.9	587*	3 da.
				847	9.6	359	4.5	2296	4.4	1443*	7.5	1500	4.8	1977	0.3	..	..	1171	5.6		
						866*	7.9	..	..	1584	8.0	1931	5.9	2128	0.8						
Av.	..	..	..	..	12.4	..	9.9	..	5.7	..	10.4	..	5.5	..	2.9	..	..	..	6.8	..	3 da.

* Fatal cases.

TABLE 256.—VARIATIONS IN BLOOD-PRESSURE OF TWO HUNDRED AND TWENTY INDIVIDUAL CASES DURING DIFFERENT PERIODS OF OBSERVATION.

Period of observation, years.	Total cases.	Rise.	Constant 5 mm.	Fall.
5	24	11	8	5
6	38	18	11	9
7	29	12	7	10
8	16	3	8	5
9	26	7	10	9
10	16	8	4	4
11	14	4	8	2
12	12	4	5	3
13	12	4	4	4
14	16	8	4	4
15	8	3	2	3
16	3	2	..	1
17	1	1	..	..
18	2	2	..	..
19	2	2	..	..
24	1	..	..	1
Total	220	89	71	60

4 rose 70 mm. Hg.
2 rose 60 mm. Hg.
2 rose 50 mm. Hg.
7 rose 40 mm. Hg.
1 fell 60 mm. Hg.
1 fell 50 mm. Hg.
4 fell 40 mm. Hg.

The average blood-pressure of 220 cases varied only slightly with the duration of the disease. Averages were made for a series of cases, the duration having extended from one to three or more years up to thirty years. The extremes in average blood-pressure were found to be 131 and 161. The average variations in blood-pressure for the duration one to ten years inclusive were between 138 and 146; those for eleven to twenty years between 131 and 147; those for twenty-one to thirty years, made up, it is true of only 32 cases, varied between 131 and 161.

Case No. 727, with onset of diabetes at the age of fifty-one years, showed 7.6 per cent of sugar when she was first seen at the age of fifty-five, May 14, 1914. The systolic blood-pressure was 220 mm. (Riva Rocci). The changes in the urine and in the blood-pressure during the course of treatment are given in Table 257. She did remarkably well and like so many of such cases evidence of disease of the gall-bladder was demonstrated. Later a suture of the bones of the knee resulted successfully, and happily in the year 1923 she was rewarded for her faithfulness in the past by the use of insulin. Her diet satisfies her and she is better than for years. The extraction of sixteen teeth under local anesthesia at two sittings was undergone without event. This patient shows both a rise and a fall in the blood-pressure during the course of treatment.

Marañon[1] has noted such a fall of blood-pressure quite commonly

[1] Marañon: Zentralbl. f. inn. Med., 1922, **43**, 169; Presión arterial y metabolismo hydrocarbonado. Madrid, 1925.

as the duration of the diabetes progressed. Conversely, he has observed that a high blood-pressure may precede the onset of diabetes, as it did with Case No. 872.

TABLE 257.—CHANGES IN BLOOD-PRESSURE DURING THIRTEEN YEARS OF TREATMENT FOR DIABETES. CASE NO. 727.

	Sugar, per cent.	Diet in grams.				Insulin, units.	Weight, lbs.	Blood-pressure, mm. Hg.
		C.	P.	F.	Cals.			
1914.								
May 14	7.6	...	..	...	....	...	...	220
17	6.2	188	..	...	....	...	114	
25	2.2	103	..	...	....	...	113	
June 4	0	10	..	...	....	...	111	
Aug. 13	0	45	..	...	....	...	122	180
Nov. 17	0	0	..	...	....	...	127	170
Dec. 31	0	70	..	...	....	...	128	160
1915.								
Mar. 29	0	70	..	...	....	...	128	160
July 22	0	70	..	...	....	...	125	150
Nov. 2	0	...	..	...	....	Attack of gall stones		
1916.								
Feb. 23	0	70	..	...	....	...	123	180
1917.								
Mar. 1	1.0	...	..	...	....	...	123	160
1922.								
June	Broke knee.							
1923.								
May 16	2.4	...	..	...	....	...	116	200
June 7–8	0.2	104	53	55	1123	0–1–2	...	180
1927.								
Sept. 13	0.2	...	..	...	....	0	108¼	170–180
1928.								
Mar. 22	0.3	75	42	100	1368	0	106	168–210

An illustrative case is No. 629, who, after several years of circulatory symptoms with annoying angina pectoris, developed diabetes at the age of seventy-one; also Case No. 872 who had a blood-pressure of 250 at the age of sixty-five without quantitatable sugar in the urine, but in whose urine three years later 5.2 per cent of sugar was found. After treatment of the diabetes sugar disappeared, and the blood-pressure fell in succeeding years to 230, 220 and 210. Coincidently there has been marked amelioration of the anginal pains of which patient complained on her initial visit. The improvement may have been due to gradual loss of weight which occurred following the onset of diabetes.

The blood-pressure in coma is discussed on p. 656. In general it falls much below normal if the case is progressing unfavorably.

The advantage of a high blood-pressure and the dangers of a low blood-pressure in circulatory diseases of the lower extremities are emphasized by Bernheim.[1] "The individual who has circulatory disease of the extremities plus a high blood-pressure almost never develops a gangrenous limb." But Bowen's series of cases with a high blood-pressure were more prone to gangrene than were his cases with hypotension.[2]

F. HEART DISEASE IN DIABETES.

By Burton E. Hamilton,[3] M.D. and Howard F. Root, M.D.

Heart disease is second only to gangrene as a substitute for coma in causing diabetic deaths today. The proportion of cardiac deaths to total deaths in the Banting Era was treble that of the Naunyn Era (see Table 161, p. 375). It is possible, however, that some of the deaths judged years ago to be from heart disease were, in fact, due to hypoglycemia (see Case No. 2079, on p. 218), and it is likely that of the patients who succumb in the early stages of diabetic coma, some may die because of complicating cardio-vascular disease, rather than because of the coma itself.

The types of heart disease complicating diabetes depend primarily on the age of the patients and duration of the diabetes. Since 60 per cent of all cases of diabetes develop after the age of forty years, and fifty years is the most frequent age of onset, arteriosclerotic heart disease should not be rare. Indeed, the accelerating influence of diabetes on the development of arteriosclerosis should add to its incidence, unless improvements in diabetic treatment counteract it. As Fitz and Murphy[4] have pointed out, the discovery of sugar in the urine is too apt to lead one to forget a more serious arteriosclerosis. Certainly the increasing duration of life of diabetic patients will have at least an equal effect in swelling the incidence of arteriosclerotic heart disease as a cause of death in diabetes, that increasing prolongation of life has in the general population.

In contrast with arteriosclerotic heart disease, rheumatic heart disease developing during the course of diabetes is rare, although, as this is written (July, 1927) Case No. 2197, aged 56.9 years, is recovering from acute rheumatic fever and pericarditis, and Case No. 2451, aged 59.5 years, underwent a typical attack of rheumatic fever in October, 1926. Case No. 3727, aged sixteen years, developed diabetes during an attack of rheumatic fever.

[1] Bernheim: Southern Med. Jour., 1927, **20**, 311.

[2] Bowen, Koenig and Viele: Bull. Buffalo Gen. Hosp., 1924, **2**, 35.

[3] Dr. Burton Hamilton has been of great assistance to my associates and me in the treatment of circulatory complications among our diabetics. Dr. Root and he have worked much together and it is fortunate that they are now able to analyze the material. It is a great satisfaction to see data utilized. (E. P. J.)

[4] Fitz and Murphy: Am. Jour. Med. Sci., 1924, **168**, 313.

In reviewing 400 of the cases, Dr. E. C. Miller found a history of rheumatic fever, before the onset of the disease, in 6 per cent, and Barach[1] noted an incidence of 16 per cent in 226 cases of diabetes. This suggests that diabetic patients have not possessed throughout their lives any striking immunity to rheumatic fever, though it must be confessed that histories of rheumatic fever are uncertain. It is noteworthy that Barach found in 37 diabetics who gave a history of rheumatic fever, only 1 case of valvular heart disease. It may be, as Barach concludes, that when rheumatic fever attacks a potential diabetic, the heart is comparatively immune to involvement. Perhaps the explanation is that not many children or young adults with severe rheumatic heart disease live through the twenty-five to thirty-five years that are necessary to bring them to the age when diabetes is common. Only the more fortunate patients who, in spite of rheumatic fever in youth, had no severe involvement of the heart would be likely to survive to the average age for the onset of diabetes. Whatever the cause, it appears that rheumatic heart disease is uncommon in diabetics, both clinically and at autopsy.

Syphilis is no more common among diabetics than in the general population and has had no important influence on the cardiac complications. Positive Wassermann tests were obtained in 2.2 per cent of 2065 diabetics. In 122 cases of angina pectoris, the Wassermann reaction was done in 71 cases, 38 male and 33 female. In 2 males and in 1 female it was positive, or 4 per cent. This percentage is to be compared with 4.5 per cent in a series of 200 non-diabetic cases of angina pectoris reported by Dr. Harlow Brooks.[2]

Hypertension plays an important role in the cardiac complications of diabetes. Hypertension precedes the onset of diabetes not infrequently, see p. 700, and in occasional cases where the blood-pressure was normal at the time of hospital observation, an antecedent hypertension could be suspected from the character of the changes in the retinæ. O'Hare[3] found diabetes common as a late development in his cases of hypertension. Among 46 patients in whom hypertension and glycosuria were discovered in a routine examination, Mohler[4] found only 16 true diabetics. It will be of value to know the future history of the remainder.

A coincident hyperthyroidism has accounted for a few cases of auricular fibrillation among diabetics.

Foster[5] commented on the action of the heart in coma and found myocardial degeneration in every case at necropsy. Blitzen and Schram[6] found notching in the main deflections of electrocardiographic curves more common in diabetics than in controls.

[1] Barach: Am. Heart Jour., 1926, **2**, 196.
[2] Brooks: Jour. Am. Med. Assn., 1927, **88**, 1991.
[3] O'Hare and Walker: Boston Med. and Surg. Jour., 1924, **190**, 683.
[4] Mohler: Jour. Am. Med. Assn., 1925, **84**, 243.
[5] Foster: Jour. Am. Med. Assn., 1925, **84**, 719.
[6] Blitzen and Schram: Arch. Int. Med., 1925, **36**, 770.

1. **Angina Pectoris and Coronary Thrombosis.**—(*a*) **Incidence.**—Among 4676 cases of diabetes seen since 1895, a diagnosis of angina pectoris or coronary occlusion was made 122 times. We have omitted 26 cases of sudden cardiac death which could not be classified definitely as deaths in angina pectoris, although we have little doubt from the scanty descriptions that in most instances they were truly deaths from coronary disease.

It is not profitable to attempt to distinguish between angina pectoris and coronary occlusion in this series of cases. Among diabetics, angina pectoris is to be interpreted as evidence of coronary sclerosis. Many cases with chronic angina pectoris, produced only by exertion, have had an attack, which could best be interpreted as a coronary occlusion, as the first symptom of their coronary disease; and many end with coronary occlusion. In some cases a fatal occlusion is the first symptom of coronary disease.

Among 2174 cases of true diabetes over thirty years of age who have been seen since January 1, 1922, 54 cases of angina pectoris have already developed, although many of these patients came under observation early in the course of their diabetes. Sixty-eight cases occurred in the first 2502 patients coming for treatment between 1895 and 1922. The relatively higher incidence in this earlier group is doubtless due to the fact that a greater percentage of these earlier cases have had time to grow old, and of necessity, a very much larger number of them have died. However, it is not unlikely that the second, the recent group, will eventually have a higher incidence since their expectation of life is increased by reduction of deaths from coma. The association of angina pectoris and diabetes occurred in 10 of 82 cases of angina pectoris reported by Kahn,[1] and in 7 of 103 cases reported by S. A. Levine.[2]

Angina pectoris trebles in the second ten years of diabetes as compared with the first ten years of the disease. This is shown by Table 258 in which the incidence for the cases with a duration from ten to fourteen years was 3.8 per cent, between fifteen and nineteen years was 6.7 per cent, while the cases over twenty years yielded 12.6 per cent.

TABLE 258.—THE DURATION OF DIABETES AND THE INCIDENCE OF ANGINA PECTORIS.

No. of cases.	Duration of diabetes, years.	Angina pectoris.	
		Cases.	Per cent.
552	10–14	21	3.8
239	15–19	16	6.7
142	20+	18	12.6

[1] Kahn: Am. Jour. Med. Sci., 1926, **172**, 195.

[2] Levine: Jour. Am. Med. Assn., 1922, **79**, 928. In a personal communication, March 29, 1928, Dr. Levine states that among 145 definite cases of coronary thrombosis he found 34 in whom an outspoken history of diabetes was present or an appreciable glycosuria, during the attack of coronary thrombosis. More than half of this number belong to the first group. See his forthcoming article in *Medicine*, 1928.

(*b*) **Pathology.**—The causes of death of diabetic patients with angina pectoris are predominately cardiac. Cases Nos. 2532 and 2803, however, died of coma and Case No. 3468, aged sixty-one years, of septicemia and gangrene. Case No. 4862, aged sixty-four years, suffered an amputation for gangrene and died some weeks later with congestive heart failure following coronary occlusion. Case No. 3210, Mrs. S., aged sixty-four years, died in an attack of angina two hours before she was to have an amputation of her leg for gangrene. In death certificates of patients who died in attacks of angina pectoris the diagnosis was given as "angina pectoris" in 55 cases, and as "coronary occlusion" (with acute infarction of the heart) in 24 cases. The latter condition is probably more common than these diagnoses suggest. In 10 autopsied cases of angina pectoris at the Deaconess Hospital, the causes of death were judged to be acute infarction 5, coronary sclerosis 4, (angina pectoris 2, congestive failure 2), gangrene and septicemia 1. At least two factors serve to disguise the severity of the cardiac damage: (1) Diabetic patients, notably in the past, less so since the use of insulin, have been weak, inactive and hence less likely to impose sufficient strain on the heart muscle to provoke anginal symptoms; (2) the sensitiveness of the diabetic nervous system to pain is less than that of the normal. In this connection, it would be of interest to study the occurrence of tender spots on the chest wall, as described by Kahn,[1] in cases of suspected angina pectoris associated with diabetes. An extraordinary degree of coronary sclerosis and narrowing together with myocardial sclerosis is found in cases with little or no angina.

At autopsy, in 40 diabetic cases over forty years of age at the time of death, coronary sclerosis was present in 24 and sclerosis of the myocardium was present in 27. Wilder[2] also found extensive degrees of coronary sclerosis and myocarditis in 17 cases out of 49 or 34 per cent and especially noted advanced coronary disease in cases who had gangrene of the extremities. In 4 of 7 cases with gall-stones[3] marked coronary sclerosis suggested that excessive deposits of cholesterol may be harmful to two distinct types of tissue.

(*c*) **Clinical Features.**—In the group of 122 cases with coronary disease the onset of diabetes preceded that of angina pectoris in 106 cases, followed it in 13 cases and in 3 instances the two were discovered at the same time. Errors in the date of onset of diabetes may occur, and in general they are in the direction of postponing the date of onset.

The males numbered 71 and females 51 in contrast to the much greater preponderance of males in statistics of angina pectoris among

[1] Kahn: Am. Jour. Med. Sci., 1927, **173**, 363.
[2] Wilder: Southern Med. Jour., 1926, **19**, 241.
[3] Root and Warren: Boston Med. and Surg. Jour., 1926, **194**, 45.

the general population. Is the more equal sex incidence of angina pectoris in diabetes due to the leveling influence of diabetes in respect to physical activity and the development of arteriosclerosis? The systolic blood-pressure was 150 or above in 31 males and 41 females, and below 150 in 32 males and in 7 females. This shows a striking preponderance of hypertension in the female cases. The average age at onset of the diabetes was 50.7 years in the males and 51.4 in the females. The average age at the onset of the angina pectoris was 59.7 years in the males, and 59.9 years in the females. In the fatal cases, the duration of diabetes was 9.5 years in the males and 10.4 years in the females. The duration of the angina pectoris was 2.1 years in the males and 1.4 years in the females. The apparently short expectation of life for a diabetic with angina pectoris may be due to faulty histories, but a striking number of cases were under close diabetic observation both before and after the onset of angina. The explanation may be in the two factors mentioned: (1) A relatively low sensitivity to pain; (2) a relatively low level of physical exertion. Both tend to retard the onset of symptoms until coronary disease is far advanced. A few cases lived much longer than the average periods. In 6 of our series, the duration of angina pectoris was more than five years. Case No. 4434, aged sixty-two years, a housewife, when last examined had had diabetes seventeen years and angina pectoris for twenty years. Her sudden death a few months later was reported officially by the Medical Examiner as due to "coronary thrombosis." At the time of her stay in the hospital, we almost suspected that her symptoms were functional, so surprising was a history of angina pectoris of twenty years' duration in a diabetic.

The variable manifestations of coronary disease are often puzzling, and the following cases will serve as illustrations:

1. *Infarction of the Heart Simulating Coma.*—Miss P., Case No. 1794, aged thirty-three years, diabetes of eight years' duration, had taken insulin for nearly four years. She had gained 50 pounds. On June 4, 1925, she weighed 122 pounds and was taking 80 units of insulin. She had had slight precordial pressure and pain in the left shoulder at intervals for six weeks only. At 4 P.M. on June 8, 1925, her urine was sugar-free and blood sugar was 0.11 per cent. In the absence of her nurse, she broke her diet at supper and at 1 A.M. waked with pain in the left shoulder and vomited. By noon the next day acidosis was extreme as shown by plasma CO_2 of 22 volumes per cent and blood sugar of 0.66 per cent. During the next twenty-four hours pain over the sternum, repeated vomiting, and Stokes-Adams seizures were followed by collapse and death. At autopsy coronary calcification and occlusion with infarction of the interventricular septum and the wall of the left ventricle were found.

2. *Angina Pectoris and Gall Stones.*—Fifteen cases presented this combination, often a problem in diagnosis. Case No. 870, a clergyman, aged fifty-two years, duration of diabetes seventeen years, had had no recognizable angina. He had had a number of severe attacks of gall-stone colic. A gall-bladder filled with stones was removed. Fourteen days after operation, he had symptoms of coronary occlusion, and died three days later. At autopsy both fresh infarction and extensive old infarctions were found.

3. *Paroxysmal Auricular Fibrillation and Angina Pectoris.*—Case No. 3918, developed angina pectoris in 1920. Though in 1923, and probably at intervals since, she has had attacks of paroxysmal auricular fibrillation, in January, 1927, the heart rhythm was regular, and angina occurred only after walking several blocks.

4. *Angina Pectoris and Heart-block.*—In spite of the large number of patients with sclerotic heart disease, only 3 cases have been observed with complete heart-block and Stokes-Adams seizures. Case No. 1794 has been described. The other 2 (Cases Nos. 3569 and 4652) recovered from attacks of coronary occlusion, but heart-block remained. Mohler[1] has described a diabetic who developed heart-block during severe acidosis and made a remarkable recovery.

5. *Coronary Sclerosis Leading to Congestive Failure.*—At least 8 of the 122 cases may be so classified.

6. *Infarction with Recovery.*—Healed infarcts occurred in 7 cases as discovered at postmortem.

7. *Angina Pectoris and Coronary Occlusion with Lowered Blood Sugar.*—Case No. 1520, Mrs. E., aged seventy years, was brought to the Deaconess Hospital at midnight unconscious and rigid. Her blood sugar was 0.03 per cent. She had been given insulin three times a day elsewhere without testing the urine. In spite of injections of glucose, she never fully recovered. She died after a few days and a fresh infarction of the heart was found in addition to several old healed infarctions. Case No. 705 had had mild attacks of angina pectoris for three years. Three days after beginning insulin treatment and diet, he died suddenly at four o'clock in the morning in a typical attack of angina. No infarction was present, but the coronary arteries were calcified and practically occluded. Case No. 1794 has been described on page 705.

Hetényi[2] reports 2 cases of diabetes with angina pectoris in which he states that the attacks were influenced by insulin. In one, a man aged fifty-eight years, angina had been present for two months with rapid increase in frequency of attacks. On admission his urine contained 3.9 per cent of sugar, and diacetic acid; his blood sugar was

[1] Mohler: Jour. Am. Med. Assn., 1923, **91**, 1342.
[2] Hetényi: Hetényi Wien. Arch. f. inn. Med., 1926, **13**, 95.

0.24 per cent. It was observed that when he was given insulin 20 units at a time, within a few hours he had severe pain under the sternum accompanied by sweating and cold skin. A reaction being suspected, he was given glucose intravenously and the pain was immediately relieved. The second man had syphilitic aortitis and twice had severe attacks of angina following insulin injections. When the insulin was given together with glucose, he had no anginal attacks. Van den Bergh[1] holds that the sclerotic heart may require an unusually high level of blood sugar, and Büdingen[2] has suggested that there are three cardiac dystrophies dependent on the utilization of glucose by the heart muscle:

1. A hypoglycemic dystrophy due to a general hypoglycemia.
2. A loss of the sugar-using capacity of the heart muscle.
3. A need for higher concentration of sugar in the blood than normal.

Hetényi thinks that hypoglycemia in the region of the liver, lungs, and heart is due to the insulin action in preventing glycogenolysis in the liver. He advises high-carbohydrate diets if insulin is used in patients with coronary disease.

The heart muscle like other muscle tissue is dependent upon a supply of glucose in the blood not only to maintain its store of glycogen, but to carry on its work. In normal mammalian hearts, Visscher and Müller[3] found that insulin caused a slight increase in power of the cardiac contraction, but no stimulation of oxidative metabolism in an isolated heart. Edwards, Page, and Brown[4] found in dogs that insulin hypoglycemia caused a lessening of the dynamic function of the heart which was restored by injection of glucose. In diseased hearts or in the sclerotic diabetic heart long accustomed to an increased blood sugar, it seems likely that sudden alterations in the blood sugar may be dangerous, whether produced by sudden restriction of diet or by insulin. Of the 122 cases, 39 have taken insulin for periods varying from a few days to thirty-four months. The amount has varied from 5 units to 25 units, although 1 patient received 40 units daily for three days after an amputation of the leg and another took an average of 30 units for about thirty-three months. We shall spare no pains to protect the hearts of elderly and sclerotic diabetic patients with an adequate supply of glucose.

In the incompetent heart with edema insulin acts less well. This may be explained by the accompanying edema and the inactivity of the muscles. Cajori, Crouter and Pemberton[5] observed hyper-

[1] Van den Bergh: Berlin, Julius Springer, 1926, p. 222.
[2] Büdingen: Zentralbl. f. Herz. u. Gefässkrankh., 1925, Nos. 14–15.
[3] Visscher and Müller: Jour. Physiol., 1927, **62**, 341.
[4] Edwards, Page, and Brown: Proc. Soc. Exper. Biol. and Med., 1923, **21**, 170.
[5] Cajori, Crouter and Pemberton: Jour. Biol. Chem., 1925, **66**, 89.

glycemia when there was artificial interference with the circulation of large areas of muscles.

2. **Rheumatic Heart Disease.**—In a series of 56 autopsies upon diabetics at the Deaconess Hospital, there has been but 1 case of rheumatic heart disease either in children or adults. Case No. 2989 with mitral stenosis and auricular fibrillation successfully underwent a gastro-enterostomy under local anesthesia.

3. **Pericarditis.**—Pericarditis was present in 5 autopsied cases. In Case No. 4304 a purulent exudate occurred as part of a general infection resulting from pyelonephritis. In Case No. 4507 a purulent exudate developed during the course of a staphylococcus septicemia arising in an infected foot. Case No. 2988 developed bronchopneumonia and coma. She emerged from coma, but a high pulse-rate and leukocytosis of 40,000 still persisted. A bread and butter type of shaggy exudate was found in the pericardium. Case No. 5983 developed rheumatic fever following an acute tonsillitis. At autopsy a bread and butter type of pericarditis with rheumatic myocarditis, as shown by typical Aschoff nodules, was found. Case No. 5726 had old healed pericarditis with calcified adhesions.

SECTION XI.

TREATMENT OF COMPLICATIONS.

The complications and sequelæ of diabetes are more serious for the patient than the disease itself and the same holds true for intercurrent disease. Fortunately coma, the most dreaded of all these complications, is fast disappearing, but in its stead arteriosclerosis has come to the fore and presents a much more difficult problem to treat. Intercurrent diseases are far less a menace than formerly. As for the complications, their variety and the number of patients so affected are being reduced with the improvement of the hygiene of the patient and his greater resistance to infections, each the result of better treatment. The various maladies which may supervene upon or follow diabetes are dangerous, often not so much because of their own severity, but because, as in the case of infections, they make diabetes more severe. To these changing conditions treatment must conform until recovery restores the diabetes to its former character. On every occasion, however, treat the diabetes as well as the complication and then the patient will be kept in the best fighting trim, but do not err in the thought that the same type of diabetes is present in the same patient on successive days. An infection changes the character of the diabetes and the type hardly remains constant for successive twenty-four hours. Furthermore, it is the inadequately treated diabetic who develops many of the complications and sequelæ of diabetes. From these conditions patients should remain free, because diabetics are, or should be, constantly under the doctor's eye and his prophylactic care.

The duration of life of diabetic patients in the past has been so short that the dangers which might result from peculiarities of treatment have been neglected, because in the space of five or six years these would not manifest themselves. Today with the duration of the disease so much prolonged, all these factors must be taken into account, and the diabetic should be taught how to live out his normal expectation of life.

A. INFECTIONS.

An infection makes a diabetic worse. This rule is so exact that one can make a safe prediction upon the condition of the infection by the course of the diabetes and conversely whenever a diabetic

does badly, search for an infection, hyperthyroidism or cancer of the pancreas. The effect of a carbuncle upon the diabetic process is an excellent example. With its advent a diabetes almost quiescent for years becomes intensely severe, but with its subsidence resumes its mild character. Case No. 4097 showed 6 grams sugar in the urine with a diet of carbohydrate 78, protein 60, fat 116 and was given 10 units insulin at the height of his carbuncle. Subsequently he was sugar-free without insulin and taking carbohydrate 108, protein 77, fat 130.

If the infection is local, it should receive prompt surgical treatment; if it is general, the danger of acidosis must be realized, due largely to the fever with its resulting increase of metabolism. It is rarely possible to keep a patient sugar-free in the presence of an infection, whether local or general. This is where the family doctor has often scored on the supposedly wise consultant. The latter would order a fat-protein diet and death would result from coma. If the case is doing well, either leave the diet alone or make gradual changes and there will be more chances of having the individual for a patient during years to come than if brilliant dietetic orders are written. It is safer to undernourish than to fan the flame of metabolism by overfeeding, and better to take an intermediate course and give not over 1 gram of protein per kilogram body weight. It is true that the patient may lose weight but so may a non-diabetic in fever, and it is wiser to trust to Nature to draw from the body the requisite stores of protein and fat than to insist upon the taking of food that may be harmful. The administration of little protein and liberal carbohydrate was accidentally and fortunately adopted with an Italian who had typhoid fever at the Boston City Hospital in the summer of 1908. He was given a diet composed exclusively of oatmeal and olive oil which he took with avidity until his recovery was complete.

Carbohydrate in the form of oatmeal gruel, orange juice and even purée vegetables, protein as whites of eggs, oysters, fish and chicken, and fat in the form of cream will tide over many emergencies. In the hospital the nurse, in charge of the diabetic nursing, asks for the carbohydrate, protein and fat allowed and then arranges for its administration according to the patient's whims.

Infections do not make the diabetes permanently worse. Before the discovery of insulin this seemed to be the case, but it is not so now. Evidently the islands of Langerhans are only temporarily injured by an infection or else not injured at all and the obvious harmful effect of an infection is to be explained by neutralization of the power of the insulin by a stimulation of the thyroid and suprarenal glands.[1]

[1] Lawrence: British Med. Jour., 1926, ii, 983.

Rosenthal and Behrendt[1] found that when fresh pus was mixed with insulin and injected into rabbits the influence of the insulin was abolished. It would be interesting to compare the effect of insulin in pneumonia, typhoid fever, and leukemia.

Insulin will not maintain a sugar-free urine during active infections unless given in heroic doses which I believe to be more dangerous than the infection itself. At almost any moment during an infection, recovery may begin and the need for insulin suddenly abate. It is true the patient may be brought out of an hypoglycemic attack, but nevertheless an insulin reaction is a harrowing procedure for the patient if he is in a weakened condition and the late effects may lead to death even though there is recovery from the immediate effects.

When death results from an actual infectious disease, such as gangrene, pyelitis, pneumonia or appendicitis the blood-sugar percentage may be just as high as in coma. It seems strange to read that the highest blood-sugar percentage found by Petrén outside of coma, and not immediately followed by coma, was 0.42 per cent. These observations are distinctly at variance with our findings at the New England Deaconess Hospital. Thus Case No. 1887 with blood sugar of 0.5 per cent lived seven months after this determination. Five cases (Cases Nos. 2201, 2266, 2716, 2798 and 2870) showed blood-sugar percentages of 0.53, 0.54, 0.43, 0.45 and 0.64. Of these, 4 died within four years, while the fifth is still alive (December, 1927). I will acknowledge, however, that without cautious treatment such values are critical.

1. **General Infections.**—(*a*) **Pneumonia.**—Pneumonia has been by far the most important infection, if one can judge by its frequency in mortality tables. One hundred and twenty cases of diabetes out of a total of 1756 have succumbed to it and as a cause of death it ranks with tuberculosis. Yet not all diabetic patients die who acquire pneumonia, as Table 259 shows.

The diagnosis of pneumonia must often be faulty in diabetes and the errors are probably both ways. An autopsy alone will satisfy the tenets of scientific accuracy. Coma may be blamed for a death which pneumonia has caused, Case No. 2446, and the reverse may be true, Case No. 3010. A pain in the chest at the beginning of coma by no means always signifies pneumonia.

The treatment of the patient during an acute infection varies from hour to hour or at least every four hours. If insulin has been given twice a day it is safer to halve each dose and administer it four times a day, increasing the size of each dose if necessary until the total insulin is doubled or more. The urine is tested before each

[1] Rosenthal and Behrendt: Ztschr. f. d. ges. exp. Med., 1926, **53**, 562.

dose and if sugar-free twice in succession the insulin can be omitted for that period. The insulin can be raised to 100 units, but generally I am able to get along with less than this quantity. I am aware that Carrasco Formiguera[1] has used 200 units daily for a week and made a patient with a carbuncle sugar-free. My colleague H. F. Root[2] has reported the result of excessive insulin dosage in diabetic gangrene. On the contrary, Stanley L's mastoid healed beautifully after operation despite high glycosuria and acidosis; and so did he, my diabetic boy of 9 years' duration, after McKittrick removed his gangrenous appendix, which the father diagnosed in February, 1928. See Case No. 2680, p. 577.

TABLE 259.—RECOVERY FROM PNEUMONIA IN DIABETES.

Case. No.	Age at onset of diabetes, years.	Duration. Before pneumonia, years	After pneumonia, years.
8	60	12.5	1.1
19	47	0.6	9.0
36	42	7.0	3.3
46	62	20.0	0.3
131	37	12.5	8.6
352	49	22.0	0.2
358	53	17.0	1.0
435	33	23.0	10.3
844	32	33.0	1.5
895	55	12.0	9.0
911	57	7.0	2.3
1274	56	4.0	18.0[3]
1350	38	10.0	11.0

Even a trifling coryza will lower tolerance for carbohydrate. During an attack of herpes zoster the carbohydrate tolerance of Case No. 521 fell markedly . This is interesting because it suggests the infectious etiology of this disease.

(*b*) **Acute Rheumatic Fever.**—Acute rheumatic fever seldom occurs in a diabetic despite his many infections. Case No. 694, a mild diabetic, had a slight attack in the spring of 1917. Surely not more than 4 other such cases have come to my attention in the 6000 diabetics under my care. Case No. 2451, had a typical attack of rheumatic fever and I was able to exhibit her to Professor Labbé during an attack. Case No. 2197 was successfully carried through her typical attack by Dr. Walker of Andover, Massachusetts. In each instance tonsils were a factor. Mrs. A.,Case No. 958, had acute arthritis of the ankle in December, 1920, while under the care of Dr. A. A. Hornor. Mrs. G., Case No. 5983, died of rheumatic pericarditis in March, 1927. The rarity of rheumatic fever among

[1] Carrasco Formiguera: Lancet, 1925, ii, 1076.
[2] Root: Lancet, 1926, ii, 544.
[3] Still living. Duration to July, 1927.

diabetics while under my observation, 6 in 6000, is all the more notable, because these cases cover an experience of twenty-nine years and the average duration of the fatal cases covers about six or seven years. Diabetics have many infections. There must be some reason why they acquire rheumatic fever so infrequently. See p. 707, for Case No. 2989.

Chronic arthritis is not uncommon. Schmitt and Adams[1] at the Mayo Clinic noted its presence in 10.8 per cent of their cases and I am sure it is even more common in my own.

B. GASTRO-INTESTINAL COMPLICATIONS.

1. **Constipation.**—Constipation is less frequent today than in the period of treatment by undernutrition. The larger quantities of carbohydrate allowed have made obsolete the enormous quantities of 5 per cent vegetables prescribed and of washed bran consumed. Coincidently the bulging abdomens of the children have disappeared. Upon more than one occasion temporary intestinal obstruction followed the use of bran and the muscles of my associate's hand were lame for some days following the digital evacuation of the rectum at a consultation in a distant city. When constipation does exist, it can be relieved by such simple means as the use of mineral oil, which can be made palatable in the form of salad dressing. However attention should be called to the fact that Dutcher[2] *et al.* have shown that liquid petrolatum may act as a solvent for vitamin A thereby depleting ingested foods of their supply of this factor. Mellanby[3] also showed that mineral oil diminishes the nutritive value of any food with which it is admixed by delaying digestion and absorption in the small intestine. The ordinary compound rhubarb pill of the U. S. Pharmacopœia is the cathartic most in use at the Deaconess. One occasionally obtains a false diacetic acid reaction with rhubarb pills, due to the oil of peppermint which they sometimes contain. Agar-agar jellies, p. 918, are not now a necessary routine.

Raw vegetables and coarse vegetables are, of course, useful. Great pains, however, should be taken to impress upon the patients the necessity of preparing coarse vegetables in a simple manner. It is perfectly possible to cook cabbage, cauliflower, turnips, parsnips, radishes, cucumbers and onions so as to be unirritating to the digestive tract and yet preserve their laxative qualities. Patients whose tolerance allows potatoes are encouraged to eat them with the skins on. Diarrhea should be carefully avoided.

[1] Schmitt and Adams: Jour. Am. Med. Assn., 1926, **86**, 535.
[2] Dutcher, Ely, and Honeywell: Proc. Soc. Exper. Biol. and Med., 1927, **24**, 953.
[3] Mellanby: Jour. Phys., 1927, **64**, 331.

A bottle of liquid citrate of magnesia may contain as much as 11 per cent, 35 grams, sugar, and lead to erroneous conclusions regarding the carbohydrate balance.

Roentgen-ray examination is apt to disclose an atonic bowel, according to L. B. Morrison, in which the proximal colon is full and distended and the haustral markings less distinct. The distal colon becomes smooth.

Physical exercise is the best of all treatment for constipation. The constipation of Case 348, whose prostate was successfuly removed by A. L. Chute in July, 1915, vanished when he began to saw wood, and he kept it up for years until he died of cardiac disease in June, 1925.

The following exercises for the relief of constipation were prepared for the use of my patients by Mr. Gustaf Sundelius. These are easy to execute and suitable for weak and elderly people:

1. *Abdominal Kneading and Stroking.*—Kneading,—Lying down, with knees slightly drawn up. Place hands one on top of the other on the abdomen at the right groin; with small circular movements and deep pressure work upward until the ribs are met, then across toward left, following the boundary line of the chest, then downward to the left groin. Repeat twenty to fifty times. Stroking.—With hands similarly placed, make long, steady and deep strokes following the same route. Repeat twenty-five to one hundred times.

2. *Leg Rolling.*—Lying down, take hold of both legs just below the knees, press the knees up close to the abdomen, then carry them apart, then down and inward until they meet again, thus letting the knees describe two circles. Repeat ten to twenty times.

3. *Abdominal Compression.*—Standing against the wall with hands clasped behind neck, draw the abdomen forcibly in, using the abdominal muscles, hold a second, then let go. Repeat ten to forty times.

4. *Trunk Rolling.*—Standing with hands on hips, feet apart and legs well stretched, roll the upper body in a circle on the hips by bending forward, to the left, backward and to the right. Then reverse, and repeat six to twelve times each way.

2. **Diarrhea.**—Diarrhea is a grave complication. It may lead to coma, due to abstinence from food and the consumption of body protein and fat plus the loss of body fluids. On the other hand it may provoke a severe insulin reaction, because the efficacy of insulin is increased by the low metabolism and the non-absorption of carbohydrate. Therefore treat diarrhea in a diabetic seriously.

Rest in bed, temporary fasting, and preservation of body warmth should be carried out from beginning to end of the attack. Hot water, solutions of hot, weak tea or cracked cocoa may be given.

The carbohydrate of the diet should be continued in the simplest form such as gruels, crackers, toast, rice, macaroni or even grape juice or ginger ale. For carbohydrate content see Food Tables, page 924. The return to the diabetic diet is rendered easy by the

use of cottage cheese, soft cream cheese, lean meats, oatmeal gruel, milk, cream, biscuits, eggs, purée vegetables. The carefully prepared, tender vegetables are frequently better borne than a diet containing considerable quantities of albuminous and fatty food.

If the water content of the body is threatened give salt solution subcutaneously.

When the indication is plain, the bowels should be cleared out with castor oil or, even better, a Seidlitz powder. Avoid strong cathartics because diabetic patients with diarrhea are usually too feeble to withstand their action. Should the cause of the diarrhea be in the large intestine give enemata. Bismuth subcarbonate, a teaspoonful before each meal and after each loose movement, and, if necessary, opium are indicated.

The dose of insulin should be varied according to the presence of glycosuria. Usually it should be lowered and the interval of administration shortened. The patient must be under the closest supervision because of the small quantity of carbohydrate which he may take or absorb. An instance in point is Case 2909 (page 46).

The tolerance of a diabetic may increase during an attack of diarrhea. This has been marked on several occasions and it has also been noted that when the diarrhea has ceased the tolerance has again fallen. Guelpa[1] produced diarrhea along with fasting when he prescribed salts. Hirschfeld[2] mentions the favorable effect of diarrhea and he cites Külz as having observed this. Sugar was not found in the feces.

Case No. 2909, just mentioned, experienced a rise in tolerance from 63 grams carbohydrate on October 22, 1922, to 113 grams carbohydrate on November 8, 1922. Another patient, Case No. 2099, whose tolerance had been as low as 6 grams carbohydrate in February, 1921, during an attack of diarrhea in August, 1921, was able to take 45 grams carbohydrate without glycosuria. This is the patient who before coming for treatment took a gallon of olive oil in the course of some weeks by mistake for mineral oil, and developed acidosis. In June, 1923, with 36 units of insulin she was sugar-free on a diet of carbohydrate 50 grams, protein 50 grams, and fat 100 grams, and her weight had risen from 57 pounds in 1921 to 86 pounds. In 1927 her diet is carbohydrate 95, protein 65, fat 120, insulin 42 units. She now weighs 128 pounds.

The circulation of a diabetic is woefully weak when he is attacked with diarrhea.

Absence of free hydrochloric acid from the gastric juice may predispose to diarrhea. Bowen and Aaron[3] examined 10 diabetics with diarrhea and in no instance was hydrochloric acid present. Of 20

[1] Guelpa: Loc. cit., p. 40.
[2] Hirschfeld: Ztschr. f. klin. Med., 1896, **31**, 219.
[3] Bowen and Aaron: Arch. Int. Med., 1926, **37**, 674.

cases without hydrochloric acid the average duration of the diabetes was 6.5 years and the diabetes was invariably severe. Among the group with normal hydrochloric acid the duration of the diabetes was 2.8 years, while the gastric subacidity group represented an average duration of 3.6 years. The age of the patient was not a factor. Bowen and Aaron suggest that achlorhydria may be the result of long standing or severe diabetes. Death from inanition and asthenia might easily ensue.

Carvalho and Fonseca[1] noted no action on the external secretion of the pancreas. See also Cascao de Anciaes.[2]

Pancreatic insufficiency theoretically could easily lead to diarrhea and in several cases this has appeared to exist. In one such case it was proved for me by Chester Jones. His work on the deficiency of the external pancreatic juice has already been discussed on page 411. The depancreatized dogs naturally show the effects of lack of trypsin (see page 24). Sansum, I believe, has considered this a factor in certain cases of intestinal indigestion in diabetes. The subject merits further therapeutic investigation.

3. **Ulcer: Gastric or Duodenal.**—Hunger is a characteristic symptom in diabetes, but not until 1923 did the many sources of diabetic hunger come to my attention. (1) There is the hunger of the untreated diabetic, due to the excretion of enormous quantities of sugar in the urine with attending polyphagia. (2) There is the hunger of undernutrition, which came to the fore when this type of treatment was introduced in 1914. (3) There is the hunger accompanying the hypoglycemia caused by an overdose of insulin. And finally (4), there is the hunger which is often a symptom of gastric or duodenal ulcer; it is with this we are concerned.

Of the first 2700 cases coming for treatment before June, 1922, no instance of ulcer of the stomach or duodenum, developing after the onset of diabetes, was recognized, but soon striking examples began to appear. Of these Case No. 564 was the most pathetic. With severe acidosis and 3.4 per cent of sugar he entered the hospital in December, 1912, and only became sugar-free three months later through the help of a diabetic nurse at home. Courageously he went through boarding school and entered college, invariably keeping sugar-free, demonstrating that if adherence to a weighed diet is absolute, daily examinations of the urine can be omitted and reliance placed upon monthly blood-sugar tests. On November 15, 1922, in California, he suddenly developed pain, succumbed in three days, and an ulcer of the stomach was found to have perforated.

The second instance was almost as tragic. Case No. 2559 devel-

[1] Carvalho and Fonseca: Comp. Rend. de la Soc. de Biol., 1926, **95**, 1262.
[2] Cascao de Anciaes: Compt. Rend. de la Soc. de Biol., 1926, **95**, 1258.

oped diabetes at the age of fifty-four years, came under treatment in March, 1922, became sugar-free, acquired a tolerance of carbohydrate 96 grams, protein 71 grams, and fat 99 grams, and returned to business. Without ever having had a symptom of indigestion so far as his family recall, in July, 1922, he suddenly had a violent hemorrhage, and despite transfusion, died within two days. At autopsy there was a double ulcer of the duodenum.

The third case was a delight. Case No. 2989, a working man of forty-seven years, with eight children, entered the hospital on February 24, 1923, with 5.3 per cent of sugar. Distress in the stomach led to examination, which disclosed retention of food, the presence of blood, and, by Roentgen-ray, pyloric obstruction. The Wassermann reaction was negative. Double aortic and mitral murmurs were to be heard in the heart. Auricular fibrillation was present at times. Notwithstanding all this, the patient became sugar-free with the help of insulin, acquired a tolerance for carbohydrate 75 grams, protein 48 grams, and fat 85 grams, and with novocaine anesthesia underwent at the hands of D. F. Jones a successful gastro-enterostomy. For nearly a week after the operation the heart fibrillated with a pulse-rate of 180, but five weeks later the man was back at light office-work and sugar-free with the aid of a few units of insulin. He died of heart disease in March, 1925.

A fourth case of duodenal ulcer, Case No. 2350, occurred before the patient developed diabetes, and indeed the diabetes is of slight degree as it is with a fifth patient, Case No. 2890, who had had indigestion all his life. These patients are alive in 1927. The sixth patient, Case No. 1122, also gave a history of a duodenal ulcer, the first symptoms of which began in 1910, at the age of twenty-eight years. From then on he was troubled more or less constantly, experiencing three distinct attacks, during the last of which, in 1913, he had rigorous treatment. Diabetes began three years later, in 1916, and he showed 8.4 per cent of sugar when he first came under my observation. With a carefully planned diet, faithfully carried out under the supervision of B. H. Ragle he has come back to life with insulin and remains alive. The seventh patient, Case No. 2600, is the only female in the group. Her diabetes began in December, 1920, and symptoms of ulcer in the same year. The Roentgen-ray showed this to be located in the duodenum. With suitably adjusted diet and insulin, she has made marked improvement, gaining 8 pounds and in 1927 is alive.

Since my attention was directed to this complication or association of ulcer of the stomach and duodenum with diabetes 9 other cases of gastric ulcer and 13 of duodenal ulcer have been found ocurring either before or after the onset of the diabetes and I am

sure that more exist. In my last 1000 cases of glycosuria, however, there was a history of ulcer or the presence of ulcer in but 4 instances. Case No. 3105 recovered from the perforation of a duodenal ulcer by the aid of L. S. McKittrick. Dr. Jordan[1] of the Lahey Clinic tells me that in looking over the records of 351 gastric or duodenal ulcers, she found only 1 case in which glycosuria and high blood sugar were present.

When searching a series of 300 non-diabetic records for the presence of transient glycosuria, it was found that this was present in 50 (16 per cent) and the sugar could be quantitated in 25 of this number. Of these latter there were 6 instances in which the glycosuria was associated with disease of the stomach, duodenum, pancreas, or gall-bladder. Hijmans van den Bergh and Siegenbeek van Henkelom[2] found in a number of patients with gastric and duodenal ulcers a moderate hyperglycemia and an increased glycemic reaction together with glycosuria after ingestion of 50 grams of glucose. Possibility of a more frequent association of sugar in the urine with lesions in the region of the duodenum should lead to the reinvestigation of such patients for diabetes. Recently two of my non-diabetics with duodenal and gastric ulcer died of coronary thrombosis. Does the diet of the ulcer patient contain too many eggs and so promote arteriosclerosis?

The diet of the diabetic furnishes ample reason for the development of an ulcer of the stomach or duodenum. It is a coarse diet; it is often associated with the use of highly seasoned food, with hot food, and ofttimes is distinguished by an abundance of meat. That in the past ulcers of the stomach and duodenum have not been noted frequently with diabetics is not strange, because in the past diabetics lived too short a period to develop and die of such conditions. If the investigations of Bowen and Aaron are confirmed and hydrochloric acid decreases with the progress of the diabetes, one would expect to find peptic ulcers in the early rather than late stages of the disease. Four of the 10 severe diabetics of McPherson[3] showed achlorhydria, 4 others a diminished secretion. In his tabulation of the causes of death of 292 diabetic patients von Noorden records 1 death from ulcer of the stomach with hemorrhage. Rosenberg and Kallner[4] found gastric ulcer or nervous irritability of the stomach in about 1 per cent of diabetic patients.

In the care of diabetic patients in the future one will do well to remember the 4 causes of hunger mentioned above.

[1] Jordan, Sara: Personal communication.

[2] Hijmans van den Bergh and Siegenbeek van Henkelom: Deutsch. Med. Wchnschr., 1925, **51**, 645.

[3] McPherson: Glasgow Med. Jour., 1927, **107**, 340.

[4] Rosenberg and Kallner: Deutsch. med. Wchnschr., 1927, **52**, 183.

4. **Gastro-intestinal Hemorrhages in the Diabetic.**—Hemorrhage into the gastro-intestinal tract of diabetic patients occurs very readily. Perhaps the commonest form of hemorrhage in non-diabetics is the rarest in diabetes—namely, that from a gastric or duodenal ulcer. Diabetic coma is almost invariably associated with a gastric hemorrhage and it is possible that at times such a hemorrhage accounts for the leukocytosis in coma. A third cause of gastric hemorrhage in the diabetic is a severe insulin reaction. In an adult with convulsions after an overdose of insulin there was a gastric hemorrhage, and in several children a gastric hemorrhage has been observed in the course of a severe reaction in which the child was unconscious several hours.

If hemorrhages occur so readily in the stomach in diabetic coma and during insulin reactions, might they not occur elsewhere—in the eye after a cataract operation, in the brain producing hemiplegia? Dr. Sisson suggests that hemorrhages into the brain in insulin reactions might be the cause of convulsions. Could they explain the peculiar epileptiform attacks of John C., Case No. 3019, the little boy who developed diabetes at 1.6 years, but 1.2 years later began to have these attacks which have rendered him an invalid (see p. 732). Grafe[1] cautions about too energetic treatment with insulin in those conditions of the eye which are prone to hemorrhage, and this possibility was also raised by a physician from Holland whose letter I have misplaced.

C. THE SKIN.

Professor Charles J. White and Dr. Arthur M. Greenwood have been of great assistance to us all at the Deaconess Hospital in the care of our diabetic patients with complications of the skin. Recently the latter[2] has published his observations upon 500 successive diabetics occurring in the service of Dr. F. G. Brigham and myself. From this report I quote freely.

The average per cent of sugar in the blood of the above-mentioned 500 diabetics was 0.19. This is twice the normal fasting value and at first thought would appear to be a factor which might predispose to disease. Yet one should remember that in health after meals the percentage of blood sugar may rise to 0.16 per cent. The disparity between the blood sugar in diabetes and in certain conditions of health therefore largely disappears. Furthermore, there is by no means universal agreement that an increase of sugar in the blood leads to pathology of the skin. Experiments *in vitro* show that blood to which 0.5 to 1 per cent dextrose has been added is no better cul-

[1] Grafe: Von Noorden and Isaac: Loc. cit. p. 319.
[2] Greenwood: Jour. Am. Med. Assn., 1927, **89**, 774.

ture medium for staphylococcus than normal blood and that adding dextrose does not diminish the blood's bactericidal power. Indeed Theobald Smith[1] found sugar harmful to pus cocci. In diseases of the skin in non-diabetics the blood sugar has been found both above normal and normal so that little light is thrown upon the problem by this method of research. Even in the sweat of each one of 28 non-diabetics Talbert and Silvers found sugar, 5.6 to 40 mg. per 100 cc., the average being about 15 mg. Usher and Rabinowitch[2] of Montreal were kind enough to show me the results of their investigation of the relation of sugar in sweat to eczema which suggest a causal relationship between the two. Those cases of eczema which presented a diminished tolerance for carbohydrate exhibited both an increase in the excretion of sweat and of sugar. Ayres[3] studied the glucose tolerance reaction in 86 consecutive cases of eczema and found fifteen times as many decidedly abnormal reactions in the eczema series as in the normal control series. Loeb[4] in a series of 462 cases found an absolute increase in the blood sugar in certain skin lesions, while a definite hypoglycemia existed in certain others. In fact, Darnet[5] advises investigation of blood sugar in all cases of chronic skin lesions, suggesting that if a high content is found insulin should be tried.

The sugar in the skin of diabetics was found by Palmer[6] to be 50 per cent of the blood sugar and usually much less. Trimble's observations (personal communication)[7] showed that the concentration of the sugar in the skin of non-diabetic fasting dogs averages 65 mg. per 100 grams of skin when the blood sugar averages 80 to 90 mg. per 100 cc. When sugar is injected intravenously the concentration in the skin rises and reaches a numerical value only slightly lower per 100 grams of skin than that found per 100 cc. of blood. Samples of skin taken at various intervals after injections show that the sugar concentration of the skin and of the blood fall off in a nearly parallel manner. The concentration in the skin is always slightly under that in the blood.

A comparison between the incidence and variety of skin affections in the group of 500 diabetics and various series of non-diabetics has been drawn by Greenwood. First of all it may be said that 25 per cent of the diabetics gave a history of skin disease and 75 per cent denied any skin trouble. Skin disease was present in 11.4 per cent of the number as compared with 10 per cent for the general clinic

[1] Smith: Centralbl. f. Bakt., 1895, **18**, 1.
[2] Usher and Rabinowitch: Arch. Dermat. and Syph., 1927, **16**, 706.
[3] Ayres: Arch. Dermat. and Syph., 1925, **11**, 628.
[4] Loeb: Arch. f. Dermat. u. Syph. (Berlin), 1926, **152**, 529.
[5] Darnet, J. J.: Semana Med. (Buenos Aires), 1927, **34**, 769.
[6] Palmer: Jour. Biol. Chem., 1917, **30**, 79.
[7] See also Folin, Trimble, and Newman: Jour. Biol. Chem., 1927, **75**, 263.

at the Out-Patient Department of the Massachusetts General Hospital and 5 per cent in private practice. (Lane.)

Pruritus appeared in 33 cases, approximately 1 case in 15 cases. This was local in 17 patients and general in 16.

Pruritus pudendi frequently occurs in diabetes and will usually vanish within a few days, but occasionally not until two weeks after the disappearance of sugar from the urine. General pruritus, on the other hand, is exceptional, may be annoying and persist for weeks, and resist all forms of treatment with which I am conversant. It does not occur in young diabetics. If pruritus pudendi does not clear up promptly, as the urine becomes sugar-free, an examination will probably disclose a local cause, such as a prolapse, leucorrhea or urinary incontinence. Rest in bed, absolute cleanliness, simple douches and the simplest of ointments are indicated. The free use of oil to prevent irritation during micturition is helpful. Patients with chronic nephritis are often relieved of pruritus when the protein and salt in the diet are reduced. There may be cases where $\frac{1}{4}$-skin

TABLE. 260.—A COMPARISON OF CERTAIN AFFECTIONS OF THE SKIN IN DIABETICS, IN THE OUT-PATIENT DEPARTMENT OF THE MASSACHUSETTS GENERAL HOSPITAL, AND IN A GENERAL PRACTICE. (GREENWOOD,[1] LANE.[2])

Disease.	Diabetics.		Mass. Gen. Hosp.,	Lane,
	Number.	Per cent	Per cent.	Per cent.
Furunculosis	7	1.4	0.9	0.24
Carbuncle	3	0.6	0.12	0.2
Erysipelas	2	0.4	0.04	0.11
Psoriasis	12	2.4	0.23	0.1
Eczema	14	2.8	4.0	0.5
Epidermophytosis	198	40.0	0.8	
Seborrheic dermatitis	1	0.2	0.27	0.2
Xanthoma palpebrarum	9	1.8	0.02	
Dupuytren's contractures	8	1.6	0.016	

unit doses of Roentgen-ray become necessary to allay the itching. In Hédon's depancreatized dog this was only accomplished when he received cystine. One patient secured some relief with very mild exposure to the ultra-violet ray. Pruritus is a frequent symptom in the latent stage of diabetes according to Marañon.

Pruritus ani in diabetics according to Greenwood can be separated into three types: (1) Those in which the skin around the anus is definitely infected with bacteria; (2) those in which it is definitely infected with fungi; and (3) those in which the skin shows no change. It is almost impossible to tell from appearances alone how to distinguish between the first two. The only way it can be done accurately is by careful microscopic search for fungi. In general the

[1] Greenwood: Jour. Am. Med. Assn., 1927, **89**, 774.
[2] Lane: Jour. Am. Med. Assn., 1927, **89**, 776.

mycotic infections are apt to show outlying lesions and also a peculiar white macerated appearance back of the rectum in the intergluteal fold.

As a treatment Greenwood has used mercurochrome or a similar substance in the bacterial types. For the second type, Whitfield's ointment, or more commonly an ointment of salicylic acid and sulphur, āā 2; petrolatum 30—or strong potassium permanganate up to 30 grains to the ounce. For the last type, local anti-pruritic methods and roentgen-ray are used, although at times he uses roentgen-ray for all types, but he agrees with Dr. L. B. Morrison that unless there are very definite results after three treatments it should be discontinued. If possible, in all these cases take every means to prevent scratching, even going so far as to splint the arms at night.

The dryness or moisture of the skin was recorded in 442 instances. Of these it was noted present in 26 per cent and absent in 74 per cent. In contrast to 43 per cent of the patients with dry skins only 29 per cent of those with moist skins had skin disease.

Epidermophytosis was the most common disease. Including all types there were 198 cases, 40 per cent, in which this was present in the feet. Every other patient over twenty years of age had a fungus infection of the feet. This is about the same percentage which Hulsey and Jordan[1] found among university students, 67 per cent, but above the percentage for men in the United States naval service.[2] In diabetes these epidermophytotic infections are most serious. They give to the skin a mouldy or parboiled appearance and render it, especially between the toes, quite susceptible to infections. Many a diabetic patient has subsequently lost a toe or a foot from resulting osteomyelitis. The overwhelming frequency of epidermophytosis in diabetics as compared with patients in an out-patient department or in general practice is shown in Table 260. Incidentally it will be seen that in this group of 500 diabetics furunculosis, carbuncles, erysipelas, psoriasis, xanthoma palpebrarum and Dupuytren's contractures as well as epidermophytosis show higher percentages in contrast to eczema which is lower in the hospital group. Greenwood points out the possibility of epidermophytosis and xanthoma palpebrarum being overlooked in a general hospital clinic.

Epidermophytosis is frequently seen in women about the genitals. Case 1217 was the first patient of this type whom I sent to C. J. White, who taught me the correct name of the disease and cured

[1] Hulsey and Jordan: Jour. Am. Med. Assn., 1925, **169**, 267.
[2] Butler *et al.*: U. S. Naval Med. Bull., 1924, **21**, 615.

the case. He describes the condition, and from his article[1] I abstract a few sentences:

"*Anus and Intergluteal Fold.*—The clinical appearances are almost identical in these neighboring tissues and consist of redness, moisture and at times a decided maceration which results in a lusterless, dirty-white center and a narrow, angry, red, moist periphery.

"*Labia.*—The results of epidermophyton infection here are unusual. The most marked feature is the intense itching which is really cruel. The skin remains dry, dull red, perceptibly thickened and possibly furfuraceously scaling, but nothing more. One cannot appreciate any such appearances as usually exist on the contiguous thighs. The plant probably runs over onto the mucous surfaces. . . . The infectious agent in the disease under discussion is at times the epidermophyton inguinale, first definitely proved and established by Sabouraud, in 1910, but more often the trichophyton. . . . The disease on the thighs, on the pubes and in the axillæ will rapidly disappear after the application of an ointment containing precipitated sulphur, 2; salicylic acid, 2; and benzoated lard, 30; plus rigid but gentle antisepsis; but care must be taken that the skin of the penis and the scrotum is not overstimulated, and that the treatment must continue long enough to kill the plant in the horny layer as well as on it. The disease elsewhere, so far as I know, will not yield to this ointment or easily to any other combination of the ordinary drugs. Whitfield's modified ointment (*i. e.*, salicylic acid, 1; benzoic acid, 1.65; soft paraffin, 10; cocoanut oil, 22) is probably the most successful ointment for the dry types of the disease, and a 1 per cent aqueous solution of permanganate of potash is perhaps the best means of conquering the vesicular and moist phases of the process."

For a recent summary of the subject of epidermophytosis see an article by Mitchell[2] and by Weidmann.[3]

The percentage of furunculosis rose to 6.6 per cent, of carbuncle to 1.8 per cent and of erysipelas to 1 per cent when the histories of the patients as well as what they presented upon examination were combined.

Infections of the skin demand immediate, thorough, yet gentle, treatment. One of the first duties of the physician is to tell diabetic patients to keep the skin exquisitely clean and to report the beginning of an infection at once. Patients should be warned of the

[1] White: Jour. Cutan. Dis., 1919, **37**, 501, also Jour. Am. Med. Assn., 1921, **77**, 1297.

[2] Mitchell: Jour. Am. Med. Assn., 1927, **89**, 421.

[3] Weidman: Jour. Am. Med. Assn., 1928, **90**, 499.

danger from slight wounds, should specifically be advised not to allow manicurists or chiropodists to draw a drop of blood and cautioned to report promptly any injury to the skin. Finger and toe nails should be cleaned with a blunt, not sharp, tipped file or, better, an orange stick. Absolute cleanliness of the body is essential.

A diabetic is more liable than others to skin diseases, and especially to those of an infectious nature. He is particularly prone to these if he has a dry skin and his feet are so commonly infected by fungus diseases that they deserve particular care.

Subcutaneous injections can be given as in any normal individual, but scrupulous asepsis should be practised. From injections of insulin either among old or new cases under treatment I think not more than two infections are seen yearly.

Furunculosis.—If there is the slightest tendency to furunculosis at once adopt simple measures analogous to those described by Bowen.[1] The patient is advised to wash the whole body twice a day with soap and water, using a fresh piece of sterilized gauze and powdered or liquefied soap and to dry the skin with a freshly boiled towel without rubbing, so as to avoid breaking open any pustule; the whole body is then bathed with a saturated solution of boracic acid in water, with the addition of a small proportion of camphor water and glycerin. I have often advised a solution of 2 parts medicated alcohol No. 1 and 1 part water to advantage, but I notice that Bowen, in his second paper, still prefers the boracic acid. Individual furuncles may be treated with the following ointment according to Bowen:

Boracic acid	4
Precipitated sulphur	4
Carbolated petrolatum	30

One should be careful, however, not to overtreat the skin. Harm may result from frequent dressings. The simplest lotions should always be employed. In severe cases the patient should be put to bed, all linen changed twice daily and the patient treated in as aseptic a way as possible. In a few cases vaccines have appeared to be of a marked benefit. "This procedure—thorough bathing and soaping, the application of the borated solution and the dressing of the individual furuncles—is repeated, as has been said, morning and night. A further point of vital importance relates to the clothing that is worn next to the skin. Every stitch of linen worn next to the skin should be changed daily, and in the case of extensive furunculosis all the bedclothing that touches the individual, as well as the night-clothing, should be subjected to a daily change.

[1] Bowen: Jour. Am. Med. Assn., 1910, **55**, 209; Boston Med. and Surg. Jour., 1917, **176**, 96.

Naturally, this treatment must be continued for several weeks after the last evidence of pyogenic infection has appeared, and this fact must be emphasized to the patient at the outset" (Bowen). Stannoxyl, 1 pill with water after each meal, is well worth a trial.

For the management of infections and carbuncles in diabetes, see pages 710 and 782.

Impetigo Contagiosa.—Impetigo contagiosa occurred in a young woman with severe diabetes (Case 2218, described elsewhere). Dr. C. J. White wrote me as follows: "She has a remarkable impetigo contagiosa circinata—remarkable in the extraordinary number of synchronous foci of infection. It would be possible to produce such a condition, I would suppose, by the forceful use of an infected towel in a susceptible individual—in this case a diabetic." Under his care recovery was prompt.

Xanthoma Diabeticorum.—Xanthoma diabeticorum is a disease of considerable frequency in a diabetic clinic, but apparently not very common in dermatological clinics. Thus, C. J. White, in 1920, wrote me he had encountered but 3 or 4 cases. Major[1] has described 3 cases and collected 74 from the literature. They are tumors often brilliant yellow and associated with a red periphery which differentiates them from all other types of xanthomata. The eruption may appear somewhat suddenly, and may extend over the body generally. The tubercles are most numerous on the outside and back of the forearm, and especially about the elbows and knees, where they are confluent. They are usually absent from the flexures of the larger joints. The tubercles are of various sizes, some being as large as a small pea, together with shining colorless papules.

Xanthochromia is a yellow discoloration of the skin frequently seen in diabetes, but this common appearance is not to be confused with xanthoma diabeticorum. It is particularly noticeable on the palms of the hands. It may be seen on the face, but more rarely over the body generally. The pigment which causes it may also be found in the blood. It is a lipochrome and the discoloration must be considered due to an excess of lipochrome in the blood and tissues, which in turn is derived from food. One of the pigments is carotine, as demonstrated by Palmer. Writers quite generally agree that the lipochrome found so constantly in the blood of diabetics is due to their food which is especially rich in lipochrome. Green vegetables, spinach, salad, egg-yolk, butter all contain a large proportion of lipochrome. I see less of these cases now than formerly. Stoner[2] has recently written a concise article on carotinemia and summarized the literature to which Hess was an early contributor. Rabinowitch[3] considers it an unfavorable prognostic sign.

[1] Major: Johns Hopkins Hosp. Bull., 1924, **35**, 27.
[2] Stoner: Am. Jour. Med. Sci., 1928, **175**, 31.
[3] Rabinowitch: An unpublished paper.

However, this is not the only factor responsible. There is evidently some disturbance in the patient's ability to excrete or destroy lipochrome. Xanthochromia occurs in severe, not mild diabetes, as this *à priori* is usually associated with disordered fat metabolism. It is more commonly encountered in the obese child. (Klose.)

A peculiar color of the skin due to vegetables I understand is noticed with the Laps and in certain sections of Japan.

A diet poor in lipochrome will cause amelioration of this condition. The presence of xanthoma is recorded in 6 of my patients, but I suspect there have been at least five times as many instances of it. Three of these cases, Cases Nos. 1705, 2245, 3017, were males, and 3 Cases Nos. 1753, 1936, 2980, females. The age of the youngest patient was twelve years. The duration of the diabetes when the patient was first seen varied between three and eight years. Of these cases, 1 died of coma six months after the first visit, making the total duration of the disease in this instance five and a half years; another died of coma with a duration of 3.8 years; and a third died of heart disease with a duration of diabetes of eight years; the other 3 cases were alive in 1927. The blood fat was 1.1 per cent and 1.4 per cent in 2 cases, and the blood sugar in 5 cases ranged from 0.22 to 0.35 per cent. All of the cases belonged to the moderately severe type of diabetics. Case No. 1701 had multiple tumors upon her fingers which were so large as to be unsightly. One was removed by R. C. Cochrane, but contrary to expectation it was reported as not containing cholesterol. Nevertheless a few months after the omission of eggs these multiple tumors totally disappeared.

The blood-fat in xanthoma diabeticorum is usually reported to be increased. This was true of Major's cases. In the 2 cases observed by Nicholson,[1] among his 600 diabetics, the cholesterol was 1.26 per cent with one and the creamy blood of the other showed 4.4 per cent (Bloor) blood-fat. The latter case confirms C. J. White's favorable prognosis of the condition in that, with the improvement of the diabetes, there was a disappearance of the xanthoma. Major also emphasizes the degree of blood supply which permits absorption of the substances in the xanthomatous lesions. Later on this returned when the diet was relaxed and subsequently the blood-fat rose to 7 per cent and the patient died in coma.

Peculiar processes of involution of xanthoma diabeticorum have been described by Goldstein and Harris.[2] Following the use of insulin, the lesions on the palms disappeared completely, those on the elbows coalesced and left large pigmented patches, while those

[1] Nicholson: Clifton Med. Bull., 1923, **9**, 12. Lyon: Edinburgh Med. Jour., 1922, **28**, 168. Griffith: Jour. Am. Med. Assn., 1922, **78**, 1836.

[2] Goldstein and Harris: Am. Jour. Med. Sci., 1927, **173**, 195.

on the legs and thigh passed through degenerative changes resulting in extensive scar formation.

Purpura.—Case No. 4932 had a general purpura in July, 1926.

Lanugo.—Downy hair often appeared upon the backs of patients in the days of treatment by undernutrition. When improvement took place with insulin, it gradually disappeared and one never sees it today save in neglected cases.

Fatty Atrophy of the Skin.—When insulin is injected frequently in one area of the body there occasionally results induration and necrosis of the underlayers of the skin. As a result insulin is poorly absorbed. Subcutaneous fatty atrophy of the skin has been reported by Barborka.[1] "The depressed lesions varied in diameter from 2 to 7 cm. and from 1 to 3 cm. in depth. There were 2 lesions on the upper arm, 4 on the left thigh, and 2 on the right thigh. There was no evidence either of recent or of old inflammation at any of these sites, and the overlying skin appeared to be healthy. There was no evidence of loss of substance or of weakness in the underlying muscle, or of any sensory or other neurological disturbance, either at the site of the lesion or elsewhere. The abnormality consisted of disappearance of the subcutaneous fat in localized areas, the sites of previous insulin injections."

The lesions in the second case were in every respect like those described in Case I. "Neither patient had received proper instructions in the technique of administering insulin, and one injection after another had been made in the same site. Neither patient suffered any particular pain or soreness from injections, and at no time had there been evidence of infection. In both cases the atrophy began about six months after the insulin injections were started." Depisch[2] from Falta's clinic in Vienna reports 5 cases in which fatty atrophy took place after insulin injections during seven or more months. Four of the 5 cases were in women. Mentzer and Du Bray[3] likewise report an instance of fatty atrophy resulting from injections of insulin. The patient presented depressed areas on the left thigh, 6 x 9 cm., and on the left arm, 3 x 4.5 cm. at the sites of insulin injections during the course of four and eight months respectively. Fat atrophy was apparently the only pathological lesion and there was no evidence of an inflammatory condition such as occurs after injections of narcotics. I have seen but 3 cases, Mrs. H., Case No. 6126, Mrs. F., Case No. 3448, and Mrs. K., who along with localized atrophies had suffered pain in the areas. I hope Clymer will report the neurological aspects of this case. Since most cases of diabetes treated with insulin do not show this lipid dystrophy there may be a special disposition toward it in certain cases.

[1] Barborka: Jour. Am. Med. Assn., 1926, **87**, 1646.
[2] Depisch: Klin. Wchnschr., 1926, **5**, 1965.
[3] Mentzer and Du Bray: California and Western Med., 1927, **26**, 212.

Davison[1] reports a patient, whose diabetes was of three months' duration. The urine and blood contained 7 per cent and 0.31 per cent sugar respectively. Following insulin injections areas of erythema developed with itching and burning which gradually increased to a diameter of 10 to 12 cm. in three to four days, and then slowly subsided. The reaction to insulin was atypical, at times seemingly no effect was obtained from injections, and at others an unexpected insulin reaction might occur.

The phenomena did not result from subcutaneous injections of water, normal saline solution or 0.5 per cent tricresol solution, but did occur with 1 to 100, 1 to 50, and 1 to 25 dilutions of insulin and even with a supposedly low-protein insulin. Attempts to desensitize the patient were unsuccessful.

Five months later she returned in a precomatous state, her insulin having been omitted, but after a few injections of insulin she was relieved and although the local reactions recurred as before, they soon ceased to appear and she was discharged on a diet of carbohydrate 55 grams, proteins 50 grams, and fat 155 grams, with insulin 20, 20, 20 units.

Four months later local fat absorption was observed in the areas of the thighs where the insulin was injected and though no insulin was given in these regions for the next two months no evident deposit of fat took place.

D. THE TEETH.

The teeth of diabetics usually are not good. Among 300 consecutive cases I found 41 per cent had poor or false teeth and Miss Beatrice Kelsey, the dental hygienist at the Deaconess Hospital, among 600 diabetic patients, confirms my findings. Her detailed report is given in Table 261. She has classified the patients in four age groups, under twenty years, twenty to forty years, forty to sixty years, and over sixty years. In the first group 34 per cent had good teeth and in the last only 4 per cent. Poor teeth varied between 17 per cent and 63 per cent for the same respective group. In fact only 9 per cent of the patients over sixty years of age had more than one-half of their teeth and 60 per cent had false teeth. Pyorrhea varies between 12 per cent and 74 per cent for the extremes of age, abscessed teeth between 24 per cent and 54 per cent, approximately one-half of all cases showed caries and in approximately one-fourth of the total number it was extreme.

Poor teeth are by no means necessary, even in diabetes of long duration. Cases which are carefully treated from the outset and are cautioned about care of the teeth have little more trouble than

[1] Davison: California and Western Med., 1927, **26**, 210.

healthy individuals. Then, too, patients with diabetes of long duration are occasionally seen with perfect teeth. This may happen even though they have not dieted strictly.

TABLE 261.—RESULTS OF EXAMINATION OF MOUTHS OF 600 DIABETIC PATIENTS. (COMPILED BY BEATRICE KELSEY.)

	Under 20.	20 to 40.	40 to 60.	Over 60.
Number of patients	68	88	282	162
Mouth condition (per cent):				
Good	34	19	9	4
Fair	49	52	53	33
Poor	17	29	38	63
Number of teeth (per cent):				
More than one-half	100	84	41	9
Less than one-half	0	11	22	31
All false (per cent):	0	5	37	60
Pyorrhea (per cent)	12	33	70	74
Abscessed (per cent)	24	33	39	54
Caries (per cent):				
Little	60	50	65	54
Average	14	21	14	22
Much	26	29	21	24

Bad teeth should be removed and all pockets of pus drained. I consider one of the greatest services rendered the patients at the Deaconess Hospital to be the removal of their bad teeth. The hospital retains on the average more than a tooth per patient. It is so much better to send the patient home with his mouth clean and without the apprehension of dental extractions. The time spent by the patient in the hospital should be utilized to have the mouth and the feet put in perfect condition, just as much as one attempts to treat the blood, the skin, the digestive, the circulatory and respiratory systems.

The extraction of teeth has probably often resulted in the death of the patient, due presumably to the anesthetic. In illustration of this point, and as an example *par excellence* of a needless diabetic death, I would cite Case No. 729.

Death Subsequent to Extraction of Teeth (Ether Anesthesia).—Case No. 729, female, married, teacher; first seen, May 16, 1914; no diabetic heredity. Greatest weight, 163 pounds, although 124 at the first visit. One child born in 1905 and well. In September, 1907, sugar first found, while five months' pregnant. Confinement was normal, and the child was living and well eight years later. The patient became sugar-free and remained so until January, 1911, when she was again pregnant, but miscarried in the following March. In July, 1911, she became pregnant and the child was born at term and is also well. Sugar was absent at this time, but it soon came back and persisted. A miscarriage occurred in February, 1914, and there was a history of two other miscarriages. Under dietetic treatment at the New England Deaconess Hospital in June, 1914,

the sugar decreased from 6.2 per cent to zero, and the patient acquired a tolerance varying between 15 and 45 grams. On April 26, 1915, three months after her last visit to me and without my knowledge, all her teeth were taken out with ether as an anesthetic. The extraction took place at the dentist's office. "She was very sick after getting home, and all that night and the next day complained of the awful weakness and pressure, so that it was hard for her to breathe. April 28 her mind was wandering, and it was difficult to bring her back to consciousness." She died in coma, April 30, 1915.

The same rules which govern the use of anesthetics in surgery apply in dentistry. Gas or gas and oxygen are undoubtedly the best anesthetics. Novocaine may be advantageously employed and obviates in these days the dangers of general anesthesia, but it should be used with caution because the infiltration of the tissues may be distinctly harmful. Ether might be employed if the occasion demanded, because the patient could be protected from hyperglycemia and acidosis by means of insulin.

The teeth and tonsils of all diabetics coming under observation should be more sedulously cared for than with non-diabetics, because an infection makes a diabetic worse. One would like to conclude that subsequent gains in tolerance for carbohydrate in these patients are directly due to removal of these infecting agents, but proof is often lacking because the dietetic treatment of the disease begins coincidentally with local treatment. Higgins,[1] however, reports an excellently studied case with a rise in tolerance from 60 grams of carbohydrate before operation to 100 grams after operation.

E. NEUROLOGICAL AND MENTAL COMPLICATIONS.

By Elliott P. Joslin, M.D., and Alexander Marblé, M.D.

Although internists and neurologists alike quite generally have the feeling that there are certain neurological lesions characteristic of diabetes, the conditions found are so ill-defined that few observers have expressed their views in writing. This is particularly true in this country. Foreign articles, particularly French, are more numerous, but taken as a whole, the literature is largely that of twenty or thirty years ago. In his monograph Labbé[2] devotes a large section to the neuritides and the neuralgias. Kraus[3] has described the neurological manifestations in a group of 700 cases at the Vanderbilt Clinic; in that series he found only 1 instance of

[1] Higgins: Cincinnati Jour. Med., September, 1922.
[2] Labbé: Loc. cit., p. 88.
[3] Kraus: Med. Clin. North America, 1920, **4**, 225.

polyneuritis and that patient was also a chronic alcoholic and Wohl[1] only 1 instance in a series of 80 diabetics. In 1922 Root[2] described 1 case of peripheral neuritis and 2 cases of peroneal paralysis in our series and there have been a few others. In a distinctly neurological clinic I understand that such cases as well as cases of paralysis of the external ocular muscle are fairly frequent. Major[3] has described a case of pseudotabes and Wilder at the Mayo Clinic showed me another. In addition there are the older papers of Williamson,[4] Grube,[5] and Schweiger,[6] as well as the more recent study by Miles and Root[7] upon psychological tests as applied to diabetic patients.

Diabetes does not in our opinion result in any specific disease of the nervous system. Such association if any is through the development of arteriosclerosis. I do not believe that hyperglycemia causes neuritis. If it did the latter condition would be far more frequent. The freedom of Hédon's and Macleod's dogs from neuritis and other neurological manifestations confirms the above statement.

1. **Insanity.**—Few diabetics become insane. This corresponds with the rarity of syphilis in the etiology of diabetes. Eight instances alone were found. It would be valuable to secure the incidence of diabetes in institutions for the insane. Not only would light be thrown upon the incidence of insanity in diabetes, but also upon the etiological relation of syphilis and arteriosclerosis to the disease. The sequence of my case numbers (34, 472, 493, 787, 902, 1163, 2173, 3622) illustrates how infrequently the older cases have developed insanity and how exceptional it is for me to see a recent case. Such cases would not be overlooked in the 1926–1927 fatal group of diabetics.

2. **Senile Dementia.**—This is far more common than insanity and if one should be critical I fear it would include a shockingly high percentage of hospital diabetics. Twelve instances were of marked degree. The mental age of the average patient is certainly low, as I can testify from observation in my diabetic classes, but this is not peculiar to diabetes. Closely linked with such individuals are the hemiplegics and partial hemiplegics and their precursory states. Thus 82 cases of the 1756 fatal cases up to July 1, 1926, have succumbed to cerebral hemorrhages or allied conditions.

3. **Hemichorea.**—One of the 2 distressing cases of hemichorea, Case No. 4529, aged at onset sixty-one years in 1912, completely

[1] Wohl: Jour. Am. Med. Assn., 1926, **87**, 901.
[2] Root: Med. Clin. North America, 1922, **5**, 1433.
[3] Major: Jour. Am. Med. Assn., 1924, **83**, 2004.
[4] Williamson: British Med. Jour., 1894, i, 398; Lancet, 1905, i, 855; Rev. Neurol. and Psychiat., Edinburgh, 1907, **5**, 550.
[5] Grube: Deutsch. Ztschr. f. Nervenheilk., 1918, **60**, 302.
[6] Schweiger: Arbeiten an den Neurologischer Inst. an der Wiener Univ., 1908, **14**, 391.
[7] Miles and Root: Arch. Int. Med., 1922, **30**, 767

recovered in 1925 but is now in August, 1927, in the hospital with dry gangrene. The other, Case No. 4166, aged sixty-one years at onset in 1912, lived but eight weeks after choreic symptoms developed and died in 1924.

4. **Paralysis Agitans.**—Parkinson's disease has become increasingly frequent as shown by the sequence of the 7 cases Nos. 630, 1583, 3842, 3996, 4369, 4882, 4887. Nothing distinctive of diabetes or Parkinson's disease has been noted and treatment has been equally unsatisfactory. Insulin, however, has been of service in relieving diabetic symptoms. Kückens[1] observed paralysis agitans in five generations and in the same family diabetes was present four times, being especially grave in 2 univitelline twin boys, aged fifteen years.

5. **Meningitis.**—Two of the 4 cases of meningitis were subsequent to infections of the mastoid—1 was of tuberculous origin and 1 of unknown origin.

6. **Epilepsy.**—No clear cut case can be found among my 6000 glycosurias of whom 5086 are true diabetics. John C., Case No. 3019, described on p. 831, has epileptiform attacks and I remember one young man with epilepsy, but as his case cannot be found I think he must have been proved non-diabetic. A patient with epilepsy associated with arteriosclerosis under my care for years eventually developed diabetes when sixty-four years old, Case No. 1745. She is alive at the age of seventy-two years. Case No. 5744 is a boy, aged seventeen years, with neuropathic heredity, a trace of sugar in the urine and blood sugar 0.18 per cent one hour after a meal, in whom a tentative diagnosis of epilepsy has been made by the Psychopathic Hospital. Dr. Geyelin tells me he has 2 diabetics with epilepsy. This is not strange, because of his known interest in both diseases.

7. **Hysteria and Hypochondriasis.**—Hysteria is almost unknown. My associates and I do not remember a case. Many diabetics became dietetic hypochondriacs, but with the advent of insulin such states soon vanished.

In the first ten years of my experience with diabetes I was much impressed with the tendency of inadequately treated patients to cry, but even then, with the methods in vogue, it was interesting to see how depression disappeared with the decrease or disappearance of sugar in the urine. This could not be explained by the mental encouragement which a patient derived from his knowledge of the decrease in sugar excretion. Even when patients became free from sugar but developed acidosis mental symptoms often improved, and to so great an extent that one could say that with treatment, even though it did end in coma, the patient enjoyed life far more thor-

[1] Kückens: Klin. Wchnschr., 1925, **4**, 2289.

oughly than when untreated, his life ended with debility or tuberculosis. Greeley explained to my patients how diabetes has largely been robbed of its terrors. He urged the simple life as a great aid in treatment and told them not to try to be first in the Iberian village and be ill, but rather to be second in Rome and keep well. He told them to have a hobby, and not to make it a labor; to be cheerful and to keep their minds occupied; and as far as possible to continue the previous currents of their lives.

Heavy responsibilities should be avoided as well as nervous upsets and emotional excitements. It is almost as dangerous for a diabetic to get angry as for a man with angina pectoris, because in addition to his diabetes he may have angina pectoris as well. Case No. 1157 had been sugar-free for five days, but it came back when he had an important conference with one of his superintendents.

Psychological tests were applied by Miles and Root[1] to 40 diabetic patients prior to the introduction of insulin, and an average decrement of 15 per cent was found at the beginning of treatment in their performance of memory and attention tasks. With treatment the patients improved rapidly in psychological status but did not quite reach normal.

In accuracy and quickness of movements 5 treated diabetics of long duration were 20 per cent below normal.

8. **Syphilis of the Central Nervous System.**—This is a rare complication. I remember but 2 cases of tabes dorsalis, Cases No. 4182 4582, and my Boston friends interested in diabetes cannot add to the number.

9. **Asthma.**—Although asthma is not a distinctly nervous disease I include it here for want of a better place and simply to record the rarity with which it is encountered in diabetes. There have been but 6 cases.

W. R. Ohler in a personal communication states that 14 asthmatics had sugar tolerance tests which were found to be abnormally low. A. A. Hornor tells me that he has seen 2 diabetic asthmatics. The asthma improved not with the development of the diabetes, but rather with the institution of dietetic treatment. One of the patients had taken adrenalin chloride subcutaneousiy for sixteen years, at no time less frequently than every forty-eight hours, but since becoming sugar-free in July 15, 1923, has required it but twice and then when unloading a car load of horses.

Dr. F. M. Rackemann, who treats many cases of asthma, had met with no instance of its association with diabetes until I sent him Case No. 3717, a boy with bronchial asthma since infancy, who was alert enough to balance the adrenalin with insulin in his severe attacks, as did Case No. 5079. Dr. I. C. Walker, in a personal

[1] Miles and Root: Arch. Int. Med., 1922, **30**, 767.

communication, reports that he has seen but 2 cases of diabetes among 2500 to 3000 asthmatics.

The asthma disappeared with onset of diabetes in Case No. 1112. Sensitivity to ragweed disappeared in one patient, Case No. 2382, when the diabetes began, but the hay fever persisted despite development of diabetes.

10. **Pseudotabes.**—Three cases were observed. Cases Nos. 1443, 3317, and 5494. The Wassermann reaction was negative in blood and spinal fluid of all three. See Major's[1] article for the literature.

11. **Paralysis Due to Insulin.**—Transient hemiplegia was noted following hypoglycemia in Cases Nos. 4115 and 4697, paraplegia in Case No. 2856, and epileptiform seizures of unusual degree in Cases Nos. 2364 and 2633. All these cases recovered completely, but in Case No. 2856 the hemiplegia persisted for several days and in Case No. 4697 for several months. The persistence of symptoms in this latter patient would indicate an organic basis for the same and suggests that a somewhat analogous condition may exist in John C., Case No. 3019. This latter patient may have epilepsy.

12. **Neuritis.**—Neuritis is most uncommon among my patients. The explanation is simple, because three of the common causes of neuritis have been infrequent. In twenty-five years, I have attended but 2 of my diabetic patients for acute alcoholism and have seldom prescribed alcohol. Syphilis has been diagnosed in only 105 of 6000 cases and of the last 1000 patients seen there have been only 0.6 per cent with positive Wassermann reactions. Tuberculosis has caused but 5 per cent of 1756 deaths. Neuritis yields as obstinately to treatment in diabetes as when it occurs in association with other diseases. Fortunately it is rare, but unfortunately it does not always disappear with the removal of the glycosuria. This cannot be due to the increased quantity of sugar persisting in the blood long after it has disappeared from the urine, because hyperglycemia of many years' duration is so seldom accompanied by neuritis. Indeed, primary "neuritis" in diabetes is usually a misnomer. It is secondary to some form of circulatory obstruction or some form of arthritis. Sciatica is the most frequent type of neuritis which occurs in diabetes. From the help which modern orthopedic treatment has afforded my patients, it appears probable that the hydrotherapeutic measures avail much in neuritis, but when this is an indirect result of an arthritis, fixation of the part, and in sciatica fixation of the sacro-iliac joints, brings most relief, as my orthopedic friends have been able to demonstrate upon intractable cases. In some cases of this type symptoms persist despite such treatment, but sometimes these can be explained as habit pains. Moist flannel applications changed every one or two minutes almost invariably give comfort.

[1] Major: Jour. Am. Med. Assn., 1924, **83**, 2004. See also Angle: U. S. Naval Med. Bull., 1928, **26**, 81.

Mental diversion, brought about by change in surroundings, often produces good results. Similarly, the improvement in the general condition which follows rigorous dietetic and physical treatment is of great advantage. Such cases are particularly helped by a brief stay in a hospital, or by having a well-trained diabetic nurse in the home.

The type of neuritis most commonly encountered has occurred in the lower extremities. When diminished sensation, pain and tenderness exist there is always doubt whether the condition is a true neuritis or simply the result of poor circulation. It is certainly true that a pure type of neuritis in other parts of the body in diabetes is seldom seen. For this reason I am inclined to believe that the poor bloodvessels of the lower extremities are the chief offenders. On account of this fact it is well to instruct all diabetics after the age of sixty to exercise the bloodvessels of their legs and avoid round garters but depend upon other means to hold up hosiery. They should not remain long in one position, should walk frequently, get in the habit of flexing and extending the feet on the legs, easily accomplished by rising on tip toes and standing on heels, when the clock strikes. It is remarkable what will be accomplished by persistent effort combined with the stimulus wrought by improvement in the state of the diabetes. One must never despair of these cases.

Six cases of neuritis were multiple in type, Cases Nos. 2182, 3151, 4078, 4282, 4964, 5841. Case No. 2182 has been described by Root[1] in detail. Two of these were alcoholic. Recovery has taken place in all cases save in one of the alcoholics. Case No. 4078 was an extremely severe instance, appeared almost hopeless, required much morphine and yet eventually made a complete recovery and omitted his morphine.

The 10 patients with peroneal paralysis in 1 of whom, Case No. 4282, it was bilateral, were treated with orthopedic measures. Case No. 1987 was an unclassified diabetic with peroneal paralysis. Cases Nos. 2499 and 2581 are reported by Root.[2] Recovery is recorded in Cases Nos. 3869 and 4151.

The return of absent knee jerks in diabetes was observed by Mosenthal and recorded by Rennie.[3]

Retrobulbar neuritis in diabetes has been described by Francis and Koenig who also review the literature. Apparently the condition is more common in other series of cases than my own or else I do not recognize it. These authors consider the condition a clinical entity.[4]

13. **Herpes Zoster.**—Few patients have suffered from herpes zoster. It was distressing and persisted in Case No. 899 when she

[1] Root: Med. Clin. North America, 1922, **5**, 1433.
[2] Ibid., **5**, 1433.
[3] Rennie: Jour. Am. Med. Assn., 1925, **84**, 1700.
[4] Francis and Koenig: Jour. Am. Med. Assn., 1926, **87**, 1373.

was eighty-five years old. The other cases, Cases Nos. 1100, 1587, 1885, 2260, and 3821, were not notable save that with Case No. 1885 lingering pains persisted for four years.

14. **Suicide.**—Suicide was also rare when one considers the desperate situation of the patients in former times. There were only 9 cases, Cases Nos. 103, 671, 1059, 1623, 1697, 1837, 2103, 3180 and 3776. It is encouraging that 7 cases occurred in the first 3000 and only 2 cases in the second 3000. The abortive attempts were not numerous and can be counted on the fingers of one hand. Secher[1] reports one unsuccessful attempt with insulin.

15. **Miscellaneous.**—Other neurological states were represented by a few examples, such as neuropsychosis (anxiety type) Case No. 103 and psychoneurosis, Cases Nos. 3131, 4191. I remember but 1 case of neuralgia, Case No. 5348, a thyroid diabetic who obtained relief with an alcoholic injection at the hands of Dr. Lahey.

F. EYES.

Ocular complications in diabetes are frequent. Von Noorden in 1912 reports that of 279 patients, 58.3 per cent had trouble with the eyes attributable to the diabetes, and of those patients over fifty years of age, 80 per cent. He summarizes the results of the examination of the eyes of 477 diabetics taken in succession. Defects were found in 279 instances; in 259 of these cases there was no etiological cause other than the diabetes. A summary of the data is given in the following table:

TABLE 262.—OCULAR COMPLICATIONS IN DIABETES (VON NOORDEN[2]).

	No. of cases.
Retinitis	81
Retrobulbar neuritis	23
Atrophy of the optic nerve	18
Cataract	62
Iritis	2
Amblyopia without organic change	33
Diabetic myopia	21
Other conditions	39

Anderson[3] examined the eyes of 292 diabetics and found only 25 per cent with ocular affections traceable to the diabetes.

F. M. Spalding and W. S. Curtis[4] studied 307 successive diabetics of my series. They found that 46, 14.9 per cent, showed retinal arteriosclerosis with no other changes and 16, 5.2 per cent, showed a retinitis with arteriosclerosis and 32 patients or 10.4 per cent had

[1] Secher: Ugeskrift f. Laeger, 1927, **89**, 365.
[2] Von Noorden: Loc. cit., p. 217.
[3] Anderson: Acta Ophth., 1924, **2**, 199.
[4] Spalding and Curtis: Boston Med. and Surg. Jour., 1927, **197**, 165.

cataracts. Changes in refraction were observed in 22 cases and in 2 of these there was temporary loss of sight. For a discussion of the latter condition see Dykman.[1]

Wagner and Wilder[2] have reported upon retinitis in 300 cases of diabetes and Freidenwald[3] has tabulated all his cases of retinitis. Among these he found retinitis punctata centralis in 33 cases of diabetes and in 18 without diabetes. Of this special type Spalding and Curtis and Wagner and Wilder each found but 2.

Hypertension is a consistent finding in cases with retinal sclerosis and with retinitis according to Spalding and Curtis. They believe that the retinitis found in diabetes is that of hypertensive cardio-vascular-renal disease. That diabetes plays but a minor role is seen from the fact that 207 of the 307 diabetics had normal retinæ with accompanying normal blood-pressures in 91 per cent of the number and normal renal function in 98 per cent. Yet these cases have had diabetes of greater average duration and of no less severity than the cases with retinal changes. Every case of retinitis had retinal arteriosclerosis.

Retinitis centralis punctata diabetica occurred in only 4 instances in the 607 diabetics of Wagner and Wilder and Spalding and Curtis. And the 2 of these seen by Spalding and Curtis also had marked hypertension and renal damage. The possibility of diabetes being a cause for this condition is therefore remote. However, Chauffard[4] *et al.*, observed a case of "central punctate retinitis" in a man aged sixty-eight years, without hypertension or renal insufficiency in which immediate improvement followed insulin treatment, which he ascribed to the influence of insulin on the lipid deposits in the retina.

E. Grafe[5] has evidently had much experience with diabetics who have been under the care of von Noorden and Isaacs. He considers that all cases of diabetes save the mildest are accompanied by vascular changes and that every diabetic of eight years' duration develops a retinitis and that the retinal changes are indicative of similar changes in other vascular areas throughout the body.

With the institution of progressive treatment the eyesight often temporarily fails, and more than once patients in the course of a few days have become unable to read, and once even to recognize individuals. The explanation of this condition is undoubtedly due to changes in the water balance of the body and the disappearance of sugar. These incidentally involve the lens, causing refrac-

[1] Dykman: Am. Jour. Ophthalmol., 1926, **9**, 825.
[2] Wagner and Wilder: Jour. Am. Med. Assn., 1921, **76**, 515.
[3] Freidenwald: Jour. Am. Med. Assn., 1925, **85**, 428.
[4] Chauffard, Grizant, and Nida: Comptes Rend. Soc. Biol., 1925, **92**, 1356.
[5] See von Noorden and Isaac: Loc. cit., p. 319.

tive changes. Elschnig[1] describes such a case in which one lens had been removed for cataract. The diabetic hypermetropia occurred only in the other eye. One can always reassure such patients with the statement that the return of their former eyesight and even an improvement in it will eventually take place. It is remarkable to how great an extent the eyesight may return in a long-standing, but neglected case of diabetes. Case No. 181 was unable to read his name when he entered the hospital, but after three weeks' stay he was able to do so. Case No. 924 showed marked failure of eyesight on October 28, 1915. Her eyes were examined at this time by Dr. F. M. Spalding, who reported a shrinking and flattening of the lenses. With a convex lens (+2) in front of each eye the vision later came up to normal.

Cataracts occurred in 10.4 per cent in a series of 307 of my cases studied by Spalding and Curtis, and in 13 per cent of 477 successive cases in von Noorden's series. One can easily understand that the ophthalmologist, Grafe, found cataracts in one-fourth of all his diabetics. The haziness of the lenses in beginning cataract may diminish with constitutional treatment and improvement of the diabetes. In the series of Spalding and Curtis no case was under fifty-three years of age, the average age being 64.5 years. The average duration of the disease was 6.6 years with a range of from one to twenty years. In his discussion of 609 cataracts in diabetics and non-diabetics Gallus[2] does not admit diabetic cataracts as an entity, but relates them to premature senility or heredity.

Cataracts may have a definite relation to the hyperglycemia, because they occur in young diabetics who have had the disease many years or in diabetics with a high blood sugar. Sherrill[3] reports from Allen's Clinic a boy who lived for several years with double cataracts after he had been operated upon, was happy and had secured partial restoration of vision. In one of my cases there were double cataracts which developed in a child. This little girl, Case No. 1898, was the daughter of an ophthalmologist and became diabetic at the age of eleven years and eleven months, showing at one time 10 per cent of sugar and a blood sugar of 0.9 per cent. This value for the blood sugar was checked in two laboratories. She died in coma three years and four months after the onset of diabetes, but the cataracts were discovered at the detection of the disease which was five months after the onset. Her father wrote: "She had cataracts, which at that time were mostly in the posterior poles of the lenses, although there were scattered opacities throughout the lenses. The vision at that time came up with a weak cylinder to 20/20, but

[1] Elschnig: Med. Klinik., Berlin, 1923, **80**, 968.
[2] Gallus: Deutsch. med. Wchnschr., 1919, **45**, 658.
[3] Sherrill: Jour. Metab. Res., 1922, **1**, 667.

since then they had steadily increased until the vision dropped to 15/200, but as the opacities were to a great extent central and to a limited extent peripheral, she managed to get along fairly well by looking over them. In the twenty-five years that I have been engaged in the line of ophthalmology, that is the first time I have seen diabetic cataracts in the case of a child." In another of my patients, Case No. 4978, aged eighteen years, the cataracts were bilateral. F. G. Brigham also had a case of a diabetic child with bilateral cataracts. These are the pure diabetic cataracts, according to E. Grafe. Nicholson[1] describes a seventeen-year-old boy in whom opacities over both lenses showed marked improvement one month after insulin was begun only to reform later. Strouse and Gradle[2] report a cataract in a girl, aged ten years, with successful operation. Major and Curran[3] report cataracts in an infant.

Operations for cataract have been successful as well as uneventful under the care of F. M. Spalding, G. S. Derby, F. E. Jack, L. P. Tingley, and E. R. Williams. A retrogression of the cloudiness of the lens was observed by Grafe in 2 cases as a result of treatment with diet and insulin. It is usually easy to arrange to have the patients in excellent condition from the diabetic standpoint prior to operation. In my limited number of cases I have not known of an ocular hemorrhage to occur after removal of a cataract in any patient treated either with or without insulin. Such an instance has been called to my attention when 45 units of insulin were used. The morning blood sugar in this case was 0.20, but whether hypoglycemia occurred later in the day I do not know. Of course, in all such cases one would be cautious in lowering the blood sugar just as in the patients with angina pectoris.

According to Takahashi[4] the decrease in blood sugar caused by insulin provokes an increase in fibrinogen and fibrin ferments which in turn increases the coagulability of the aqueous humor and thus may prevent hemorrhage.

Case No. 806, cited on page 618, showed a retrobulbar neuritis, but it was probably due to syphilis and not to diabetes.

Lipemia retinalis occurs not infrequently, though is generally unobserved. Gray and Root,[5] in my clinic, have discovered and reported 2 cases (Cases Nos. 2216 and 2842). The condition usually disappears with modern dietetic treatment and insulin in *hours* instead of in days.

Subsequently other cases of lipemia retinalis have been reported.

[1] Nicholson: Clifton Med. Bull., 1923, **9**, 54.
[2] Strouse and Gradle: Jour. Am. Med. Assn., 1924, **82**, 546.
[3] Major and Curran: Jour. Am. Med. Assn., 1925, **84**, 674.
[4] Takahashi: Arch. f. Ophthalmol., 1926, **117**, 479.
[5] Gray and Root: Jour. Am. Med. Assn., 1923, **80**, 995.

the first by McCann[1] who considers the appearance due to a film of fatty lymph in the perivascular spaces or to fat deposits in the adventitia. It is certainly not related to the percentage of fat in the blood alone. Rowe[2] describes the thirty-first case in the literature. The diabetes of his patient was of short duration, severe and even at the end of four weeks of energetic treatment the plasma was still milky. Bantin's[3] case was associated with fat embolism in the retinal vessels and he raises the query as to whether the attendent pneumonia and dysfunction of the kidney might be due to this cause. Still another case is reported by Chase.[4]

Glaucoma and melanosarcoma in a diabetic is reported by Guion and Berens.[5] They also emphasize the relation of the pain to the blood-pressure and to the power of the patient to metabolize sugar.

The soft eye balls which are characteristic of coma are related to the content of salt and sugar in the ocular fluids.

G. THE EAR.

No distinctive aural conditions have developed in my series of diabetics. To me the most interesting case with an aural complication has been Case No. 2680 who developed an inflammation of the mastoid and was successfully operated upon by Lyman Richards. Despite constant hyperglycemia, glycosuria and ketonuria Dr. Richards said he never had a patient with mastoiditis who showed such marked recuperative power (see p. 577).

In 2 other instances operation upon the mastoid resulted most favorably, Case No. 4371, aged sixty-three years, at operation by Dr. G. L. Tobey was found to have a thrombosis of the lateral sinus, yet made an uneventful recovery in spite of her age, emaciation and diabetes. Case No. 2879 also made a surprisingly rapid recovery after drainage of the mastoid by Dr. L. G. Richards.

Two instances of otogenous meningitis resulted fatally. Case No. 523, male, aged sixty-three years, underwent operation upon an abscess in the scar of a mastoid operation. Headaches persisted and six weeks later he was sent to the Deaconess Hospital for treatment of suspected coma. Although diacetic acid was present in the urine, the plasma CO_2 was 46 volumes per cent. A stiff neck, Cheyne-Stokes respiration and a cloudy spinal fluid containing 18,000 leukocytes per cubic millimeter and many streptococci proved that his death was really due to meningitis. Case No. 2587, aged forty years, also developed meningitis with a mastoid infection in spite of an operation not long delayed.

[1] McCann: Johns Hopkins Hosp. Bull., 1923, **34**, 302.
[2] Rowe: Jour. Am. Med. Assn., 1924, **82**, 1168.
[3] Bantin: Jour. Am. Med. Assn., 1926, **86**, 546.
[4] Chase: Canadian Med. Assn. Jour., 1927, **17**, 197.
[5] Guion and Berens: Jour. Am. Med. Assn., 1924, **82**, 1024.

H. TUBERCULOSIS.

Tuberculosis formerly was responsible for about one-half of the deaths of diabetic patients, but today, in private practice, it seldom occurs. In Europe it is more frequent.[1] In Japan, according to a personal communication of Murayama and Yamaguchi, tuberculosis was diagnosed in 8.9 per cent of 633 cases and was the cause of death of 22 per cent of 49 fatal cases. It was the cause of death of 19 per cent of Carrasco Formiguera's 42 fatal cases.[2] Montgomery,[3] who has published an excellent critical summary of the literature upon diabetes mellitus and pulmonary tuberculosis, concludes that tuberculosis is not more frequent among diabetics than among the rest of the population of similar age. My statistics would support this view. Among 8000 cases of pulmonary tuberculosis Wassmud[4] found 60 diabetics.

Von Noorden, writing later than did Naunyn, records a still lower percentage among his cases, though in Vienna von Noorden found it nearly twice as common among hospital diabetics as in Frankfort. This is a striking illustration and a warning against exposure of diabetic patients to tuberculosis. Case No. 838 died of tuberculosis in August, 1922, and his brother, Case No. 2314, who contracted diabetes in 1915 showed tubercle bacilli in the sputum in June, 1923, and died in January, 1924.

Prophylaxis is important. Unfortunately a tuberculosis, latent for nearly a lifetime, may break out in the presence of diabetes, as it did in Case No. 629, at the age of sixty-nine years, and in Case No. 344, in whose family there had been much tuberculosis, though he himself had never shown recognizable signs of it. No matter how well the diabetic patient may appear, he remains a vulnerable individual. By far the greater number of tuberculous diabetics whom I see today are past middle life.

The percentage of deaths due to tuberculosis to the total number (1756) of diabetic deaths in my own series is 4.8 per cent. This percentage has been remarkably constant as the compilations have been made from year to year. In this community, Massachusetts, the percentage of deaths due to tuberculosis of the respiratory system to the total number of deaths was 5.6 in 1926, and the death-rate per 100,000, 70.3. It would, therefore, appear that tuberculosis was the same among my diabetics as among the population in general in this region.

Our autopsies at the Deaconess Hospital confirm our clinical data, obtained either from the patients in the wards or from the reports of cases who have died elsewhere.

[1] Labbé and Cumston: Diabetes Mellitus. Wm. Wood & Co., New York, 1922.
[2] Carrasco Formiguera: Loc. cit., p. 590.
[3] Montgomery: Am. Jour. Med. Sci., 1912, **144**, 643.
[4] Wassmud: Beitr. z. Klinik d. Tuberkulose, 1927, **67**, 552.

TABLE 263.—TUBERCULOSIS AND TRUE DIABETES.

Case No.	Age at onset diabetes.	Duration diabetes, years.	Case No.	Age at onset diabetes.	Duration diabetes, years.	Case No.	Age at onset diabetes.	Duration diabetes, years.
10	39	12.0[1]	1101	50	8.8	3143	17	2.7
44	42	5.6[1]	1112	54	6.4	3176	41	17.3
56	44	7.7	1221	50	8.0	3200	55	3.1[1]
68	42	0.3	1227	20	2.8	3284	68	8.0
75	35	6.0	1233	26	2.6	3331	57	9.4
106	31	9.0	1257	55	19.7[4]	3443	35	4.3
134	38	3.9	1271	53	3.8	3462	47	11.2
143	40	17.0	1319	27	2.2	3510	57	3.7
160	46	1.6	1442	45	8.8	3559	45	6.0
166	52	4.0	1458	27	3.3	3626	32	4.6[4]
200	61	5.2	1512	39	20.0	3686	63	6.3
205	51	5.0	1538	46	9.2	3716	28	3.7[4]
206	41	7.1	1560	24	0.9	3992	20	0.6
209	27	8.6[1]	1569	28	3.8	4043	22	8.3
245	30	3.0	1577	21	4.0	4045	60	0.7
300	7	1.8[4]	1629	32	2.4	4205	62	2.4
324	52	2.0	1642	54	7.4	4287	54	6.9[4]
344	40	8.4	1644	52	3.6	4508	64	2.9[4]
353	53	2.5	1869	50	6.3	4624	30	4.9[4]
403	55	6.1[2]	1871	48	8.5	4626	48	2.0
404	60	10.0[2]	1890	53	6.5	4634	35	13.8[4]
443	55	17.5[4]	1923	55	7.0	4765	25	1.9
453	49	4.9	1955	53	5.0	4832	32	0.9[1]
521	39	9.9	2075	27	7.3	4837	39	11.8[4]
543	62	2.6[1]	2125	50	14.3[4]	4873	62	2.0[4]
559	72	7.6	2140	20	1.9	5110	12	1.7[4]
629	71	13.4	2148	41	12.9	5130	69	0.5
633	51	1.8	2158	32	1.6	5146	45	1.3[4]
684	56	7.6	2274	6	6.5[4]	5200	33	2.4
761	52	3.7	2290	55	6.9	5231	58	11.7
810	27	2.9	2314	37	8.9	5288	35	2.9[4]
838	37	8.1	2357	62	4.0	5434	36	1.0[3]
861	51	2.2	2407	56	5.6	5449	51	2.8[4]
862	26	3.5	2518	47	4.7	5525	39	1.0[4]
886	29	2.3	2541	28	5.2	5571	76	1.6
916	58	3.5	2585	38	1.8[1]	5659	34	1.4[4]
968	45	12.2[4]	2670	25	5.0	5716	64	4.5[4]
1002	52	1.7	2846	57	1.7[1]	5719	25	0.9[4]
1023	44	3.2	2947	30	1.6	5738	42	10.0[4]
1029	32	4.5	2992	48	6.6	5884	62	4.5[4]
1060	27	18.4	2999	27	2.8	5917	57	6.5[4]
1083	54	1.8	3058	46	12.8	5990	51	3.7[4]
1084	34	5.0						

[1] Cause of death, coma.
[2] Cause of death, gangrene.
[3] Cause of death, myocarditis.
[4] Alive, July 1, 1927.

The number of fatal cases of diabetes with tuberculosis in my series is 103 or 81.1 per cent of the total cases (127). There are 24 patients with tuberculosis known to be alive. Among the first 3000 diabetic case numbers there are 84 true diabetic patients with tuberculosis and among the remaining 3000 there are 43 cases.

Obviously the longer that diabetics are under observation the greater the opportunity to discover tuberculosis and this may be the explanation of the marked decrease in recent years rather than any diminution in tuberculosis.

The average age at onset of diabetes in those patients who developed tuberculosis was forty-five years and the decade of greatest frequency the sixth. But 4 cases were found under twenty years of age and only 22 in the third decade. Tuberculosis in diabetes is therefore a complication of later life.

The average duration of the diabetes in the 103 fatal cases was 5.5 years. The diabetic with tuberculosis is therefore a diabetic of long duration, because the average duration of all the fatal diabetics in the Naunyn Era was 4.7 years, in the Allen Era 5.4 years, and in the Banting Era 7.7 years.

The duration of the diabetes of all my fatal cases in whom tuberculosis has been demonstrated is shown in Table 263, as well as of the 24 living cases Dr. Root, Dr. White, and I recall. I cannot state how many of my living cases have had tubercle bacilli in the sputum. So far as I can remember Case No. 1555, a patient of Dr. B. H. Ragle, whom I saw in consultation in 1919 when her diabetes was of 1.5 years' duration and she twenty years of age, has made the best progress of any of my patients, because now in 1927 she is free from tubercle bacilli and her diabetes under control. She has not had children.[1] Sansum showed me 2 cases of severe tuberculosis and diabetes who after years of treatment on account of tuberculosis were at work and apparently in blooming health although still requiring insulin. They had been treated in accordance with his high-carbohydrate diet. A year later I learn that one of these has developed the disease in one kidney; still later I learn she is recover ing after its successful removal.

Nine of the 103 fatal cases, or 8.7 per cent, died in coma. This is far below the percentage of deaths from coma in the whole group of diabetics. It suggests that the diabetes decreased in severity, due to the emaciation and lack of food consumed. Ninety-one patients apparently died in the ordinary manner of an uncomplicated tuberculous case. Among 56 cases of tuberculosis, my records disclose that tuberculosis was present in another member of the family in only 13 instances.

Tuberculosis occasionally occurs before the diabetes. The explanation lies in the fact that the tuberculosis, though it existed for a longer period, was of a latent or mild type. The development of diabetes during the active course of tuberculosis is most unusual in my experience and from reports of cases of tuberculosis treated in sanatoria. Montgomery[2] found that of 31,834 cases of tuberculosis

[1] Regretfully I record her death in August, 1927.

[2] Montgomery: Am. Jour. Med. Sci., 1912, **144**, 643.

treated in sanatoria there were 101 cases, 0.3 per cent, of glycosuria and 51 cases, 0.16 per cent, of diabetes, and he states that practically no case of diabetes following tuberculosis has occurred at the Phipps Institute, in sanatoria or under the care of physicians with whom he is acquainted. Combining the data for glycosuria and diabetes we have 0.5 per cent incidence among 31,834 individuals. If this percentage among the tuberculous was applied to the population of the entire United States it would indicate half a million glycosurics and diabetics, a figure which is more consistent with my surmise than some other data suggest.

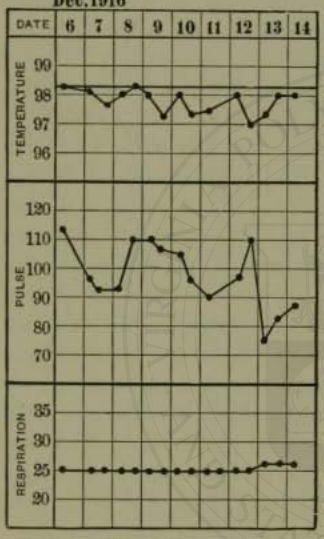

FIG. 37.—Insidiousness of tuberculosis in diabetes. The temperature, pulse and respiration chart of Case No. 916.

Tuberculosis comes on in diabetes even more insidiously than usual; more than once I have been surprised at discovering not only its presence, but the advance which it has made. Unless cases were frequently detected suspicion would arise that other cases were being overlooked. One should always be on the watch for tuberculosis, taking for granted that it will not appear in an open manner, and therefore making complete physical examinations of all diabetics when the interval since the last visit is four weeks. It is a very easy mistake for the physician to be so wrapped up in the treatment of the diabetes that he neglects the general condition of the patient. The diabetic seeks the doctor for health insurance and not merely for a test of the urine or blood and it is only for the former that I charge my patients. Loss of weight is often attributed to the diabetes, and the characteristic absence of temperature throws the physician off his guard. Recollection of Fig. 37 has been of help in the diagnosis of many later cases. I can confirm older writers in the rarity of hemoptysis, though present in Case No. 861. A suggestive family history should always put one on guard. It is now approaching a routine for all diabetics to have Roentgen-ray examinations of the lungs, heart, and teeth, and for the elderly, examinations of the bloodvessels of their lower extremities. Instructive cases are reported by Fitz[1] who emphasizes the importance of periodic examinations of diabetic patients.

The presence of tuberculosis in Case No. 633 was first disclosed

[1] Fitz: Med. Clin. North America, 1927, **10**, 1163.

at autopsy in March, 1914. It was supposed by those of us in attendance that the patient's decline was wholly due to severe diabetes, ultimately culminating in pneumonia. The postmortem examination revealed extensive tuberculosis. Such a mistake is not extraordinary, for shortly after, bearing it in mind, a similar case in the wards of one of the best hospitals in the country was seen where this diagnosis had not been entertained. When the diabetes is doing well and the patient doing poorly suspect tuberculosis; when the diabetes is doing poorly and neglect of treatment is not the obvious cause, suspect cancer of the pancreas, hyperthyroidism or latent suppuration and more rarely tuberculosis. The diagnosis of tuberculosis may be suspected, if the tolerance of the patient is gradually improving, and he is losing weight. On the other hand, an error was made in Case No. 1083 by neglect to observe the rise in temperature upon two days during his hospital stay. Temperature charts are now kept in plainer view.

The prognosis of diabetes complicated by tuberculosis was bad, and is still serious. So often the tuberculosis is far advanced when first detected and so often its appearance is in the neglected, the old and decrepit and poor. Treatment must be persistent for years if one would have good results.

Rosenberg and Wolf[1] consider that with large doses of insulin the prognosis of tuberculosis in diabetic patients is the same as in non-diabetic subjects. Sosman and Steidl,[2] however, are still pessimistic about the combination of diabetes and tuberculosis even with insulin.

Older writers laid emphasis upon the rapid extension of the tuberculosis in diabetes after it first appeared, and for this reason gave an especially unfavorable prognosis. Examples of this character are only too many, but while they are not encouraging from the therapeutic point of view, they should not be considered too discouraging. Many of these cases had poor treatment not only for the diabetes but for the tuberculosis as well. The duration of the tuberculosis as well as of the diabetes in my cases absolutely controverts this former pessimistic view. Of the 46 cases in which the duration of the tuberculosis is recorded, in only 18 instances has the patient died during the first year of the tuberculosis. In one instance only did the diabetes last for less than one year.

Yet tuberculosis, plus angina pectoris, plus arthritis, which was relieved by the removal of bad teeth, plus old age, and diabetes are compatible with a useful life and a fair degree of health. In Case No. 629 diabetes developed at the age of seventy-one in 1909, tuberculosis became active at seventy-five, and angina pectoris

[1] Rosenberg and Wolf: Klin. Wchnschr., 1927, **6**, 936.
[2] Sosman and Steidl: Am. Jour. Roentgenol., 1927, **17**, 625.

at seventy-seven. The patient was first seen in July, 1913. Six months later tubercle bacilli were found, though previous physical examinations had disclosed no lesions. Undoubtedly tuberculosis had existed in latent form since youth. Under the close supervision of a devoted nurse, thoroughly trained in diabetes, the patient attended to active duties, and was living in comfort at the age of seventy-nine, not yielding to death by tuberculosis until March, 1922. With insulin he might have recovered. At any rate, his devoted nurse and he taught me that fasting was unnecessary in the aged. Small and old he remained sugar-free and nearly held his weight on carbohydrate 69 grams, protein 42 grams, and fat 94 grams.

Case No. 443, a woman, aged fifty-five years, first seen on September 20, 1911, gave a history of congestion of the lungs at the age of twelve, hemoptysis at sixteen, and again to a marked degree at the age of twenty-four. Tuberculosis was confirmed by Drs. Flint and Loomis of New York. Tubercle bacilli were never found, but the evidence of tuberculosis was undoubted. A roentgen-ray examination on September 21, 1911, showed general peribronchitis with numerous broken-down glands with healed borders, increased density and mottling with an appearance of healing at the right apex, small area of calcification, slight emphysema. The patient was sugar-free in September, 1911, and is still living and well, July, 1927. Case No. 1861, a mild diabetic, showed tubercle bacilli in the sputum in 1910 and again in 1920, yet now is in good health and actively engaged in business.

Case No. 5738, aged fifty-one years, after nine years of diabetes with a total loss of 30 pounds and a tolerance for 84 grams carbohydrate, developed active bilateral pulmonary tuberculosis with positive sputum. In the course of a year he gained 20 pounds in weight, became sputum-free, and raised his tolerance for carbohydrate 100 grams and in so doing used but 24 units of insulin daily.

Diabetes, even of the severest grade, may practically disappear when tuberculosis intervenes and reaches an advanced stage. Many writers have observed such instances and it has repeatedly come to my attention. Unexplained improvement in the tolerance of a diabetic for carbohydrates always awakens suspicion. The patient whose course is here and elsewhere described, see pp. 189 and 322, is fundamental in this regard. I am inserting the three pages of charts partly for this reasons, but more especially because the patient tolerated severe acidosis for years, and eventually, even though the diabetes had seemed nearly complete, acquired tolerance for carbohydrate, thus proving that either the pancreas regenerates with time, or, as Dr. Allen's keen observation led him to suspect in this instance, the diabetes improved because the

burden upon the pancreas had been decreased by undernutrition. With this latter explanation I am not wholly satisfied, because it seems illogical to attain strength through weakness.

Case No. 344, cited hitherto as having an extremely severe type of diabetes, in 1911 developed tuberculosis after eight years of diabetes. Eventually the acidosis, which had amounted to the most extreme grade I have met outside of coma, completely disappeared, and the minus carbohydrate balance of 40 grams, that had existed for months, changed to a positive carbohydrate balance of 60 grams. The complete record of the case is given in Table 264.

The disappearance of the acidosis is explained by the development of a positive carbohydrate balance. The explanation of the body's return of power to utilize carbohydrates was difficult until I showed the records of the case to Dr. F. M. Allen and told him that if he could explain the improvement of the diabetes, which was coincident with the development of tuberculosis, a key to a valuable method of treatment of diabetes would be found. A few days later he said to me that he believed he could duplicate the case with his depancreatized dogs. At the time he gave no inkling of his plan, but how well he succeeded is known everywhere today by his experimental work upon animals, which showed that fasting and loss of weight will improve the tolerance of even the severest diabetic patients. (Even if one does not make a discovery, it is a satisfaction to record the facts which may help another to do so.)

The treatment of diabetes complicated by tuberculosis is the same as for diabetes alone and the discovery of insulin has not altered this principle. Adherence to the principle of treating the diabetes first and the tuberculosis second was put to a severe test when undernutrition was first employed. That Janney and Newell from a diabetic standpoint and Landis and Funk[1] and Montgomery from the standpoint of tuberculosis found their best results were achieved when undernutrition was employed is good proof that one should treat the diabetes as the primary disease. Even though one hesitated to employ undernutrition in a wasting disease like tuberculosis the diabetes responded so favorably to it that soon undernutrition could be discarded and the patient fed a liberal amount of food. Insulin aids in the maintenance of a generous diet, but advanced cases of tuberculosis will proceed to a fatal termination in quite the same manner as without it.

With Nadler's[2] 6 cases the tuberculosis became quiescent in 3 and less insulin was usually required. Hyperglycemia seemed to predispose to the extension of the tuberculosis and normal glycemia to promote healing. I have never known a case of diabetes complicated by tuberculosis in whom I thought insulin did harm.

[1] Landis and Funk: Jour. Am. Med. Assn., 1922, **79**, 1073.
[2] Nadler: Jour. Am. Med. Assn., 1926, **86**, 902.

TABLE 264.—CASE 344. ILLUSTRATION OF THE OLD-FASHIONED TYPE OF TREATMENT OF DIABETES. SEVERE ACIDOSIS, DECLINE IN CARBOHYDRATE TOLERANCE, DEVELOPMENT OF PULMONARY TUBERCULOSIS WITH IMPROVEMENT IN TOLERANCE COINCIDENT WITH EMACIATION. DISAPPEARANCE OF ACIDOSIS. (See page 747.)

Date.	Volume of urine, c.c.	Specific gravity.	Diacetic acid.	β-oxybutyric acid, gms.	Nitrogen, gms.	Ammonia. Total gms.	Ammonia. $\frac{NH_2\text{–}N}{\text{Total N}}$ per cent.	Sugar. By copper reduction, gms.	Sugar. By rotation, gms.	Diet. Carbohydrate,[1] gms.	Diet. Alcohol, gms.	Carbohydrate balance, gms.	$NaHCO_3$, gms.	Body weight without clothing, kilos.	Remarks.
1908.															
April 13–14	2000	1033	Trace	..	23.6	1.1	3.8	..	38	15 ±	..	− 25	..	..	Strict diet.[9]
17–18	1600	1026	Trace	..	..	..	..	..	5	10	..	+ 5	..	63.9	Vegetable day.
18–19	1700	1025	Trace	..	..	0.6	..	..	0	10	..	+ 10	..	..	Vegetable day.
19–20	1650	1022	Trace	..	6.6	..	..	..	5	180 ±	..	+175	..	64.8	Oatmeal day.
20–21	1900	1018	0	..	6.4	0.3	3.9	..	8	180 ±	..	+170	..	..	Oatmeal day.
21–22	2000	1016	0	..	5.9	0.4	5.6	..	7	180 ±	..	+175	..	65.3	Oatmeal day.
22–23	2900	1019	0	..	9.9	0.6	5.0	..	0	..	..	..	..	..	Vegetable day.
23–24	1840	1025	+	..	12.3	0.7	4.7	..	15	10	..	− 5	..	64.8	Vegetable day.
24–25	1900	1024	+	..	14.1	..	..	..	2	10	..	+ 10	..	65.2	Strict diet; meat once.
29–30	1880	1024	Trace	..	10.6	0.3	2.3	..	3	10	..	+ 5	..	..	Vegetable day.
April 30 / May 1	2000	1024	+	..	..	0.5	..	..	2	10 ±	..	+ 10	..	65.4	Vegetable day.
6– 7	1600	1036	+	..	12.8	0.4	2.6	..	46	..	..	..	..	..	Strict diet; meat once.
7– 8	1600	1027	+	..	..	..	..	..	9	10 ±	..	0	..	..	Vegetable day.
1909.															
Jan. 2– 3	..	1024	..	..	..	..	..	0.5[2]							
Dec. 27–28	..	1026	..	..	..	..	..	0.9[1]							
1910.															
June 19–20	2100	1029	++	..	..	..	..	91	..	..	0	..	..	..	Rarely a hyaline cast.
28–29	1720	1034	++	8.7	22.5	2.6	9.5	48	38	10 ±	0	− 40	14	60.5	
July 4– 5	2240	1027	+++	30.1	19.6	4.6	19.3	52[3]	37	10	0	− 40	14	58.5	Vegetables and eggs.
6– 7	3340	1028	+++	28.9	22.5	5.7	20.8	107	73	20	0	− 85	24	58.2	Strict diet; vegetables in 5-6-10 per cent. groups, cream 250 c.c., half grapefruit.
10–11	2975	1028	++++	21.7	19.3	4.8	20.5	107	83	50	0	− 55	24	58.9	Strict diet; vegetables 5-6-10 per cent., cream 250 c.c., half grapefruit, oatmeal 36 gms., peas 1 tablespoonful.
17–18	2960	..	..	..	18.8	..	..	88							
24–25	2780	..	..	..	16.5	..	..	81							
31 / Aug. 1	2680	..	..	..	22.0	..	..	116							
7– 8	2630	1028	+++	28.4	15.0	2.2	12.1	90	68	55	15	− 35	24	59.0	Strict diet; vegetables 5-6-10 per cent., cream 375 c.c., half grapefruit, oatmeal 36 gms., peas 1 tablespoonful.
14–16	2800	..	..	..	18.3	..	..	105							
22–23	2800	1029	+++	31.9	18.5	4.5	20.0	88	67	55	15	− 10	..	57.6	Diet for Aug. 22–23 same as for Aug. 7–8.
23–24	2320	1027	++++	26.1	16.7	3.8	18.7	64	46	20	15	− 45	24	58.2	Vegetables 450 ± gms., cream 250 c.c., 14 eggs, bacon 215 gms.
24–25	3020	1024	++++	21.6	15.9	3.0	15.5	36	12	15	10	− 20	24	58.1	Vegetables, broths.
25–26	3030	1027	+++	33.6	15.1	3.3	18.0	79	73	55	15	− 25	24	57.4	As August 8.
28–29	2840	1032	++++	31.6	17.3	2.3	10.9	108	85	55	15	− 55	24	57.9	As August 8.
Sept. 7– 8	3760	1030	+++	32.9	20.6	4.5	18.0	122	98	70	15	− 50	24	56.7	Strict diet; cream 250–375 c.c., half grapefruit, vegetables 5-6-10 per cent., peas 1 tablespoonful, oatmeal 36 gms., potato 90 gms.

1910.															
Sept. 14–15	2560	1029	++++	32.8	16.8	4.1	20.1	63	41	20	8	− 45	20	57.2	250 c.c. cream, 6 eggs, vegetables 450 gms., bacon 150 gms., claret 75 gms.
15–16	3250	..	++++	27.6	12.9	..	..	119	..	125[4]	40	+ 6	20	56.8	Oatmeal 180 gms., cream 300 gms., eggs 3, brandy 60 gms., claret 90 gms., butter 262 gms.
16–17	2900	1027	+++	38.5	11.7	4.4	30.9	69	46	20	30	− 50	20	57.1	Cream 125 c.c., vegetables 500 gms., eggs 6, bacon, bouillon, much butter.
17–18	3200	1028	++++	19.6	13.6	5.0	30.2	92	64	45	23	− 45	14	56.1	Strict diet; oatmeal 36 gms., cream 375 c.c., half grapefruit, vegetables 200 gms.
21–22	3340	1020	++++	40.7	18.4	4.2	18.8	113	80	55	23	− 60	20	55.8	As August 8.
Oct. 5– 6	3570	1029	+++	37.0	17.2	3.9	18.6	128	96	70	30	− 60	20	55.8	Strict diet; vegetables 5-6-10 p.cent.groups, 1 tablespoonful 15 per cent., oatmeal 36 gms., cream 250 c.c., half grapefruit, potato 90 gms.
30–31	3230	1029	..	..	19.2	..	..	111							
Nov. 6– 7	3175	1028	++++	29.3	17.4	4.2	19.9	82	70	20	30	− 60	20	57.2	Vegetables, eggs 7½, bacon, cream, 300 c.c.
16–17	3625	1031	..	..	22.4	..	..	143							
27–28	3680	1030	++++	42.3	18.5	6.2	27.6	132	110	70	30	− 60	20	54.8	
Dec. 7– 8	3500	1025	++++	42.6	15.8	5.1	26.5	77	56	20	30	− 55	20	56.1	Butter, 7 eggs, vegetables, bacon, cream, alcohol.
26–27	2800	1027	++++	26.8	14.7	2.8	15.7	64	50	20	30	− 45	20	58.0	Butter, 7 eggs, vegetables, bacon, cream, alcohol.
1911.															
Jan. 11–12	4130	1024	+++	39.6	17.0	4.2	20.3	74	58	20	30	− 55	20	57.6	Butter, 7 eggs, vegetables, bacon, cream, alcohol.
25–26	4130	1029	++++	48.4	19.3	7.4	31.5	145	124	90	30	− 55	20	..	Strict diet; vegetables 5-6-10 per cent. groups, 1 tablespoonful 15 per cent., oatmeal 36 gms., cream 300 c.c. half grapefruit, potato 90 gms., bread 30 gms.
Feb. 19–20	4500	..	+++	..	19.2	8.0	34.3	..	153	125	30	− 30	20	..	Strict diet; vegetables 5-6-10 per cent., oatmeal 18 gms., potato 90 gms., bread 60 gms.,cream 500 gms., grapefruit, half orange, bananas 45 gms., macaroni 60 gms.
Mar. 5– 6	5120	1029	++	..	18.3	6.1	27.4	200	174	125	30	− 75	20	56.3	Essentially the same.
16–17	4380	1027	+++	52.7	19.5	7.1	29.9	180	158	125	30	− 55	20	..	" "
April 2– 3	3475	1030	++	26.3	14.8	4.4	24.5	139	111	125	30	− 15	20	55.9	" "
26–27	4500	1028	+++	51.0	16.3	6.3	31.8	185	162	130	30	− 55	20	55.7	" "
May 10–11	3500	1028	++	42.4	13.2	5.3	33.0	158	133	125	30	− 35	20	..	" "
12–13	548[5]	..	..	..	2.6	..	..	..	..	..	..	..	..	55.3	" "
28–29	4220	1026	++	49.8	..	6.0	..	186	152	125	30	− 60	20	54.5	" "
July 5– 6	3150	1027	++	18.9	11.4	..	..	..	126	125	30	0	20	56.5	" "
30–31	3900	1026	+++	36.2	14.1	5.1	29.8	..	117	125	30	+ 10	20	..	" "
Aug. 9–10	..	1023	+++	..	..	..	..	2.5[2]	1.6[2]	20	30	..	23	55.7	4 eggs, cream 375 c.c., bacon, vegetables 5-6-10 per cent.

TABLE 264.—CASE 344. ILLUSTRATION OF THE OLD-FASHIONED TYPE OF TREATMENT OF DIABETES, SEVERE ACIDOSIS, DECLINE IN CARBOHYDRATE TOLERANCE, DEVELOPMENT OF PULMONARY TUBERCULOSIS WITH IMPROVEMENT IN TOLERANCE COINCIDENT WITH EMACIATION. DISAPPEARANCE OF ACIDOSIS.—(*Continued.*)

Date.	Volume of urine, c.c.	Specific gravity.	Diacetic acid.	β-oxybutyric acid, gms.	Nitrogen, gms.	Ammonia, Total gms.	Ammonia, NH_3-N / total N per cent.	Sugar, By copper reduction, gms.	Sugar, By rotation, gms.	Diet, Carbohydrate,[1] gms.	Diet, Alcohol, gms.	Carbohydrate balance, gms.	$NaHCO_3$, gms.	Body-weight without clothing, kilos.	Remarks.
1911.															
Aug. 10–11	3140	1027	++	36.3	9.8	4.8	40.3	122	94	95	30	− 25	23	55.8	Oatmeal 120 gms., cream 250 c.c., vegetables 5-6-10 per cent.
11–12	3600	1024	++	46.7	8.7	4.7	44.4	97	86	95	30	0	13	56.3	Oatmeal 120 gms., cream 250 c.c., vegetables 5-6-10 per cent.
12–13	3310	1020	..	51.5	8.6	4.6	44.0	46	26	20	30	− 25	27	56.2	As on August 9–10.
16–17	3500	1029	+++	39.9	11.3	4.6	33.5	126	119	125	30	0	23	55.6	As on February 19–20.
Sept. 6– 7	3420	1029	+++	38.3	13.2	4.1	25.5	150	137	125	30	− 25	23	55.4	As on February 19–20.
17–18	3800	1029	++++	52.0	12.6	4.5	29.4	141	106	130[6]	30	− 10	23	55.0	Vegetable protein only, except protein in 3 eggs and 300 c.c. cream with usual carbohydrate.
27–28	3030	1032	+++	..	..	4.6	..	158	127	177[6]	30	+ 50	23	55.7	As on February 19–20.
28–29	2980	1031	+++	..	..	4.4	..	143	113	130[6]	30	− 15	23	55.6	As on September 17–18.
29–30	3870	1028	++++	..	..	5.2	..	155	116	130[6]	30	− 25	23	55.2	As on September 17–18.
Oct. 30 / 1	3800	1031	+++	..	..	5.5	..	182	152	126	30	− 55	23	54.7	As on February 19–20.
8– 9	3800	1030	++	..	..	5.5	..	190	152	135	30	− 55	23	54.6	Same, +10 gms. carbohydrate.
22–23	4000	1027	++++	34.9	14.2	7.1	41.1	180	144	135	30	− 45	23	53.8	Same, +10 gms. carbohydrate.
Nov. 12–13	4400	1027	++	52.0	13.0	5.5	34.8	198	158	135	30	− 65	23	54.3	Same, +10 gms. carbohydrate.
14–15	3800	1028	+	34.6	17.0	5.4	26.1	141	122	115	60	− 25	23	54.1	Butter 60 gms., oatmeal 150 gms., 2 cups broth, 600 c.c. cream = 180 gms. fat.
15–16	3800	1028	+++	..	11.4	5.4	39.0	144	114	130	45	− 15	23	54.2	As on September 17–18.
Dec. 30 / 1	4200	1028	++	46.2	13.4	5.2	31.9	168	151	135	45	− 35	23	53.7	As on October 8–9.
25–26	4700	1027	+++	54.8	14.5	6.3	35.7	188	160	135	45	− 55	23	50.4	As on October 8–9.
1912.															
Jan. 9–10	4840	1028	++	..	..	6.5	..	198	194	150	45	− 50	23	..	Same, +15 gms. carbohydrate.
14–15	4000	1029	++	..	13.8	5.1	30.4	132	120	100	45	− 30	30	53.2	
15–16	3860	1029	+	..	9.9	4.8	39.9	154	154	170	60	+ 15	30		
17–18	4945	1024	+	..	10.8	4.5	34.3	124	109	105	60	− 20	30	53.1	
Feb. 4– 5	5270	..	..	..	..	..	..	..	..	150	45	.	25	49.9	
6– 7	4820	1029	Slight +	..	17.3	5.2	24.7	198	183	150	..	− 50	25		
12–13	4864	1027	Slight +	..	16.0	6.2	31.9	184	146	100	45	− 85	25		
25–26	5175	1027	++	..	14.3	6.2	35.7	191	176	150	45[7]	− 40	25		
Mar. 14–15	4200[5]	1020	0	..	9.6	..	..	126	134	150	45[7]	+ 25	15		
17–18	2940	1020	0	6.1	9.1	0.9	8.1	82	82	150	45[7]	+ 70	15		
22–23	2700	1026	0	6.3	12.1	..	..	135	118	150	45[7]	+ 15	10	34.5	
26–27	2400	1032	0	2.6	9.9	1.3	10.8	134	115	150	45[7]	+ 15	5		
April 2– 3	2100	1030	0	..	..	..	..	105	105	150	45[7]	+ 45	5		
7– 8	1680	1033	0	..	11.6	..	..	99	87	160	45[7]	+ 60	5		

[1] Carbohydrates in diet up to June 29, 1910, are only approximately correct, but subsequent to that date are most accurate.
[2] Per cent.
[3] By fermentation.
[4] Protein, 60 ± gms.; nitrogen, 10 ± gms.; fat, 345 ± gms.!!
[5] Not twenty-four-hour urine.
[6] 75 gms. of protein Sept. 17–18, 28–29, and 29–30; 79 gms. Sept. 27–28.
[7] Approximate.
[8] Twenty-two hours.
[9] By "strict diet" is to be understood here a fat-protein diet.

Measures which are desirable in the treatment of pulmonary tuberculosis without diabetes can be employed in its presence. This applies even to the use of artificial pneumothorax which was utilized in 2 cases with advantage to both diseases by Taub.[1]

Coma in diabetes complicated by tuberculosis is susceptible of recovery. I have had 1 case, Walters and Ruby report another on the edge of coma who also had pneumothorax. The latter patient was given 450 units of insulin during one day.

Lundberg[2] in an inaugural thesis, based upon 12 cases of diabetes with tuberculosis, calls attention to the increase in tolerance for carbohydrate and the consequent disappearance of the glycosuria and ketonuria, with lessening need for insulin and especially a liability to the sudden accession of hypoglycemia. He attributes this to a substance, parainsulin, which can be demonstrated in tuberculous tissue which is capable of lowering the blood sugar. Many of the symptoms of tuberculosis might be explained according to the author, by hyperinsulinism. For this reason in tuberculous diabetics one should strive toward an abundant amount of carbohydrate in the diet.

I. CANCER OF THE PANCREAS.

Cancer of the pancreas in a diabetic or non-diabetic leads to puzzling phenomena. In Wilder's[3] celebrated case the cancer attacked the islands of Langerhans in a non-diabetic and metastases developed in the liver, but instead of the secretion of the islands being inhibited, it increased to such an extent that the ingestion of 1000 grams of sugar was necessary daily to combat hypoglycemia. Among Kiefer's[4] 33 proved cases of cancer of the pancreas at the Peter Bent Brigham Hospital glycosuria was present in only 2 cases, and in but 1 case was it appreciable, in conformity with the universal experience. On the other hand when the cancer attacks the pancreas of a diabetic, the diabetes usually becomes more difficult to treat. However this is not true with secondary cancer as in Case No. 5971 in which the malignancy was a metastasis from a carcinoma primary in the ovary.

The incidence of cancer of the pancreas in the general hospital population Kiefer puts at 0.1 per cent. Among my 5086 true diabetics it appears to have been twice as frequent as there were diagnosed 11 cases or 0.2 per cent. There were 3 cases among the 675 unclassified cases of glycosuria.

[1] Taub: Med. Clin. North America, 1927, **11**, 33.
[2] Lundberg: Stockholm, Tirage a par des Acta Med. Scand., 1924, **62**.
[3] Wilder, Allan, Power, and Robinson: Jour. Am. Med. Assn., 1927, **89**, 348.
[4] Kiefer: Arch. Int. Med., 1927, **40**, 1.

In Table 265 data regarding these 14 cases of cancer are recorded. The short durations of certain of these cases suggests that diabetes really did not exist. In each instance I had good reason to consider it present, but I suspect the duration was greater.

TABLE 265.—CANCER OF THE PANCREAS IN TRUE DIABETES AND IN UNCLASSIFIED GLYCOSURICS.

Case No.	Autopsy.	Urine, sugar, per cent.	Operation.	Treatment.	Duration of diabetes, years.
896	+	6.0	0	At first controlled with diet; later uncontrolled even with insulin	10.7
1435	0	8.0	0		0.4+
1725	0	1.0	0		0.4
1765	0	3.0	0		1.8
2034	0	2.7	+		0.5+
3330	0	2.8	+	At first controlled by diet, later by insulin, later by neither	2.9
3876	0	2.5	+		0.3
4029	0	3.5	+	At first with diet, later insulin required	1.9
5105	0	7.5	0		17.2
5335	+	1.6	0		3.3
5444	0	6.0	0		2.2
1370[1]	0	+	+		3.0
1490[1]	+	+[2]	0		1.7
3109[1]	0	0.5[3]	+		0.2

Case No. 5335 had a carcinoma of the head of the pancreas. The islands in the uninvolved portion of the gland were normal in number and appearance.

Case No. 896 developed diabetes in March, 1914, at fifty-eight years of age and the disease ran an uneventful course, being controlled by diet as late as February, 1921, even during periods of severe mental depression. In October of that year glycosuria was persistent. The patient returned to my care in June, 1924, with severe glycosuria and acidosis, despite an adjusted diet and 70 units of insulin. The symptoms were then mental rather than abdominal, but glycosuria was present even after 150 units of insulin. Later in the summer debility increased and glycosuria was constant despite gain of weight, which made the diagnosis of ascites probable, although the patient was 500 miles away. This was confirmed in October. Glycosuria varied from 6 per cent to about 1 per cent,

[1] Unclassified glycosuria.
[2] Blood sugar fasting, 0.14 per cent.
[3] Blood sugar fasting, 0.17 per cent.

and the percentage of sugar in the blood usually was found to be near 0.3 per cent, although 50 units of insulin more or less were given according to the diet. CO_2 volumes per cent ranged between 43 and 49 and the non-protein nitrogen was 34.5 mg. per 100 cc. A portion of moist feces on October 26 weighed 35 grams, dry weight 3 grams and the fat extracted 2.11 grams; on November 4 the values were moist 315 grams, dry 75 grams and fat 47 grams.

The persistence of the glycosuria and still more so of the hyperglycemia, and the ready appearance of ketonuria, despite large doses of insulin and variations of carbohydrate in the diet, were the striking features of the case.

The patient died on November 25, 1924. The postmortem examination showed cancer involving the entire pancreas save 3 cm. of the tail. The tumor was composed of two types of cells, cylindrical and cuboidal with glandular arrangement. A section through the tail of the pancreas showed only islets present and they were quiet numerous. In Dillon's[1] case also, many large islands of Langerhans were present in the tail whereas the body and head showed carcinomatous tissue and associated interlobular pancreatitis, resulting from occlusion of the ducts.

The insulin refractory nature of my case was apparent from the first observation in June, 1924.

Insulin cannot be demonstrated in malignant new growths, although present in normal tissue according to Cramer, Dickens, and Dodds.[2] The cells of normal tissues oxidize glucose, whereas the cells of malignant new growths split glucose with the formation of lactic acid. Gotta[3] found glycolysis approximately the same in 13 control and 45 cases of cancer of all types and organs.

Non-pancreatic cancer in diabetes has shown no peculiarities so far as diet or symptoms have been concerned.

J. SYPHILIS.

The Wassermann test was positive in 1.6 per cent and negative in 98.4 per cent of 1000 diabetic patients who were thus tested in the first 3200 cases coming for treatment. The 1000 cases undoubtedly included a small number of potential diabetics, renal glycosurics and unclassified glycosurics. Among the number counted as negative there were 10 cases in which the first report was positive, but negative shortly afterward without instituting treatment for lues. In these first 3200 cases there was a history of syphilis or signs of syphilis in 55 or 1.7 per cent. For my 5086 true diabetics syphilis

[1] Dillon: Ayer Clin. Lab., Philadelphia, Bull. No. 8, 1924, p. 3.
[2] Cramer, Dickens, and Dodds: British Jour. Exper. Pathol., 1926, **7**, 299.
[3] Gotta: Rev. Med. Lat. Amer., 1926, **11**, 2118.

was considered present as a result of history, physical examination or Wassermann test in 1.9 per cent; in 189 potential diabetics in 1.5 per cent; in 49 renal glycosurics in 4.1 per cent and in 675 unclassified glycosurics in 0.9 per cent.

A summary of the Wassermann reports in 1000 cases together with the classification of the series into true diabetics, potential diabetics, renal glycosurics and unclassified cases occurs in Table 267.

By way of comparison Paullin reports that 17 per cent to 22 per cent of the negro patients in the Out-Patient Department at Atlanta, Georgia, have syphilis, while about 8 per cent of the negro admissions in the Pediatric Department have congenital syphilis. Of 4786 hospital admissions about 20 per cent were luetic. These figures seem remarkably low and are hardly more than at some northern white hospitals. In fact, at the Bacteriological Laboratory of the Boston Board of Health, where I have been fortunate enough to have most of my Wassermann tests performed, the percentage of positive Wassermann tests for the first eight months of 1923 was 15.5 per cent. These tests may have been performed on selected or suspected cases. Walker and Haller[1] at the Peter Bent Brigham Hospital report that 8 per cent of 89 diabetics gave a positive Wassermann reaction and that this was about one-half the incidence for the general hospital population. Williams[2] found the Wassermann test in 144 diabetics to be positive in 4, absent in 126, doubtful in 1, and 13 cases anticomplementary. Mason[3] among 168 diabetics discovered 2 strongly positive Wassermann reactions but without the history, symptoms, or signs of syphilis. These patients when treated for a short time for their supposed syphilitic infection showed marked and rapid *decline* of carbohydrate tolerance. John[4] discovered 54 cases of syphilis, 2.7 per cent, in his 2000 diabetics.

Lemann[5] also reports that 3.6 per cent of 330 diabetics at the Charity Hospital in New Orleans gave a positive Wassermann reaction, and in 210 patients at Touro Infirmary the Wassermann test was made in 101 cases and was positive in 6 per cent.

Table 266 shows the incidence of syphilis based on history and physical signs in the first and second series above mentioned.

Labbé and Tauflet[6] give an exhaustive review of the literature and conclude that syphilis is rare in diabetes.

Warthin and Wilson[7] have strikingly different views from the above regarding the frequency of association of diabetes and syphilis.

[1] Walker and Haller: Jour. Am. Med. Assn., 1916, **66**, 488.
[2] Williams: Jour. Am. Med. Assn., 1918, **70**, 365.
[3] Mason: Am. Jour. Med. Sci., 1921, **162**, 828.
[4] Personal communication.
[5] Lemann: Jour. Am. Med. Assn., 1927, **89**, 659.
[6] Labbé and Tauflet: Annal. de Med., 1923, **13**, 367.
[7] Warthin and Wilson: Am. Jour. Med. Sci., 1916, **152**, 157.

They find disease of the pancreas almost univeral in cases of latent syphilis. As yet other investigators have not substantiated the work of these authors.

TABLE 266.—FREQUENCY OF SYPHILIS ACCORDING TO CASE HISTORIES, PHYSICAL SIGNS, AND WASSERMANN TESTS.

Case Nos.	Total cases of syphilis.	True diabetes.		Potential diabetes.		Renal glycosuria.		Unclassified.	
		Total.	Syph.	Total.	Syph.	Total.	Syph.	Total.	Syph.
1 to 1000	19	906	18	13	0	0	0	81	1
1001 to 2000	14	865	13	11	0	5	0	119	1
2001 to 3000	20	839	17	27	1	16	0	117	2
3001 to 4000	23	843	22	42	0	8	0	107	1
4001 to 5000	20	809	17	47	0	13	2	131	1
5001 to 6000	9	824	7	49	2	7	0	120	0
Total	105	5086	94	189	3	49	2	675	6

TABLE 267.—SUMMARY OF WASSERMANN REPORTS OF ONE THOUSAND CASES. NUMBERS 5001–6000.

Classification.	Total No.	Wassermann reaction.			
		Positive.	Doubtful.	Negative.	Not done.
True diabetes	824	4	1	791	25
Potential diabetes	49	2	0	44	3
Renal glycosuria	7	0	0	7	0
Unclassified	120	0	1	111	8

Lemann[1] has sought to throw light upon the question of the dependence of diabetes upon syphilis by comparing the frequency of diabetes in the white and negro patients of the Charity Hospital in New Orleans along with the frequency of syphilis. Despite the greater frequency of syphilis in the negro he demonstrated that diabetes is not as frequent in that race as in the white. Thus, between the years 1898 and 1909 the negroes furnished 40 per cent of the admissions, but only 30 per cent of the diabetics. The total incidence of diabetes was 0.63 per 1000, among the whites 0.72 and among the negroes 0.47 per 1000. Between 1910 and 1919, 160,044 patients were admitted to the hospital and of this number the negroes constituted 43 per cent, but only 30 per cent of the diabetics in the hospital. An increase in the incidence of diabetes took place in both races alike. Thus, the incidence for diabetes rose among the whites to 1.4 per 1000, and among the negroes, to 0.86 per 1000, whereas the negroes furnished more than 50 per cent of all the syphilitic diseases. The discrepancy between the inci-

[1] Lemann: Am. Jour. Med. Sci., 1921, **162**, 226.

dence of diabetes in the two races might be explained by differences in the average ages of the whites and negroes. Perhaps the average age of the negroes in these series is less than that of the whites.

The rarity of syphilis among diabetics is further commented upon by Labbé.[1] He records that in 7 diabetic patients with a history of inherited or acquired syphilis the treatment of the disease was without favorable results upon the diabetes and elsewhere he says that he knows of no case in the literature in which treatment of the syphilis improved the diabetes. This view was expressed in the discussion of a report of a patient treated by Pinard and Mendelsohn[2] whose diabetes had been greatly helped by the accompanying treatment of syphilis.

TABLE 268.—DURATION OF TRUE DIABETES IN PATIENTS SHOWING A POSITIVE WASSERMANN REACTION OR PRESENTING A POSITIVE HISTORY OF SYPHILIS. 59 LIVING CASES.

Case No.	Age at onset, Syphilis.	Age at onset, Diabetes.	Duration of diabetes to July 1, 1927	Case No.	Age at onset, Syphilis.	Age at onset, Diabetes.	Duration of diabetes to July 1, 1927.
VI	26	46	17.0	LV	30	44	5.6
VIII	31	32	32.0	LVII	15	41	5.4
IX	16	30	15.2	LVIII	28	41	10.0
XII	27	58	12.6	LXI	17	43	6.3
XVI	32	34	38.6	LXII	24	51	11.0
XVIII	31	44	12.2	LXIV	21	44	4.5
XIX	35	54	11.6	LXVII	..	50	8.8
XXIII	47	75	8.4	LXVIII	17	52	9.0
XXV	..	36	17.8	LXXI	27	63	3.2
XXVIII	20	37	11.0	LXXII	..	49	6.3
XXX	49	57	7.2	LXXIII	..	50	11.0
XXXII	43	31	8.9	LXXIV	before 30	30	3.0
XXXIII	22	49	6.6	LXXV	before 59	59	5.0
XXXIV	51	54	7.8	LXXVI	..	69	2.3
XXXV	29	20	14.8	LXXVII	..	52	5.3
XXXVI	36	51	16.0	LXXVIII	36	54	4.8
XXXVII	..	65	12.9	LXXIX	37	46	3.2
XXXVIII	40	61	8.1	LXXX	..	40	11.8
XXXIX	17	46	7.8	LXXXI	25	47	6.1
XLI	24	23	6.2	LXXXII	..	66	2.5
XLII	20	54	10.3	LXXXIII	45	49	2.6
XLIII	57	49	13.1	LXXXIV	..	62	4.3
XLIV	34	46	5.0	LXXXV	..	61	11.7
XLV	25	51	6.0	LXXXVII	..	56	8.9
XLVI	12	53	13.3	LXXXIX	20	40	12.8
XLVII	19	38	5.1	XC	24	71	3.0
XLIX	49	44	9.3	XCI	..	48	7.3
LII	28	58	7.0	XCII	..	45	1.2
LIII	before 32	32	4.6	XCIV	..	52	0.8
LIV	49	39	14.0				
Total average age and duration					Av. 30.8	48.2	11.4[3]

[1] Labbé: Bull. de l'Acad. de méd., Paris, 1923, **89**, 53; Bull. et mém. Soc. méd. d. hôp., 1922, **46**, 400.

[2] Pinard and Mendelsohn: Bull. et mém. Soc. méd. d. hôp., 1922, **46**, 400.

[3] I recall no other group of my living patients with as high an average duration.

35 Fatal Cases.

Case No.	Age at onset Syphilis.	Diabetes.	Duration of diabetes, years.	Cause of death.
I	..	42	10.6	Pneumonia
II	before 42	42	17.0	Influenza-pneumonia
III	..	54	7.8	Coma
IV	25	54	19.0	Coma
V	39	54	14.0	Cardiac
VII	36	42	....	Cannot trace
X	38	41	1.6	Coma
XI	38	47	6.8	
XIII	28	44	14.5	
XIV	..	51	7.5	Coma
XV	..	38	1.1	Coma
XVII	..	39	1.0	Coma
XX	30	39	8.9	Coma
XXI	..	51	11.4	Apoplexy
XXII	..	43	8.6	Pernicious anema
XXIV	26	28	6.7	Tuberculosis
XXVI	54	53	1.8	
XXVII	46	41	8.4	Cirrhosis of liver
XXIX	23	29	2.9	Diabetes
XXXI	59	48	11.8	Cirrhosis of liver
XL	41	46	4.7	Tuberculosis
XLVIII	57	55	7.7	Coma
L	32	51	1.7	Cardiac
LI	33	44	2.1	Coma
LVI	18	50	2.4	Carcinoma of tongue
LIX	39	45	15.0	Cardiac
IX	40	63	4.0	Cardio-renal
LXIII	..	38	9.6	Appendicitis
LXV	34	47	0.5	Suicide
LXVI	before 21	21	2.0	Coma
LXIX	19	60	0.3	Carcinoma of pancreas
LXX	44	44	1.8	Influenza
LXXXVI	25	39	11.8	Tuberculosis
LXXXVIII	..	63	1.9	Pulmonary embolus
XCIII	..	45	3.7	Septicemia
	Av. 35.5	Av. 45.5	Av. 6.3	

The absence among diabetics of the common sequelæ of syphilis —tabes dorsalis, paresis, aortic insufficiency and aneurysm—is confirmatory evidence of the infrequency of syphilis as an etiological factor in diabetes. Absolute data I cannot give, but since April 1, 1919, my former and present associates, Brigham, Hornor, Gray, Root, White and I can trace but 2 cases of tabes in my entire series of diabetics, 1 case of aortic insufficiency and 1 case of aneurysm. Indeed the statement can be made with reasonable accuracy that there are but 6 patients among the 6000 diabetics who have ever been sent to an insane asylum or required treatment for insanity. It is therefore evident that if syphilis is of etiological import in diabetes, the diabetic possesses remarkable immunity to its customary manifestations.

Many of my diabetic cases with a syphilitic history have been of

long duration. This type of the disease has occurred so frequently in connection with known syphilis that one must suspect the presence of syphilis in mild diabetes. The duration of syphilis and of the diabetes is shown in Table 268. In illustration of the above the following instance is cited: Case No. 503 acquired syphilis at the age of sixteen years in 1898, and was energetically treated by the older methods and is alive in 1927. In May, 1912, when about to undergo an operation for appendicitis, sugar was found at a routine examination, and the Wassermann reaction, which had not previously been tried, was demonstrated to be positive. He was given a thorough course of treatment with salvarsan, and the Wassermann reaction has remained negative. Under dietetic treatment sugar decreased and gradually a marked carbohydrate tolerance was acquired. No further antisyphilitic treatment has been given. On August 19, 1915, the urine contained 0.5 per cent of sugar and the carbohydrate in the diet amounted to 140 grams. The blood sugar amounted to 0.16 per cent fasting. On August 7, 1922, the urine contained 0.5 per cent sugar, the blood sugar was 0.13 per cent, five hours after a meal and the Wassermann reaction was negative. The father, Case No. 711, of the patient developed mild diabetes, but his Wassermann reaction was negative.

A positive reaction has been found on 12 different occasions during 7.6 years with Case No. 630. Acquirement of syphilis is denied by the patient and he presents no stigmata of it. The diabetes is mild, amenable to diet, although the urine has contained 5 per cent sugar. Thus far it has lasted 18.6 years and at its onset the patient's expectation of life was but nineteen years. He had his first negative Wassermann reaction in May, 1927; it was again positive in October, 1927.

It would seem that syphilitic diabetes was an ideal condition for etiological treatment, but all writers agree that this is not usually the case. It is, however, true that occasionally a patient has been strikingly helped. For instance, Umber[1] recorded a case of diabetes, male, aged forty-eight years, with syphilitic infection in 1898. During 1909 indigestion, pain in epigastrium, thirst, transitory jaundice, loss of 18 pounds, and gastric tumor occurred. Upon a diet of 147 grams of carbohydrate, 113.4 grams of sugar were eliminated. Fatty stools, blood sugar 0.43 per cent, Wassermann reaction positive. Following the use of 0.4 gram of salvarsan the tumor decreased in size and the stools became less fatty. There was a continuous gain in weight for one year, and at the time of recording the case the patient lived without restriction of carbohydrate and no tumor was to be felt. Revillet[2] reports a cure with mercury.

[1] Umber: München. med. Wchnschr., 1911, **58**, 2499.
[2] Revillet: Lyon méd., 1916, **125**, 374.

Walker and Haller[1] report that energetic treatment of a case of diabetes developing six months after the initial lesions was without any influence on the diabetes. The blood Wassermann became much weaker, but never negative and the patient finally died in coma.

Remarkable improvement in the diabetes of a young woman with syphilis, considered to be of congenital origin, though the Wassermann of the mother was negative, was noted by Dr. J. E. Paullin[2] and Dr. H. M. Bowcock. The patient, aged twenty-one years, was first seen in March, 1921. Her father died of apoplexy at sixty-three years. She had always been delicate; catamenia began at fourteen, but ceased seventeen months before the first visit. The greatest weight was 115 pounds at fifteen years of age but decreased to 85 pounds. Cramping pains in the epigastrium after meals were the chief complaint in 1921, from which she obtained relief by vomiting. Upon physical examination there was thoracic scoliosis, enlarged cervical glands, rales at the apices, pupillary and patellar reflexes normal, tenderness in the hypochondrium. The red blood corpuscles numbered 2,210,000, hemoglobin 50 per cent, Wassermann was four plus in two laboratories. The roentgen-ray showed a typical syphilitic stomach. The patient was treated with neoarsphenamine 5.85 grams in 10 doses, later 6.3 grams in 7 doses and in addition iodide of mercury. The Wassermann being positive in 1923, she again had arsphenamine. The roentgen-ray showed improvement of the stomach and her menstrual periods have returned. The sugar in the urine amounted to 1.1 per cent March, 1921, but in March, 1923, she was sugar-free on an unrestricted diet. The two blood-sugar curves in April, 1921, and January, 1923, after glucose tolerance tests are to be seen in Table 265 and indicate the improvement. Dr. Bowcock adds, "We do not feel that this is an absolutely typical case of diabetes, or a typical case of pancreatic insufficiency."

Rosenbloom[3] has reviewed the literature upon the relation between syphilis and diabetes. The possibilities of syphilis as an etiological factor are numerous. The process might produce actual luetic lesions in the brain or spinal cord, and particularly of the medulla or secondarily through arterial disease. Similarly the pancreas might be affected directly or through disease of the bloodvessels. In 139 of his own cases of diabetes he found 16 with a positive Wassermann but only 8 of these showed signs of arteriosclerosis. These 8 cases were intensively treated with increase in their tolerance for carbohydrate.

[1] Walker and Haller: Loc. cit., p. 488.
[2] Paullin and Bowcock: Jour. Am. Med. Assn., 1924, **82**, 702.
[3] Rosenbloom: Am. Jour. Syph., 1921, **5**, 634.

TABLE 269.—GLUCOSE TOLERANCE TESTS IN A DIABETIC, BEFORE AND AFTER ANTILUETIC TREATMENT. (PAULLIN AND BOWCOCK.)

Time, minutes.	Sugar, April, 1921.		Sugar, January, 1923.		Sugar, July, 1923.	
	Urine, grams.	Blood, per cent.	Urine, grams.	Blood, per cent.	Urine, grams.	Blood, per cent.
0	0	0.14	0	0.08	0	0.10
30	2	0.32	0.5	0.28	+[1]	0.17
60	3.5	0.42	1.5	0.20	+[1]	0.17
90	2.5	0.28	0.5	0.18	0	0.16
120	0	0.19	0	0.06	0	0.10

The occurrence of glycosuria in the course of tabes or general paralysis does not necessarily signify diabetes. Urechia and Joseph[2] record that Siegmond found glycosuria in 27 cases out of 100 of general paralysis and Bond in 3 out of 62 such cases. They also quote Nonne as reporting a case of cerebral syphilis in which the glycosuria disappeared with antisyphilitic medication, but without any antidiabetic regime. In their own series glycosuria appeared in a proportion of 5 to 7 per 100 with disease of the brain and spinal cord.

K. THE BLOOD.

The blood in uncomplicated diabetes shows so little departure from normal that unless indications were plain counts of the red and white corpuscles and estimations of the hemoglobin have not been made. In the limited series of Fitz and Murphy those patients whose red cells were less than 4,000,000 showed serious complications. Anemia in a diabetic signifies a complicating disease. Root, White, and Thompson[3] compared the capillary and venous concentrations of corpuscles in the morning and evening in diabetic patients. In certain cases with high diastolic pressures the capillary red cell count was higher than the venous at night but lower in the morning, suggesting capillary stasis. This was most marked in cases with obvious vascular disease.

A leukocytosis is the rule in coma. (See p. 653.) Counts above 10,000 were present in 16 of 19 cases in my series and in the series of Fitz and Murphy with acidosis 25 of 28 cases showed counts of 10,000 or more. These writers suggest that the explanation may be anhydremia or due to a contemporary infection, but any interpretation should fit in with a cause for gastric hemorrhage which so frequently is an associated symptom.

[1] Greatest amount excreted was 0.35 grams.
[2] Urechia and Joseph: Ann de méd., 1921, **9**, 94.
[3] Root, White, and Thompson: Jour. Lab. and Clin. Med., 1926, **11**, 405.

The hemoglobin in the years of the Naunyn Era seemed invariably high. The large quantities of meat which the patients consumed easily accounts for this phenomenon.

1. **Pernicious Anemia.**—Pernicious anemia is seldom encountered in diabetes. There have been 5 cases in my series of 6000 cases of whom 5086 were true diabetics. Case No. 1507 developed diabetes in September, 1917, at the age of forty-three years, the glycosuria reaching 9 per cent. When I first saw him in 1919 there was no glycosuria, but the blood sugar was 0.12 per cent fasting; in 1921 a slight glycosuria, blood sugar 0.14 per cent fasting and 0.18 per cent after a meal. In 1923 a diagnosis of pernicious anemia was made in Toronto and I saw the patient again in 1924 when the blood sugar reached 0.20 per cent after breakfast. At this time the hemoglobin was 70 per cent, the red corpuscles 3,300,000 and the white corpuscles 3040. The stained specimen showed marked variation in size and shape of red corpuscles with microcytes, large oval cells, tailed forms, and polychromatophilia, several stippled cells and one normoblast. Physical examination was negative. The subsequent history confirmed the diagnosis and the patient died of diabetes and pernicious anemia March, 1926.

Y. C. Yong of Honolulu has placed at my disposal the records of a case of pernicious anemia in a woman with onset of diabetes at age of forty-one years in 1922. She soon received insulin, 90 units daily, and continued this for four years without becoming aglycosuric. Retinal hemorrhages developed, but pernicious anemia was not suspected until in March, 1927, when diabetic coma occurred. The blood sugar was 0.435 per cent. The blood showed polymorphonuclear cells 58 per cent, small lymphocytes 42 per cent. Marked variation in size, shape, and staining qualities of red corpuscles. Few normoblasts. Tallquist fat ring present. Successive blood counts and the treatment of the case are shown in Table 270.

TABLE 270.—THE BLOOD IN PERNICIOUS ANEMIA AND DIABETES. (COURTESY OF Y. C. YONG, HONOLULU.)

1927.	Hemoglobin. per cent.	Reds.	Whites.	Normoblasts.
March 22	20	1,028,000	3600	Few
March 23	Transfusion 500 cc. citrated blood			
March 28	40	1,648,000		
April 5	30	1,384,000	2600	2
April 12	Transfusion 500 cc. citrated blood			
April 19	30	1,272,000	3000	5
May 7	30	1,243,000	3000	2
May 12	Transfusion 500 cc. citrated blood			
May 14	Began liver and HCl with steady improvement			
June 9	75	3,524,000	7200	0
	Insulin 40 units and sugar-free			

Three other cases have been reported by Adams,[1] two by Wright[2] and one each by Schumann[3] and Parkinson.[4]

Schumann's patient, a woman, developed both diabetes and pernicious anemia at the age of fifty-five years. The first examination revealed 1,200,000 erythrocytes, hemoglobin 35 per cent, blood sugar 0.22 per cent. The smear showed many microcytes and macrocytes, some polychromatophilia, poikilocytosis and anisocytosis and one nucleated red cell. The color index was 1.4. Insulin treatment was most successful, but repeated transfusions gave but temporary improvement in the anemia, and she died eighteen months after her first observation. Her daughter, aged twenty-seven years, strangely enough, was found to have myelogenous leukemia and roentgen-ray therapy reduced the leukocytes from 420,000 to normal.

Pernicious anemia and diabetes were frequently encountered in the ancestry of a patient of George R. Minot and kindly placed at my disposal by him: "Patient, aged fifty-nine years, male, has undoubted pernicious anemia. Brother, aged about fifty-nine years, 'has often had sugar in urine and is said to have pernicious anemia with mild cord symptoms.' Sister, aged fifty-five years, 'anemic for eight years' undoubted pernicious anemia now. Brother, aged about fifty years, has undoubted diabetes from history given. Brother, aged about forty-nine years, well. Mother died of diabetes. Father 'showed sugar in urine in last illness and died of infected foot that became gangrenous.' Father's brother 'had anemia and died of it.' Father's sister died in thirties of pneumonia. No other brothers or sisters. Mother's sister had diabetes. Definite information given concerning this. Mother's brother died of old age. No other brothers or sisters. Patient's paternal grandfather probably died of pernicious anemia. He was said to have been very pale in last two years of life and had difficulty in walking. An ill-defined history of this man's brother suggests that he had anemia."

2. **Leukemia.**—Leukemia is likewise rare in diabetes. I have had 2 such cases, Cases No. 392 and 1983, Fitz[5] another and he cites the case of Rebitzer[6] and that of Schwarz.[7] The most recent cases are those of Glaser,[8] Rapaport[9] and Wright.[10]

[1] Adams: Med. Clin. North America, 1925, **8**, 1163.
[2] Wright: Clifton Med. Bull., 1926, **12**, 155.
[3] Schumann: Jour. Am. Med. Assn., 1925, **85**, 677.
[4] Parkinson: 1910 (cited by Wright).
[5] Fitz: Jour. Am. Med. Assn., 1920, **75**, 1331.
[6] Rebitzer: Med. Wchnschr., 1892, **17**, 356.
[7] Schwarz: Wien. med. Wchnschr., 1905, **55**, 413.
[8] Glaser: Jour. Am. Med. Assn., 1927, **88**, 1626.
[9] Rapaport: California and Western Med., 1927, **27**, 802.
[10] Wright: Clifton Med. Bull., 1928, **14**, 1.

Case No. 1983 was of the lymphatic type; Fitz's case of the myeloid type with 147,000 corpuscles; Rebitzer's case had 555,000 white blood corpuscles, but the type is not given; Schwarz's case had 344,000 corpuscles, myelogenous type; Glaser's case had 125,000 corpuscles at one stage, but as proved by autopsy was myelogenous in character although of the aleukemic type. His patient was characterized by bronzing of the skin. Glaser points out that autopsies upon 3 of these cases revealed no infiltration of the pancreas as a cause of diabetes. Rapaport's case developed myelogenous leukemia after the diabetes and subsequently as in two other similar cases had miliary tuberculosis. Wright's case had 107,200 corpuscles and was of the lymphatic type.

Case No. 392, aged fifty-two years in January 1911, was found to have 0.9 per cent sugar in the urine. At this time the white cells numbered 23,200 and the differential count was lymphocytes 93 per cent, polymorphonuclears 5 per cent, and transitionals 2 per cent. The red cells were normal. His blood sugar has never exceeded 0.16 per cent and he has accordingly been classed as a potential diabetic. I am indebted to Dr. C. W. McGavran for careful observation of his blood for many years. The white count varied from 40,000 to 79,000. In May, 1926, Dr. G. R. Minot found 88 per cent of lymphocytes, with rather more immature than normal cells, 5 per cent of polymorphonuclears and 7 per cent of probable large mononuclears. His basal metabolism at this time was but 6 per cent and he had no anemia. He had persistent diarrhea, apparently due to leukemic involvement of the intestine. In August and September, 1927, he received 3 *x*-ray treatments; on September 14, 1927 his white count was 7000, the lowest it has been since 1911. The diarrhea has subsided and he looks well.

Mrs. M., Case No. 1983, aged forty-five years, when sugar was first discovered in her urine, was so mild a case that not until six years later when her blood sugar was 0.22 per cent could she be surely classed as a true diabetic. Chronic lymphatic leukemia was found on October 18, 1926, when the white corpuscles numbered 86,300. Her basal metabolism was 40 per cent. Treatment by radiation was carried out at the Collis P. Huntington Hospital with reduction in the white cell count from 200,000 to 10,000. Unfortunately improvement was but temporary and she died January 18, 1927.

Minot has seen two children in one family, the one with diabetes and the other with chronic lymphatic leukemia. Their own cousin on the mother's side had diabetes.

3. **Polycythemia.**—This condition was present in Case No. 4551, and 2 cases are reported by Wright.[1]

[1] Wright: Clifton Med. Bull., 1927, **13**, 37.

The blood counts in Wright's cases were 7,510,000 and 9,610,000 respectively. The diabetes was definite in character and showed no peculiarities during treatment.

Case No. 4551, a Jewish merchant, aged fifty-three years at the onset of diabetes in September, 1924, with 5 per cent sugar in the urine. He entered the Deaconess Hospital in April, 1925. The urine contained 1 per cent sugar, no diacetic acid, and the blood sugar was 0.20 fasting. The red blood count was 8,760,000; white blood count, 29,600. Differential count was polymorphonuclears 74 per cent, lymphocytes 18, large mononuclears 4, eosinophiles 3, basophiles 1. He became sugar-free readily and on May 24, 1927, he returned with urine sugar-free and blood sugar of 0.12 per cent. The red cells numbered 8,480,000, white cells 34,000, and the spleen reached slightly below the crest of the ilium. He maintained that the red cheeks and smooth hairless skin of his hands had been present for twenty-five years. His mild diabetes accompanied by marked arteriosclerosis required but seven days of treatment with insulin and he then tolerated 110 grams carbohydrate without insulin.

Irving L. Cabot's[1] diabetic patient with polycythemia was treated with phenylhydrazin. "With the decreasing erythrocyte count her whole condition improved more rapidly . . ."

4. **Hodgkin's Disease.**—A single instance, Case No. 5951, has occurred in my series. Enlargement of the glands at the angle of the left jaw was noticed in November, 1924, and the onset of diabetic symptoms was in September, 1926. Roentgen-ray treatment resulted in great reduction in size of the glands and in March, 1927, the characteristic crises of fever were almost the sole evidences of the disease. At this time he required 35 units of insulin daily but later when afebrile, the urine was sugar-free without insulin with a diet containing 108 grams carbohydrate. At autopsy large tumor masses were present in liver and spleen. The pancreas was within normal limits and presented no outstanding pathology.

[1] Cabot: Med. Clin. North America, 1928, **11**, 863.

SECTION XII.

SURGERY AND DIABETES.

1. **Incidence.**—The incidence of surgery among diabetics is considerable and is steadily increasing. In the year 1923 at the Deaconess Hospital there were 69 operations or 14 per cent of the diabetic admissions, the same percentage reported by Fitz in 1922 for his compilation of surgical diabetics at the Massachusetts General Hospital. In 1925 the number had risen to 97 or 17 per cent and during the first six months of 1926 to 81 or 24 per cent. On October 10, 1927, the Staff had 25 surgical diabetics in the hospital under their combined care. The surgical cases have become so numerous and their ailments so vital that they usurp the beds. Consequently we have been compelled to shorten the stay of medical diabetics to a week and in that brief period of time to teach them how to live for the rest of their lives.

During three and a half years 322 operations were performed upon 1968 of my patients at the hospital. But these figures only partially show the incidence, because (1) there were 99 operations upon these patients during the same interval at other hospitals, (2) the patients had undergone 192 notable operations previously and, (3) there still existed 281 ailments susceptible of surgical treatment. It can be said, therefore, that every other diabetic is a surgical diabetic before he dies.

2. **Ages of Surgical Diabetics.**—Surgical diabetics fall into three age groups. About one-third (106) of the number are sixty-one or more years of age, another third (101) are between fifty-one and sixty years of age, and the remaining group, which is the largest (114) are under fifty-one years of age. It is this group of younger diabetics, the diabetics under fifty-one years of age, which is growing in numbers and the older surgical group which is lessening. The youngest group is growing because these patients now live so much longer compared with previously that there are more of them and secondly there is a greater opportunity for surgery, because improved medical methods make operations of election safe. The oldest surgical group is diminishing in numbers and should decrease still more, because preventive measures are converting what formerly was major surgery

into minor surgery or no surgery at all. In this fashion the doctors' better medical tillage of the diabetic soil is opening up for the surgeons more fertile surgical fields.

3. **The Surgical Diabetic a Serious Diabetic.**—The surgical diabetic is the serious diabetic, the diabetic who dies. The diabetic mortality for my surgical cases at the Deaconess Hospital for 1923 to 1926, August 1, was 11.5 per cent; the medical mortality during the same period was 1.7 per cent. (See Table 271.)

TABLE 271.—MEDICAL AND SURGICAL MORTALITIES IN DIABETES. AUTHOR'S PATIENTS AT NEW ENGLAND DEACONESS HOSPITAL, 1923–1926, AUGUST 1.

Year.	Total admissions.	Total operations.	Percentage of operations to diabetic admissions.	Deaths,		
				Medical.	Surgical.	Total.
1923	479	69	14	4	4	8
1924	575	75	13	10	11	21
1925	571	97	17	8	10	18
To August 1, 1926	343	81	24	6	12	18
Total	1968	322	20	28	37	65

In Naunyn's time few deaths were due to surgery. Thus based upon his autopsies there were only 12 per cent diagnosed as such, in contrast to 71 per cent for the autopsies at the Deaconess as reported by Root and Warren.[1]

The surgical diabetic requires six times as much attention as the medical diabetic, because he is six times as likely to die. Fairness to the surgeon and most of all to the patient demands that he be treated in the medical wards where he can obtain the detailed and intimate treatment which the severest medical diabetics receive. A surgeon unfamiliar with insulin should not undertake alone the care of a diabetic. Cases of diabetes in coma are visited by a physician every hour; surgical cases need almost as much medical care. For this reason it is essential that surgical cases be grouped with medical cases. Border-line wards for medical and surgical diabetics should exist in every hospital. This will save time for the nurse, doctor, and surgeon, save money for the hospital and, not the least, will save the life of the patient. In such wards surgeon and physician should meet on equal terms and appropriate facilities should be afforded for each in his care of the patient, as well as for the nursing of the patients. For a hospital to scatter its surgical diabetics hit or miss among its various surgical wards shows old fashioned

[1] Root and Warren: Boston Med. and Surg. Jour., 1927, **196**, 864.

administrative methods. Seldom is the surgeon to blame for the surgical mortality; most often he is not to blame at all, because the case comes to him too late. As a rule, the responsibility is medical and is more often remote than immediate and by that I mean that preventive measures have not been instilled early enough into the minds of the patients.

4. **Variety of Operations.**—Amputations of an extremity or part of an extremity constituted nearly one-fourth (88) of the 322 operations upon my diabetics at the Deaconess Hospital between January, 1923 and July, 1926. (See Table 272.)

Next in frequency are superficial and deep septic processes (56), caused by infections gaining entrance through the skin, such as abscesses and ulcers (46) and carbuncles (10). These two groups, amputations and infections through the skin, make up nearly one-half of the total operations. Fortunately these, the amputations and the infections, are conditions which are largely preventable and it therefore becomes the duty of all medical men to warn their diabetic patients of the dangers to which they are exposed and thus

TABLE 272.—CLASSIFICATIONS OF 322 OPERATIONS UPON DIABETICS, JANUARY 1, 1923, TO AUGUST 1, 1926.

	Total.	Fatal.[1]	Mortality, per cent.
Preventable Surgery.			
Amputations:			
Legs	56	15	27
Arms	2	1	50
Toes or fingers	31	1	3
Infections through the skin:			
Carbuncles	10	4	40
Ulcers, abscesses, etc.	46	2	4
Non-preventable and Reparative Surgery.			
Diseases of thyroid	41	3	7
Tonsillectomies	33	0	0
Laparotomies:			
Gastro-intestinal:			
Appendectomies	9	2	22
Others	15	4[2]	27
Gall stones and disease of gall-bladder	13	0	0
Hysterectomies	8	1	13
Genito-urinary	19	2	11
Pelvi-rectal	14	0	0
Cataracts	6	0	0
Mastoid and antra	5	1	20
Miscellaneous	14	1	7

save needless suffering and death. The mortality from this lamentable half of diabetic surgery is 14.6 per cent and constitutes two-thirds of the total surgical mortality. This is in sharp contrast to a mortality of 6.8 per cent for the remaining half of the cases.

[1] Within one month after operation.

[2] The 4 deaths followed operations for carcinoma of pancreas (2), liver (1) and sigmoid (1).

Non-preventable surgical conditions and reparative surgery are responsible for the other half of the surgical cases. In this second main division, operations upon the thyroid gland (41 cases) and tonsillectomies (33 cases) are conspicuous. Three of the thyroid operations resulted fatally, but none of the tonsillectomies. Before insulin, tonsils were removed from diabetics with the greatest rarity and then only when forced by necessity. Diseases of the genito-urinary tract (19 cases) are frequently associated with diabetics, more as an accompaniment of advancing years than as complications. The causes for operation range from nephrectomies for calculi and pyonephrosis to the removal of the prostate. There was but a single operation for phimosis.

Laparotomies (45 cases) of a varied nature were undertaken. In the group, gastro-intestinal lesions were frequent (24 cases) and of these 9 were appendectomies; there were 13 operations upon the gall-bladder; 8 hysterectomies complete the group. For these laparotomies the mortality was 15.5 per cent, a figure largely explained by the cause for the operation. The remaining surgical procedures consisted of those about the pelvis and rectum (14 cases), many of which were of a minor nature. Operations upon the eye (6) consisted of removal of cataracts and there were no fatalities. There were also operations (5) upon the mastoid or antra and finally a group (14) of most miscellaneous character, ranging in severity from the excision of an infected wen to amputation of the breast for carcinoma.

Dental extractions have not been classed as surgical operations, although in some instances they might well be so enumerated. This should be considered a compliment to the dentists rather than otherwise. The extractions in many instances were extensive and were they not performed with unusual dexterity, judgment and proper medical supervision they might easily have entailed disastrous results, as happened years ago. The extractions have been numerous and average more than a tooth per patient. No fatalities occurred following removal of teeth, tonsils or after operations upon the eye.

5. **Deaths.**—One-half of the surgical deaths in the past were due to septicemia and for this I am thankful. The prevention of septicemia is possible, but the prevention of cancer and arteriosclerosis is not so easy. Ten of the 17 deaths following amputation of an extremity were due to septicemia which was present before the amputation took place. In retrospect it may be said that a few years ago our hope for a better future for medical diabetics lay in the fact that most of the deaths were then due to coma and coma was considered preventable. That hope has been fulfilled. So now it is with surgery and septicemia. I expect it will not be long

TABLE 273.—CAUSES OF DEATH OF SURGICAL DIABETES.

322 Operations—37 Deaths.

Cause of death.	No. cases.
Septicemia	15
Gangrene	1
Gas bacillus infection of stump	1
Carbuncle	3
General peritonitis	1
Appendicitis	2
Meningitis (streptococcus)	1
Pneumonia	1
Cancer	4
(*a*) Pancreas	2
(*b*) Liver	1
(*c*) Sigmoid	1
Thyroid toxemia	2
Cerebral hemorrhage	1
Chronic nephritis	1
Coronary occlusion	1
Pulmonary embolism	1
Syncope under anesthesia	1
Shock	1

before better education of the patient in preventive measures, earlier treatment and better methods will largely avert it.

From everywhere come reports of a lowered surgical diabetic mortality. Weeden[1] records 2 deaths in 12 operations since the advent of insulin as compared with 59 deaths in 160 operations before insulin, Lemann[2] 43 operations with 1 postoperative death, Mason[3] reports 18 deaths in 101 diabetic operations, John[4] 7 deaths in 35 cases, Bauman[5] 15 deaths in 56 operations for gangrene, carbuncle, and cellulitis, Foster[6] 12 deaths in 103 operations, Coller and Marsh,[7] with an excellent discussion of the conditions of the feet, describe 16 deaths in 65 cases, and Eliason and Wright[8] 23 deaths in 55 instances of gangrene. Finally Judd, Wilder and Adams[9] have published 667 operations upon diabetics of which 304 were major operations and among these the mortality was 3 per cent. They had very few cases of gangrene (15) and no carbuncles which partly explain their few fatalities. Up to January 1, 1917, there were 27 of my cases who were operated upon with 5 deaths, a mortality of 18 per cent, and between April 1, 1919 and 1923 there were 61 operations with a mortality of 9 per cent and of 322 operations since that date the mortality has been 11.5 per cent.

[1] Weeden: Jour. Am. Med. Assn., 1924, **82**, 1165.
[2] Lemann: New Orleans Med. and Surg. Jour., 1926, **79**, 203.
[3] Mason: Canadian Med. Assn. Jour., 1925, **15**, 601.
[4] John: Arch. Int. Med., 1927, **39**, 87.
[5] Bauman: Surg., Gynec. and Obst., 1925, **41**, 272.
[6] Foster: Jour. Am. Med. Assn., 1925, **84**, 572.
[7] Coller and Marsh: Jour. Am. Med. Assn., 1925, **85**, 168.
[8] Eliason and Wright: Surg., Gynec. and Obst., 1926, **42**, 753.
[9] Judd, Wilder and Adams: Jour. Am. Med. Assn., 1926, **86**, 1107.

The elements which hinder or promote success in diabetic surgery can be easily summarized. Of the former there were three, but the first two of these, acidosis with coma and a liability to infection, are now largely eliminated. Coma has become only an accident. Old time surgery courted it (1) by the administration of chloroform and ether only too frequently by untrained hands; (2) by the sudden restriction of carbohydrate prior to the operation with the desire to lower the glycosuria; (3) by the attempt to relieve the patient's hunger thus caused with an excess of protein and fat, wholly unmindful that in so doing acidosis was favored; (4) by large doses of sodium bicarbonate which upset the digestion, making it still more difficult for the postoperative patient to take liquids or food freely, besides possibly releasing latent acid bodies whose excretion would irritate the kidneys. As for the liability to infections of diabetic tissues, it is a question as to whether that has ever been much of a factor. Coma can be avoided by the administration of a diet of 50 to 100 grams of carbohydrate with the simultaneous use in three to eight hour intervals of insulin sufficient to enable the patient to utilize it. A certain liability to infections may exist, but it is largely prevented by cleanliness. Campbell of Toronto says "In Macleod's laboratory it has been noted that animals receiving no insulin after pancreatectomy often suppurate, while those given adequate food and insulin, even though continuously hyperglycemic, heal by first intention." *The danger of a clean wound in a diabetic becoming infected is slight.* Think of the thousands of intravenous punctures practised by medical men upon diabetics without the sign of an infection, the thousands of injections of insulin by unskilled patients, the 13 subcutaneous injections of salt solution given to Case No. 1650 by a nurse at the Corey Hill Hospital in the space of three weeks. Just as formerly tuberculosis claimed many diabetics but, with the lessening opportunity to contract it, has become infrequent, for much the same reason sepsis subsequent to an operation upon a diabetic is rare. Given an infection, it is freely granted that the disease becomes worse; prevent the infection and healing is prompt. In so close a relation do both stand to each other that a loss of tolerance for carbohydrate may be recorded on the diabetic chart before the wound discloses a retrograde course. Allen did not find sepsis a frequent condition in his operations upon animals, and through experimental work he showed that the presence of an excess of sugar in the blood was not deleterious. The skin alone of the tissues appears to be overloaded with sugar and so often patients recover when large quantities of sugar are present in the blood that it is difficult to believe that hyperglycemia of itself is much of a factor predisposing to infection. One must differentiate closely. It is the infection which makes the diabetic worse and so favors

hyperglycemia and acidosis. Control the infection and then the diabetes and the course of the patient become smooth.

The third handicap of the diabetic, old age with attendant arteriosclerosis and consequent slow healing of old tissues, is still earnest and a real handicap to recovery. Under the topic grangrene the methods which may be employed to overcome this obstacle will be described. Indeed the age of the diabetic is largely accountable for the poor reputation he has acquired at the surgeon's hands. Gangrene, carbuncles, and gall stones, the common diabetic surgical ailments, are conditions which attach the elderly. One-half of the surgical cases in my series, formerly 63 per cent, were above the age of fifty years at the time of operation, and the average age of the gangrene cases was sixty-two years. Operate upon a series of non-diabetics of similar age and for similar conditions and the mortality likewise would be high. The prevalence of damaged hearts, arteries, and kidneys among the patients is to be blamed for the serious prognosis equally with the diabetes. Seventy-one per cent of the fatal cases had arteriosclerosis and in 41 per cent it was the cause of death. I almost dread to tell my surgical confreres that coronary disease exists in essentially all the patients with gall stones or gangrene for whom I beg their aid. Recognition of these handicaps of age, however, is essential and should lead to their appropriate preoperative and postoperative treatment and contribute to a better prognosis. Everyone knows the risk run by the old man with a broken hip who is forced into bed. The diabetic with a gangrenous toe runs still more risk, because in addition he needs exercise to help burn up his sugar. Deprive him of it and his disease gets worse. Therefore, teach him a set of movements to perform whenever the clock strikes the hour. Show him how to protect his lungs by long breaths and by turning over in bed. In short, keep him busy getting well. These patients require exercise just as much as do the patients in a fracture ward.[1] A masseur may be of great help to an elderly diabetic, especially if he combines massage with resistant motions, but self massage is cheaper. Too often the pathetically low level to which these poor old men and women have been reduced is quite forgotten, simply because the laboratory reports a positive diacetic acid reaction or a trace of sugar in the urine. Be careful! Do not treat the laboratory test instead of the patient!

The factors which favor surgical success in diabetes are first of all an early diagnosis and an early decision to operate. If surgical delays are dangerous under ordinary circumstances, in diabetes they are disastrous. An infection makes a diabetic worse; undernutrition and lack of exercise lower resistance. The principle must be recognized that the surgical necessity determines the day (or

[1] L. B. Morrison frequently calls my attention to the radiolucency of the bones due to lack of exercise.

night) and hour of operation. To the surgical condition the medical treatment must conform. Today medical treatment is labile and can be adapted to the condition in hand, and the convalescence from the surgical complication utilized to free the patient from sugar and acidosis. The surgical removal of the source of infection will promote ultimate recovery far more than the reduction of a few grams of sugar in the urine. The realization of this changed attitude toward the surgical diabetic leads to an appreciation of the advance which has taken place in the medical treatment of diabetes. The patient should be treated for the operation rather than for the diabetes. Get him successfully through the operation first, and then if you like, treat him for the diabetes the rest of his life. If you treat him first for the diabetes and second for the operation, the duration of that case of diabetes is apt to be brief. Obviously for patients whose ailments are not urgent one would secure a sugar-free urine and a normal blood sugar before operation. Yet even in these cases if they are arteriosclerotic and of long duration one must be cautious not to lower the blood sugar rapidly or as low as in the younger diabetics.

The *second factor* which favors success in diabetic surgery is the *adjustment of the diet to the surgical requirements*. If there is no need for haste, any of the well-recognized systems recommended to get the patient free from sugar and acidosis will suffice. All of these diets agree in slightly under- rather than in slightly overnourishing the patient. Such methods are conducive to the bringing of the patient to the operating table with his highest tolerance for carbohydrate, and this means his greatest safeguard against acidosis. It is a great advantage to store carbohydrate in the body and particularly to fill the liver with glycogen before an operation. If the liver is stored with glycogen, or even partially stored, less harm results from the anesthetic and the almost inevitable postoperative curtailment of nourishment. The storage of glycogen in the liver under the influence of diet and insulin makes the severest diabetic temporarily mild. Not only is the liver protected thereby, but carbohydrate is available after the operation which is just the time when the patient needs it most. Therefore, feed the patient up to within three hours before the operation begins, and never fast a patient before a surgical operation. He will most likely fast altogether too much afterward. As a corollary to the above advice, begin the administration of food as soon as possible after operating.

The forcible introduction of *liquids* into the patient after a surgical operation is a familiar sight in any hospital, but it is wiser to anticipate the patient's need by liberally supplying him with liquids the day beforehand. These should include broths on account of the salts therein contained, coffee, tea, water, and if necessary, salt

solution or tap water by rectum. It is a safe, routine procedure to inject salt solution subcutaneously before the patient leaves the operating table. Especially is this desirable if ether is used, because ether diminishes the excretion of urine, nitrogen, and glucose, and what is still more important diminishes the excretion of acetone bodies. There are few diabetics who do not need an intravenous or subcutaneous injection of salt solution at the time of an operation, and seldom one who is safe without salt solution by rectum. If you want water to remain in the body, give isotonic solution, such as Ringer's solution or salt solution; if you want it for excretion, give as tap water.[1]

Of what shall the *diet for surgical diabetic patients before and after operation* consist? If the case is one which is to be prepared leisurely for operation, no special change need be made in the regular program to free the urine from sugar and acid, save that the food should be prepared in simpler form. Coarse diabetic foods should be omitted. If the situation is acute, and but a day or a few hours are available, sudden restriction of carbohydrate, particularly when dealing with severe diabetes or elderly patients, must be avoided, and great care taken not to upset the stomach. The simplest foods are, therefore, the best. Oatmeal gruel made with water is excellent, orange juice with whites of eggs is a good alternative, or an ounce of toast with tea but without milk. It will be difficult for the patient to take too much of either. These are first-rate preparations to employ as a routine in the few hours preceding any operation. After operation guard against hyperglycemia with its attendant acidosis or hypoglycemia due to lack of food or excess of insulin. For the first twenty-four hours after operation oatmeal water gruel, ginger ale, thin milk are allowed *ad libitum*. The carbohydrate should be taken three hours after operation, as before operation. The patient should receive this by mouth, rectum or vein with insulin if necessary to insure its utilization.

Eventually most any surgical diabetic either with or without insulin can adopt a diet about as follows:

Breakfast: Grape fruit or orange, oatmeal, egg, coffee and cream.

Dinner: Meat or fish in small portion, 5 and 10 per cent vegetables in liberal or moderate quantities, a medium sized potato or 1 ounce (1 slice) of bread, and an orange or grape fruit, half banana or half a portion of ice cream (not water ice).

Supper: A meal similar to that at breakfast or less than that at noon. When the patient begins to be active in bed or out, cream can be increased to one-half pint, butter and bacon added.

If the food is not forced during convalescence, and indeed it is one of the advantages of convalescence that it cannot be forced, and if

[1] Starkenstein: Arch. f. exp. Path. u. Pharm., 1922, **92**, 339.

calories are kept at 15 to 20 per kilogram body weight, most any middle-aged adult diabetic will become sugar-free before he recovers from his surgical lesion. In fact, I look upon the surgeon as one of the greatest helps in medical treatment, and a surgical operation is ofttimes a blessing rather than a curse. Case No. 177 never once became sugar-free in the fourteen years I treated him until R. C. Cochrane kept him out of mischief by cutting off his leg. (Table 274.) The course of this patient was like that of many others in that the sugar in the urine became steadily less. There was, however, a temporary increase of glycosuria, though without acidosis, after the operation, but this fleeting increase was expected and likewise disregarded. A transient increase of sugar in the urine after an operation is a regular occurrence. It is important to remember this or the patient will be restricted in his diet needlessly. Within a few days the sugar usually disappears of itself. Aside from his gangrene, this patient had gall stones, angina pectoris, retinal hemorrhages, and had used morphine for years. The removal of a gangrenous leg is a boon to the patient apart from its effect upon the diabetes. In May, 1924, he developed prostatic obstruction, but as yet operation has not become obligatory. The renal function test of Case No. 2173 rose from 12 per cent to 50 per cent during the seven months after the operation.

The *diet after operation* should certainly contain the minimum of $\frac{2}{3}$ of a gram of protein per kilogram body weight and more often a full gram of protein per kilogram body weight. Clark's[1] experiments upon wound-healing in dogs showed that with protein-fed dogs the length of the quiescent period was zero, but might reach six days in the fat-fed animals. Consequently, protein feeding shortened the date of final healing by five days.

When dealing with infections, a rigorous attempt should not be made to get the patient sugar-free either before or after operation. That is seldom possible and, even if attained, is secured at too great a loss of body tissue or with too heroic doses of insulin. I cannot subscribe to Carrasco's criticism of this view although with more insulin available I use more now than formerly. Spencer[2] as long ago as 1892, urged that it was useless to attempt the reduction of the sugar by drugs and diet when a severe inflammatory lesion was present. It is better treatment to remove or give vent to the infection and then the tolerance for carbohydrate will improve. It is painful to look over the protocols of cases suffering from infections, in years gone by, who were terribly undernourished with the purpose to make them sugar-free. (See Case No. 513 p. 782.)

[1] Clark: Johns Hopkins Hosp. Bull., 1919, **30**, 117.
[2] Spencer: British Med. Jour., 1892, i., 1305.

TABLE 274.—UTILIZATION OF PERIOD OF CONVALESCENCE TO TREAT THE DIABETES.

(Case No. 177. Onset of diabetes at forty-four years. Operation for gangrene at sixty-six years, by R. C. Cochrane.)

Date.	Vol. cc.	Di-acetic acid.	Sugar in urine			Diet in grams			Blood sugar, per cent.
			Reduction, per cent.	Total grams.	Carbohydrate.	Protein.	Fat.	Calories.	
June, 1922									
4	Ssp.	sl. +	1.9						
4– 5	500	0	3.8	19	63	25	0	352	
5– 6	1200	0	1.6	19	102	58	0	640	0 23
6– 7	..	0	2.2	..	51	30	14	450	
	Amputation.			Spinal anesthesia.					
7– 8	1800+	0	4.0	72	57	38	30	650	
8– 9	2125+	0	1.8	38	42	36	29	573	
9–10	2800+	0	0.3	8	42	36	19	483	
10–11	2800	0	0.1	3	42	36	29	573	
11–12	3250	0	0	0	42	42	35	651	
12–13	2500	0	0.1	3	53	45	42	770	
13–14	2050	0	0.2	4	44	44	47	775	
14–15	1900	0	tr.	..	44	46	52	828	
15–16	2600	0	tr.	..	44	46	60	900	0.20
16–17	1800	0	0	0	44	46	69	981	
17–18	1260	0	tr.	0	44	46	78	1062	
18–19	1200	0	0.1	1	44	48	82	1106	
19–20	1750	0	0	0	44	52	92	1208	
23–24	2150	0	0	0	52	53	90	1230	0.16
July									
30– 1	1425	0	0	0	65	56	97	1357	0.17
3– 4	2200	0	0	0	65	56	97	1357	
4– 5	1200	..	..	..	65	56	97	1357	0.15
January, 1928 Living.									

If *acidosis* exists either *before or after operation* a vigorous attack upon it will already have been made by the inauguration of the diet above outlined and the use of insulin about to be described. (See also p. 660.)

6. **Insulin.**—If insulin has been used regularly by the patient, give the same total number of units in twenty-four hours, at the time of operation, but divide into smaller and more frequent doses, irrespective of meals. If insulin has not been employed, give it when two successive specimens contain sugar and omit it when two successive specimens are sugar-free. Avoid worry by giving small doses every three hours or four hours more rarely two or eight hours, rather than larger doses infrequently, until acquainted with the

tolerance of the patient. During convalescence when the urine is sugar-free, often test the need for insulin by omitting or reducing a single dose, usually the noon dose first, then the evening dose. It is as important to have a blood-sugar test in the late forenoon as before breakfast for a guide to insulin administration.

7. **Anesthesia.**—The *anesthetic* including its method of application is the fourth agent which contributes to the fortunate outcome of a surgical operation upon a diabetic. With the aid of insulin practically any type of anesthesia can be adopted, but none the less one should remember the effect of anesthetics *per se* and utilize this knowledge so painfully acquired before the discovery of insulin. Every effort should be made to shorten the period of anesthesia, irrespective of the type of anesthetic or of the availability of the use of insulin. If a preliminary injection of morphine is given, this should be small or else the respiration may be depressed too much. Avoid apprehension and excitement on the part of the patient. It is just as valuable to have an anesthetist accustomed to diabetics, as it is in thyroid operations to have both surgeon and anesthetist accustomed to their peculiarities. Details count and in diabetic surgery it is right to be meticulous.

(*a*) **Chloroform.**—All agree that chloroform is harmful to the patient in diabetic surgery. Its use is accompanied by hyperglycemia.[1] Either directly or indirectly through its interference with the metabolism of carbohydrate it must alter the fat metabolism, because after chloroform acidosis resulting in coma is said to be common. Blum points out that β-oxybutyric acid injected under the skin of a dog is burned without the formation of diacetic acid and acetone, but if the same experiment is repeated upon the same animal under chloroform narcosis, one will find a very definite acetonuria. This does not take place with ether narcosis. Chloroform is employed so rarely in this locality that I have had almost no experience with it. With little Buddy H., Case No. 2084, seven years of age, 37 drops worked admirably when several abscesses were incised and for such short operative procedures I am surprised it is not employed more.

(*b*) **Ether.**—Ether administered to phlorizinized dogs leads immediately to hyperglycemia, according to Sansum and Woodyatt, and they explain this as due to the transformation of liver glycogen to sugar under the stimulus of asphyxia. During etherization the formation of glycogen is said to cease. Bloor[2] has shown that ether given to normal dogs results in a marked rise, 40 to 100 per cent, in the concentration of the blood-fat, and this has been explained on the basis of an increased solubility in the blood-ether

[1] Blum: Paris Méd., 1919, **9**, 341.
[2] Bloor: Jour. Biol. Chem., 1914, **19**, 1.

mixture of fatty substances in the tissues. Perhaps interference with the carbohydrate metabolism might be as important a factor. As with dogs, ether given to normal individuals gives rise to hyperglycemia and acidosis and, what is most serious to the diabetic, temporarily diminishes the excretion of urine, nitrogen, glucose, and acetone bodies. Van Slyke, Austin, and Cullen[1] observed a true acidosis in all of their experiments with ether anesthesia with increase of the hydrogen-ion concentration of the blood and fall of the alkaline reserve, due either to introduction of acid into the blood or to withdrawal of base from it. Katsch and von Friedrich[2] found that ether was a stimulus to the external secretion of the pancreas. Might not the internal secretion be lowered in consequence?

The harmful effects of ether upon the metabolism of the diabetic are by no means confined to the observations reported above. The nausea which so frequently ensues after the administration of ether is of even greater importance, because it interferes for many hours with the intake of food and even of liquids. Furthermore, preceding ether the patient goes longer without food than preceding gas-oxygen, ethylene, spinal anesthesia or novocaine, and when this period of fasting is combined with the longer fasting interval after the anesthetic, the period without food becomes considerable. This period of fasting may be more deterimental to the diabetic than the drug itself.

The explanation why the Mayo Clinic has been so fortunate in the use of ether with their diabetic patients is readily seen. Fitz found in two series of cases, each of 100 abdominal operations, the first in the Mayo Clinic and the second in a control group, that not only was 36 per cent less ether given at the Mayo Clinic, but the period of anesthesia was 53 per cent shorter.

Yet a case not well adapted for ether may do well. Case No. 2311, a man, aged fifty-eight years, had marked osteoarthritis and an attempt at spinal anesthesia in the year 1922 failed; subsequently gas-oxygen proved to be inefficient. Ether was at length employed and, despite poor kidneys, a phenolsulphonephthalein excretion 19 per cent, with renal fixation between 1006 and 1010, and marked diabetes, a successful result was obtained. Ether has many times been used with success, but it is often dangerous. The statement will bear repetition that ether anesthesia is a burden which a light case of diabetes may easily bear, which may change a moderate to a severe case, and to a severe case prove fatal, yet with the help of insulin the harmful effects may be averted.

[1] Van Slyke, Austin, and Cullen: Jour. Biol. Chem., 1922, **53**, 277.
[2] Katsch and von Friedrich: Klin. Wchnschr., 1922, **1**, 112.

(*c*) **Gas-oxygen.** — **Nitrous Oxide.** — Both of these methods of anesthesia have worked excellently with various patients; gas-oxygen anesthesia has repeatedly been employed in long operations. Occasionally the gas-oxygen has been supplemented by a few cubic centimeters of ether, but there was an effort in the six years prior to the discovery of insulin not to use ether at all. On two occasions gas-oxygen was ineffective. In the first instance this was probably due to the previous administration of morphine to an old man, Case No. 855, which markedly depressed the respiration, so that it was so superficial he was anesthetized with difficulty. Recourse was then taken to ether, but he survived only a few days after the operation for purulent appendicitis. In the other instance it was resorted to when spinal anesthesia was impossible on account of marked hypertrophic osteoarthritis. The outcome with this patient, Case No. 2311, was more favorable and, as has been related in the preceding paragraph, no untoward effects were noted.

Illustrations of the harmful effects of ether in Case No. 348, Table 275, and the comparatively harmless effect of gas-oxygen in a second operation as compared with the first under ether in Case No. 697 can be seen in Table 276.

Case No. 348, male; age at onset of diabetes forty-two years; operation for removal of the prostate at forty-nine years of age, seven years later, in 1915, when light etherization was employed. A positive carbohydrate balance of 20 grams before the operation changed to a negative carbohydrate balance of 33 grams after the operation, and the acidosis became extreme. The patient fortunately made an uninterrupted recovery and continued well and active. (See Table 275.)

TABLE 275.—CASE NO. 348. MODERATELY SEVERE DIABETES. REMOVAL OF PROSTATE IN 1915. ETHER WITH SUBSEQUENT ACIDOSIS.

	Urine.			Diet.				
Date.	Diacetic acid.	NH_3, gms.	Total sugar, gms.	Carbohydrate, gms.	Protein, gms.	Fat, gms.	Carbohydrate balance, gms.	Sodium bicarbonate, gms.
1910								
July 21	0	..	160					
1915								
July 9	0	..	0	45	..	..	+45	
11–12	0	..	0	20	30	50	+20	0
July 11, operation—removal of prostate; Dr. A. L. Chute; anesthetic, ether.								
July 12–13	++	..	37	0	0	0	−37	0
13–14	++	..	33	0	0	0	−33	0
14–15	+++	3.3	41	0	0	0	−41	0
15–16	+++	3.2	36	5	0	0	−31	8
Aug. 1– 2	0		0					
1923								
Jan. 27	0	..	0	70	84	144	+70	0
1925								
October	Death—chronic myocarditis							

Case No. 697, male; age at onset of diabetes forty-nine years; age at operation for gall stones, fifty-five years; anesthetic, ether. The tolerance on the day before the operation was approximately 105 grams; on the day of the operation the quantity of sugar in the urine was 35 grams, and carbohydrate in the diet 8 grams, and a minus balance continued for three days more. The patient completely recovered and remained well and active until the end of 1916, when he had a recurrence of symptoms. A gall stone was then removed from the common duct by D. F. Jones. Anesthesia, gas and oxygen and 45 cc. ether administered by Freeman Allen. Acidosis was negligible and the positive carbohydrate balance maintained. This patient is now enjoying the beneficial effects of insulin.

TABLE 276.—CASE NO. 697. AGE FIFTY-FIVE YEARS. MILD DIABETES. GALL STONES.

Date.	Diacetic acid.	Urine, total sugar, gms.	Carbohydrate in diet, gms.	Carbohydrate balance, gms.	Sodium bicarbonate, gms.
1914					
Feb. 2	0	(0.8%)			
17–18	0	0	105	+105	8
18–19	+	35	8	− 27	12
February 18, operation for gall stones; Dr. D. F. Jones; **anesthesia ether.**					
Feb. 19–20	+++	105	60	− 45	18
20–21	+++	110	34	− 75	6
21–22	++	104	85	− 20	8
22–23	Sl. +	71	110	+ 40	0
23–24	0	55	175	+120	0
24–25	0	19	110	+ 90	0
25–26	0	6	120	+115	0
26–27	0	11	120	+110	0
27–28	0	0	120	+120	0
Mar. 5- 6	0	0	95	+ 95	0
Return with symptoms of obstruction of common duct.					
1917					
Mar. 15–16	0	4	35	+ 31	0
16–17	Sl. +	1	50	+ 49	0
Mar. 17, operation for removal of gall stone from common duct; Dr. D. F. Jones; **anesthesia, gas and oxygen,** with 45 cc. ether					
Mar. 17–18	+	15	20	+ 5	0
18–19	0	43	41	− 2	0
19–20	0	25	41	+ 16	0
25–26	0	0	74	+ 74	0

1923

July 1. Taking insulin "the last three days, I have felt more like my own self than for the last *fifteen* years." Dr. Banting and Dr. Best, please note this quotation. 1928 finds the patient still comfortable.

An abscess in the upper lobe of the right lung was successfully drained by C. L. Scudder. The patient, Case No. 1239, first presented symptoms of diabetes in September, 1916, at the age

of forty-six years, and three months later the disease was diagnosed. During January, 1917, pulmonary symptoms developed and in February, when he first came under my observation, after consultation with his physician and F. T. Lord, it was decided to treat the diabetes actively and the abscess of the lung expectantly for three weeks, and then operate if the pulmonary condition did not improve. From Table 277 it will be seen that the acidosis (diacetic acid and ammonia) was severe, though this was not revealed by the CO_2 tension of the alveolar air or by the blood, possibly on account of the pulmonary complication. The acidosis was gradually, but not entirely, overcome. When it was seen that improvement of the condition of the lung did not take place, the patient was operated upon by Dr. C. L. Scudder under gas-oxygen anesthesia. A large abscess of the right upper lobe was evacuated after removal of portions of the fourth, fifth and sixth ribs. The cavity was large, receiving into its interior one large gauze sponge. Prior to the operation fat was decreased in the diet and the carbohydrate increased. The highest tolerance for carbohydrate reached in the three weeks prior to the operation was 19 grams, but it later rose to over 85 grams and the wound closed. Today such an operation and such a result would not appear as remarkable. The case is reported as an illustration of what could be done without insulin in 1917.

(*d*) **Ethylene.**—Ethylene has taken preference to ether or even gas-oxygen anesthesia these last few years. No accidents have thus far occurred at the Deaconess.

(*e*) **Spinal Anesthesia.**—In operations for amputation of gangrenous legs and for the removal of the prostate this method of anesthesia has been by far the most satisfactory at the New England Deaconess and Corey Hill Hospitals. No unfavorable incident has occurred in my experience during about ten years as a result of its employment. The case of Fitz[1] which developed acidosis following spinal anesthesia is probably to be explained, as he implies, by deficiency in carbohydrate, for he says that the acidosis went as quickly as it came when carbohydrate was added to the diet. I have heard of a case who developed a psychosis by being conscious throughout an amputation for gangrene, and it must be acknowledged that the mental shock of experiencing an operation cannot be disregarded. Fortunately, nothing of this sort has occurred with my patients. Paravertebral anesthesia has not been used with my cases.

(*f*) **Novocaine. — Cocaine.** — Local anesthesia frequently works admirably, and often shortens the period of employment of one of the group of anesthetics previously discussed. In a region where the blood supply is good, one need not hesitate in clean cases to use it.[2]

[1] Fitz: Loc. cit., p. 611.
[2] Cochrane: Boston Med. and Surg. Jour., 1926, **194**, 247.

TABLE 277.—CASE 1239.[1] ABSCESS OF LUNG. OPERATION WITHOUT INSULIN IN 1917.

Date, 1917.	Diacetic acid.	Ammonia, total gms.	Total sugar in urine.	Diet in grams.				Blood CO_2, mm. Hg.	Blood sugar, per cent.	Alveolar air CO_2, mm. Hg.
				Carbohydrate.	Protein.	Fat.	Alcohol.			
Feb. 17 Spec.	+++									
Feb. 17–18	+++	..	24	..	..	..	..	....	....	37
18–19	+++	..	31	45	8	0	0	....	0.17	
19–20	++	..	19	25	5	0	0			
20–21	++++	2.4	4	10	5	0	0			
21–22	++++	2.7	0	0	0	0	0	47.7	0.14	43 40
22–23	+++	2.8	2	10	5	0	0			
23–24	+++	2.6	2	0	24	0	0	....	....	37
24–25	++	..	3	0	60	0	15			
25–26	+++	2.1	8	0	92	12	30	....	....	38
26–27	++	1.9	7	0	68	24	15			
27–28	++	..	6	5	72	41	30			
28– 1	++	1.7	0	10	76	42	30			
Mar. 1– 2	++	1.4	2	15	79	61	30			
3– 4	++	..	0	10	79	81	30	54.9	0.14	
5– 6	++	1.3	0	10	81	88	30			
7– 8	++	1.2	3	20	84	82	30	....	....	36
8– 9	+	1.0	0	15	56	21	30			
11–12	+	1.0	0	19	66	43	30			
13–14	++	1.4	4	20	76	60	30	47.7	0.18	
16–17	v. sl. +	1.1	7	49	68	13	30	....	....	38
17–18	+	0.7	20	75	33	12	0	....	....	36
	Operation: Dr. C. L. Scudder. Anesthetic: Gas, and oxygen.									
18–19	+	1.0	23	50	58	26	30	....	....	36 37
19–20	+	1.5	25	44	58	49	30			
20–21	+	1.5	9	34	56	49	21			
21–22	+	1.3	7	34	56	59	30			
23–24	+	1.1	3	34	56	69	30			
26–27	+	1.0	2	29	63	85	30			
28–29	+	0.8	2	29	66	93	30			
30–31	+	..	0	37	69	88	30			
April 2– 3	0	..	0	40	74	93				
May			Sinus healed.							

Weight at entrance, 133 pounds; weight March 10, 132 pounds; no alkalis given.

Chloral, morphine and urethan always cause hyperglycemia which is not lessened by the addition of scopolamine.[2]

The avoidance of trauma is a *fifth element* in promoting surgical success. There are various kinds of trauma, not alone the trauma due to bungling surgery, the trauma due to unnecessary tourniquets, but trauma due to the employment of strong antiseptic solutions. Indeed, antisepsis often means trauma. One shudders at the free use of 1 to 1000 corrosive sublimate and of hydrogen peroxide. Undoubtedly asepsis instead of antisepsis has contributed a great deal to the success of modern diabetic surgery. Caution is always necessary to avoid trauma of the part, and I believe this has been the reason which led D. F. Jones to avoid drainage of the stump of an amputated extremity. How delicately wounds are treated now, compared even with the period just prior to the World War.

[1] This is about the last of my cases to receive alcohol. He renounced diet, despite his gain in tolerance and well-being, and died February 5, 1920. American diabetic patients do better without than with alcohol.

[2] Pi Suner and Carrasco Formiguera: Treballs de la Soc. de Biol., 1920–21, 8, 151.

Exercise for the surgical patients when in bed or convalescent in a chair is most helpful. Already on p. 579 its value has been mentioned in the routine treatment of the medical diabetic. At the Deaconess Hospital it has been equally valuable for the surgical diabetic. Bed gymnastics have been taught by Miss Munroe under the guidance of Dr. Mark Rogers.

Ultra-violet light has also been utilized with advantage both locally and generally. We have a room so arranged that 3 patients can be treated simultaneously, thus greatly reducing expense.

8. **Carbuncles.**—Today as formerly I dread a carbuncle in a diabetic more than any other surgical complication. Carbuncles are most serious. Until the last few years it seemed as if every other diabetic who developed a carbuncle succumbed to it. Later it was found that every third patient with a carbuncle died and the mortality appeared to be the same inside the hospital as in private practice. At present I suspect that about every fourth patient dies. No sooner than one has seen a few get along splendidly than he is shocked by one of these patients dying from septicemia. *Promptly treated carbuncles in the hospital do well; the neglected carbuncles raise the mortality.* In compiling statistics it is difficult to discriminate from the records whether to classify a case as a boil or a carbuncle. Many patients with small carbuncles undoubtedly recover both in and outside hospitals, but there are many insignificant appearing infections which develop into enormous carbuncles, and their hosts suffer for weeks, waste away and die with metastatic abscesses or septicemia instead, as formerly, of coma.

Carbuncles like coma and gangrene are more apt to appear in the fat than in the thin diabetic. Among 24 cases of carbuncles there were 19 whose weight was, on the average, 27 per cent above standard. Scrupulous cleanliness is essential in order to avoid them.

"The washed neck, like the watched pot, never boils." (Brigham.)

One of the most distressing instances of neglected carbuncle with subsequent multiple infections is that of Case No. 513. It is very easy to see today that the medical treatment which he received in 1915 was poor, though well intentioned. As an illustration of the ravages of a carbuncle and undernutrition the case was described in more detail in the third edition of this book. It was remarkable for: (1) An average loss of weight of 1.6 kilograms (3.5 pounds) daily for eleven days; (2) the excretion of between 31.6 and 37.8 grams nitrogen daily for the six days preceding death; (3) a dextrose-nitrogen ratio of 3.67 to 1, when nearly fasting; (4) a variation in the daily excretion of sodium chloride between the limits of 3.3 grams and 35.8 grams.

The onset of diabetes was in October, 1911, at the age of thirty-three years, and the patient first came under observation in July

1912. At that time, while at the hospital, he became free from acidosis, but not from sugar. Upon July 29, 1915, he tottered into the office with a carbuncle on the neck of *eleven* days duration. During the first two weeks in the hospital the change in the condition of the patient was favorable, but then deep-seated abscesses began to appear in various parts of the body. His condition was most pitiable, complicated as it was, with the pains of multiple carbuncles, extreme weakness, and septicemia due to an infection with staphylococcus aureus. Death occurred thirty-five days after entrance.

The weight of the patient July 30, was 62.7 kilogram and on August 6, 66.7 kilograms, although the total calories ingested by the patient during these seven days amounted to 2531, or 362 per day. Therefore this gain in weight must have been due to a retention of water. Explanation of this is partially afforded by the 288 grams of sodium bicarbonate given during these seven days. On August 5, the quantity of sodium bicarbonate had been reduced to 24 grams, later was reduced still more, until on August 10, it was entirely omitted. Yet during this period the weight continued to rise 0.8 kilogram (1¾ pounds). Edema was manifest, but not very marked, even when the weight was greatest. During the following nine days, August 11 to 19, no sodium bicarbonate was given, and the weight rose 0.3 kilogram more; but from this period on it steadily fell, and in eleven days August 19 to 30, dropped from 67.8 kilograms (149 pounds) to 51.8 kilograms (114 pounds) after death, a loss of 1.6 kilograms (3.5 pounds) per day.

The striking *loss of 1.6 kilograms (3.5 pounds) body weight daily for eleven days*, and the coincident increase in sugar and nitrogen excreted, suggest very important changes taking place in the metabolism. That this loss was connected with disintegration of body protein as well as of fat in addition to loss of fluid is undoubted, because, as earlier noted, the *nitrogen excretion was between 31.6 and 37.8 grams daily for six days before death, while for twenty-five days before death the caloric intake had been under 600 calories daily.*

The disease was not extremely severe in this patient when the carbuncle developed, but it was made severe by the infection and the diet. This is more apt to occur in association with carbuncles than with other varieties of infection. Fortunately with healing of the carbuncle, the tolerance returns. Thus Case No. 1129 entered the Deaconess with 7 per cent sugar and a bad carbuncle. With combined surgical and medical care he did well. He was discharged sugar-free with carbohydrate 119 grams, and insulin reduced from 45 units to 20 units. Case No. 5872 was a very mild diabetic, became severe with a carbuncle, but with treatment and healing again became mild.

All diabetics should be warned against becoming infected from others in the household. This may readily take place. The husband of Case No. 1245 had boils, his wife contracted carbuncles. The length of one of the crucial incisions in her back was 10 inches, yet she recovered under the care of R. C. Cochrane. No more extensive carbuncle has come under my supervision. This woman developed diabetes in 1912, at the age of forty-four years. She first came under my observation in 1917 and in 1922 contracted a carbuncle. When both the surgical and medical condition appeared stationary, she was given iletin (insulin, Lilly) which appeared to help materially in her recovery, though the decrease in acidosis and gain in tolerance in this patient took place coincidently with her acquiring a disgust for food, maintaining her insulin, and reducing her diet to 10 calories per kilogram body weight. The case is also notable because when insulin was eventually omitted, the patient continued to tolerate 65 grams of carbohydrate, which she was able to increase to 79 grams soon after her discharge from the hospital. She is still alive in August, 1927, weighs 95 kilograms, is sugar-free with carbohydrate 82 grams and insulin 20 units. She was also a gall stone diabetic.

Two other cases, 1 of my own and 1 of Christie's, deserve mention because they recovered with treatment quite different from what I suspect either he or I would employ today.

A case, apparently hopeless with carbuncle, can get well. Such was Case No. 817; age at onset of diabetes, seventy-two; first seen a year later, in January, 1915, ten days after the beginning of a carbuncle. Urine 2400 cc., 4.2 per cent of sugar. Examination showed two carbuncles on back of the neck, extensive ulceration on the right side of the neck and another area of ulceration in front. The physician described him as "drowsy by day and delirious by night." On account of his age and pitiable condition, it was debated by those in attendance as to whether it was justifiable even to attempt further medical or surgical treatment. Finally fasting was begun, with the result that he became sugar-free, and, except for a brief interval, remained so for two years. He died of pneumonia in January, 1926.

Christie's[1] case was severe, frequently showing high dextrose-nitrogen ratios while taking 12 grams sodium bicarbonate daily, was fasted eleven days and was finally discharged sugar-free upon a diet containing carbohydrate 60 grams, protein 55 grams, and fat 225 grams. No operation upon the carbuncle was performed.

The success which Dr. Cochrane[2] has had in the treatment of carbuncles of my patients can be attributed to prompt surgical

[1] Christie: Jour. Am. Med. Assn., 1917, **68**, 170.
[2] Cochrane: Boston Med. and Surg. Jour., 1926, **194**, 247.

intervention, which has consisted of a wide crucial incision extending through the zone of induration. The flaps thus formed have then been undercut, parallel to the skin, to the full extent of the crucial incisions. This establishes complete drainage of the infection and in almost no instance has it been necessary to enlarge the original openings. The wounds have then been packed with gauze, soaked in hot boracic acid solution, and a superficial dressing of the same character applied which has been changed every two hours. At the end of twenty-four hours the packs are removed and, hemorrhage having ceased, Dakin's solution or dichloramine-T dressings are begun. In his opinion the wounds clear up most rapidly under this routine.

Vaccines have not been employed with my patients in recent years.

9. **Gangrene.**—Gangrene was found by Morrison[1] to be a contributary cause of death in *23 per cent* of 775 fatal cases of diabetes in Boston during the years 1895 to 1913. It was present in 7 per cent of all diabetic patients admitted to the Peter Bent Brigham Hospital, according to Blotner and Fitz,[2] and in 3.5 per cent at the Montreal General Hospital.[3] It has occurred in 166 cases of 3.3 per cent of my series.

The season of the year influences the frequency of gangrene of the lower extremities. Ninety-five per cent of Beard's[4] cases in Minneapolis occurred in the winter months, and in the series of Blotner and Fitz, in Boston, it was also somewhat more frequent in the winter. At the Deaconess Hospital we see more cases in the winter, although upon August 4, 1926, there were 12 diabetics in the hospital with lesions of the legs. I think this simply due to the circulation in the feet being less good, their lessened sensitiveness to heat and cold, their liability to burns from hot-water bags, and other methods of artificial heating, and perhaps most of all to their being bathed less often. Climate is not an important factor although McLester in Alabama and Paullin in Georgia found gangrene uncommon;[5] Lemann[6] in New Orleans has shown that although rare in private practice it is as frequent in hospital practice as in Boston. Therefore, it is the social status of the patient and conditions incidental to cold weather rather than the climate, *per se*, which makes gangrene common.

A much better idea of the frequency of gangrene in my diabetic clientele and its importance is seen by the study of Table 278 in which its frequency according to the age of the patient is recorded.

[1] Morrison: Loc. cit., p. 125.
[2] Blotner and Fitz: Boston Med. and Surg. Jour., 1926, **194**, 1155.
[3] Rabinowitch: Canadian Med. Assn. Jour., 1927, **17**, 27.
[4] Beard: Minnesota Med., 1925, **8**, 436.
[5] See Blotner and Fitz: Loc. cit., p. 1155.
[6] Lemann: Jour. Am. Med. Assn., 1927, **89**, 659.

My records show that 1 in every 7 of my patients who developed diabetes above the age of seventy years also developed gangrene. The frequency was but half as great in those who acquired diabetes a decade earlier, between the ages of sixty-one and seventy years, though in that decade the occurrence was more frequent than in all preceding decades combined.

TABLE 278.—GANGRENE IN RELATION TO AGE AT ONSET OF DIABETES.[1]

Age at onset of diabetes.	1898–1923, No. cases.	1923–1927, No. cases.	Total.	Per cent.
21 to 30	4	1	5	3.0
31 to 50	26	26	52	31.3
51 to 60	23	29	52	31.3
61 to 70	23	22	45	27.1
71 to 80	8	4	12	7.2

More than twice as many males (102) as females (64) developed gangrene.

The average age at which the gangrene developed was sixty-two years. Arranged by decades, as is done in Table 279, the percentage distribution according to age at onset of gangrene is still more plainly shown. The youngest patient to develop gangrene was aged thirty-six years and the age of the oldest patient was eighty years.

TABLE 279.—AGE AT ONSET OF GANGRENE OF 166 DIABETIC PATIENTS.

Age at onset of gangrene.	1898–1923. No. cases.	1898–1923. Av. age at onset.	1923–1927. No. cases.	1923–1927. Av. age at onset.	Total. No. cases.	Total. Av. age at onset.
31 to 50	8	44	3	47	11	45.0
51 to 60	28	56	23	57	51	56.6
61 to 70	40	65	42	65	82	65.0
71 to 80	8	72	14	75	22	74.0

Gangrene does not occur as a cause of death in 49 fatal cases of diabetes reported by Murayama and Yamaguchi in Japan.

Gangrene was nearly twice as common among negro patients at the Charity Hospital in New Orleans as among the whites and about eight times as common as among Lemann's[2] private patients. T. C. Smith[3] of Louisville records the recovery from beginning gangrene of a colored boy three years old.

Gangrene is an accompaniment of arteriosclerosis and therefore develops in the arteriosclerotic era of life which, for the diabetic,

[1] In this series of 166 cases are included some cases who had, primarily, infections of the feet and who eventually required amputation either because of the severity of the infection or because of the development of gangrene.

[2] Lemann: Loc. cit., p. 659.

[3] Smith: Kentucky Med. Jour., 1927, **25**, 425.

is after he has had the disease five or more years. Of the 3 patients under the age of fifty years who developed gangrene since May, 1923, the average duration of the diabetes was six years. It is usually precipitated by trivial infections, resulting from trifling traumata, which have been neglected. Epidermophytosis between the toes in recent years has become a predisposing cause of increasing frequency. On account of the impaired circulation of the extremity, due to sclerosed and narrowed vessels, occasionally thrombosed, rarely occluded by emboli, osteomyelitis and necrosis of bone results. The average venous oxygen unsaturation of 34 diabetics was 59 per cent greater than in the average normal, according to Grant.[1] This may indicate a slow rate of blood flow and thus increase the susceptibility of diabetics to infection and gangrene, independently of arteriosclerosis.

Embolic gangrene is rare in diabetes. Kiefer, Brigham, and Wheeler[2] report sudden infarction of the left foot in a boy, aged nineteen years, who was in diabetic coma complicated by pneumonia and review 52 cases from the literature. I have seen another case of Dr. Brigham's in an obese woman who died of septicemia, Case No. 127, aged sixty-four years, developed gangrene from an embolus arising from an intracardiac thrombus. Case No. 6707 has just been discharged after amputation of the arm, because of gangrene resulting from an embolus in the axillary artery.

A pulsating dorsalis pedis artery is a favorable prognostic sign in a diabetic foot, but its absence is not a contraindication for reparative surgery. The painful foot is the foot with a poor circulation and poor prognosis according to McKittrick, who also adds that the hypoesthetic foot is often the one with a good circulation.

Gangrene seldom occurs in the young diabetics or in the early years of diabetes. Out of the first 84 cases there were but 8 who acquired gangrene in the first half century of life, and all but 1 of these cases were seen by me prior to 1917. By comparing Table 278 with Table 279, it will be found that none of the 5 patients whose diabetes began under the age of thirty years developed gangrene before thirty-one years of age, that of 57 cases whose diabetes began prior to the age of fifty years there were but 11 who developed gangrene before fifty-one years of age, but that when the sixth decade is reached the interval between onset of diabetes and onset of gangrene is short. In fact, upon studying my data in detail there were discovered but 22 cases out of 166 who developed gangrene during the first year of diabetes. With 38 the duration was between one and four years. Forty-four of the patients had the disease five to ten years, 49, eleven to twenty years, and there

[1] Grant: Arch. Int. Med., 1923, **32**, 764.
[2] Kiefer, Brigham, and Wheeler: Boston Med. and Surg. Jour., 1926, **194**, 191.

were 8 patients whose diabetes extended over twenty-one years. There were 5 whose durations were unknown. In one case, No. 1924, thirty years of diabetes elapsed between its onset at twenty-three years of age and the date he acquired gangrene. In this patient when the gangrene did develop it was of the fulminating type, of ten days' duration. He entered the hospital with a temperature of 102.4° F. He was nearly pulseless after the operation and died on the third day of uremia. The blood sugar rose from 0.27 per cent before to 0.55 per cent after the operation and the non-protein nitrogen similarly rose from 39.6 mg. to 61.8 mg. Advancing years of duration of diabetes, as well as advancing years of life are therefore effective in the production of gangrene, but the latter is of distinctly less importance. Another, Case No. 3866, had diabetes thirty-four years before he acquired gangrene. He died fifteen days after operation from streptococcus septicemia.

TABLE 280.—DURATION OF DIABETES PRECEDING GANGRENE.

Years of diabetes.	1898–1923 Number.	1923–1927 Number.	Total cases Number.	Per cent.
Under 1	13	9	22	13.3
1 to 3	6	9	15	9.0
3 to 4	5	3	8	4.8
4 to 5	5	10	15	9.0
5 to 10	24	20	44	26.5
11 to 20	23	26	49	29.6
21 to 30	3	4	7	4.2
31 to 35	0	1	1	0.6
Uncertain	5	0	5	3.0
Total	84	82	166	....

A Wassermann reaction was recorded for 109 of the cases and in 4, (3.8 per cent), was positive in contrast to 1.6 per cent of positive reactions for 1000 tests in my series. For 300 cases of diabetes over the age of fifty years, the reaction was also positive in 1.7 per cent. Therefore, a *positive Wassermann reaction or history of syphilis was only two times as common among those having gangrene as among 1000 cases of diabetes, or among 300 diabetics over fifty years of age.* Of the diabetics having syphilis, 10 per cent had gangrene. Of all the diabetics, 3.3 per cent had gangrene.

Neither Blotner and Fitz[1] nor Lemann[2] have found any support in their series of cases for syphilis as an important factor in the etiology of gangrene, but the statistics of Rabinowitch[3] confirm my conclusions and he furthermore cites a case in which the institution of antiluetic treatment was most useful. Therefore I shall con-

[1] Blotner and Fitz: Loc. cit. p. 1155.
[2] Lemann: Loc. cit., p. 659.
[3] Rabinowitch: Loc. cit., p. 27.

tinue to watch for the presence of syphilis in gangrene more zealously than in my other diabetics.

Alcoholism, sufficient to lead to delirium tremens, was observed in but one patient, Case No. 2523.

The cholesterol was determined in the blood of 16 of the gangrene cases of Rabinowitch. Only 2 of the patients had normal amounts of cholesterol. This corresponds to the views expressed on page 687 upon the dependence of diabetic arteriosclerosis on cholesterol. Among an equal number of non-diabetic sclerotics Rabinowitch found 6 with a normal cholesterol. The average was, for the diabetics, 0.344 per cent, for the non-diabetics, 0.249 per cent.

The causes of gangrene, arteriosclerosis and mild infections, develop slowly, and consequently gangrene itself is usually preceded by a long duration of symptoms. Charcot pointed out intermittent claudication as a precursor of gangrene, and coldness of the extremities and numbness and pains in the feet are common signs of approaching danger.

The prophylactic treatment of gangrene is seldom preached, but it is important. Remember, 1 diabetic in 5 who comes for hospital treatment after the age of seventy years acquires gangrene and that for eighteen years in Boston 1 diabetic in 5 died with it as a contributory cause. Root found the average weight of 22 of my cases of gangrene to be 210 pounds. Of 55 diabetic patients seeking my care with lesions of the legs which later required amputation I find that 44 had never consulted me before and that 11, who were former patients, had not been seen for an average period of 2.7 years. Unfortunately, one cannot hold out this incentive to a diabetic. "if you keep sugar-free, you will avoid gangrene," but he can be told that if sugar-free there is less chance of his developing it. All the measures which are suddenly advised when gangrene appears should have been adopted in a modified and appropriate form years before its appearance. The emphasis in prophylaxis must be placed first and foremost, on treatment of the diabetes, which today is designed to prevent early disease of the arteries; second, upon cleanliness of the feet; third, upon those conditions which might predispose to an infection by abrasion of the feet. New shoes should be worn but a few hours, and blisters which may have formed pricked only under aseptic precautions; flat-foot plates should be used with care; corns and toe nails are to be cut only after thorough cleansing of the part and with good instruments and in a good light; strong liniments are to be avoided, and the dangers of hot-water bags and heaters made vivid to the patient; a stiff big toe is not uncommon and these patients must be taught to limber up their toes. Epidermophytosis must be checked, because it favors deep infections between the toes. (See p. 722.) Patients must be drilled

to report any injury to the skin so soon as it occurs. Maintenance of a good circulation in the legs is a fourth preventive measure. Murayama and Sakaguchi did not have a single case of death from gangrene in their 49 fatal diabetics, and this despite the marked arteriosclerosis of Japanese diabetic patients. The Japanese wear thick socks and sandals which do not compress the feet. Patients predisposed to gangrene must be urged to walk for short intervals several times a day. In addition, they should regularly three times a day go through such gymnastic exercises as will bring about a free flow of blood in the feet, and should be told not to remain long in one position. The legs are not to be crossed and compressing garters should be avoided. Bertnard Smith[1] uses with his diabetics the groups of exercises which he found useful in the treatment of heart disease in the army. When sitting, it is desirable to use a foot rest. Massage is useful. Warm foot-baths should be encouraged. Whereas active hyperemia will improve the circulation, passive hyperemia is dangerous and should never be employed, save with quick alteration to active hyperemia. The surgeon should never employ a tourniquet in these cases at operation. Many of the measures advocated by Stetten[2] and Bernheim[3] for the treatment of actual gangrene are applicable here.

Treatment of Feet.—*Hygiene of the Feet.*—1. Wash feet daily with soap and water. Dry thoroughly, especially between toes, using pressure rather than vigorous rubbing.

2. When thoroughly dry, rub well with hydrous lanolin as often as necessary to keep skin soft, supple, and free from scales and dryness, but not enough to render feet tender. If nails are brittle and dry, soften by soaking in warm water one-half hour each night and apply lanolin generously under and about nails and bandage loosely. Clean nails with orange-wood sticks. Cut the nails only in a good light and after a bath, when the feet are very clean. Cut the nails straight across to avoid injury to the toes. If you go to a chiropodist, tell him you have diabetes.

3. Wear shoes of soft leather which fit and are not tight (neither narrow nor short). Don't hesitate to cut a hole in a shoe and put on a patch. Wear new shoes one-half hour only on the first day and increase one hour daily.

4. If the feet become too soft and tender, rub once a day with alcohol.

Treatment of Corns and Callosities.—1. Wear shoes which fit and cause no pressure. The Japanese seldom have gangrene. Beware of nails and torn linings in old shoes and wear new shoes for the

[1] Smith: Jour. Am. Med. Assn., 1919, **72**, 103.
[2] Stetten: Jour. Am. Med. Assn., 1913, **60**, 1126.
[3] Bernheim: Am. Jour. Med. Sci., 1922, **163**, 517.

first time in the evening. It is wise to have several pairs of shoes which differ slightly from one another and to wear them on successive days.

2. Soak foot in warm, not hot, soapy water. Rub off with gauze or file off dead skin on or about callus or corn. A corn may be painted with the following mixture: Salicylic acid, 1 dram; collodion, 1 ounce. Repeat for four nights; then, after soaking in warm water, the corn will come off easily. If it does not come off easily without bleeding, repeat the treatment for four nights.

3. Do not cut corns or callosities.

4. Wear pad to distribute pressure if necessary. Use felt instead of medicated corn plaster.

5. Prevent calluses under ball of foot (*a*) by exercises such as curling and stretching toes twenty times a day, (*b*) by finishing each step on the toes and not on the ball of the foot.

Circulatory Aids: 1. Exercises. Bend the foot down and up as far as it will go six times. Describe a circle to the left with the foot six times and then to the right. Repeat morning, noon and night.

2. If subject to chilblains, wash feet daily in warm water, dry carefully, and powder lightly with borated talcum powder. Wear woolen stockings and avoid extremes of temperature.

3. Massage with lanolin.

4. Buerger gravity—hyperemia method for bed patients gives excellent results, as does the violet ray in indolent sores.

5. Do not wear circular garters. Do not cross the legs.

Treatment of Abrasions of the Skin.—1. Insignificant injuries in the diabetic may result very seriously. Early, proper first-aid treatment is of the utmost importance. Consult your physician.

2. Avoid strong irritating antiseptics, such as sulpho-naphthol and iodine.

3. As soon as possible after injury certain surgeons recommend the application of sterile gauze saturated with medicated alcohol. Keep wet for one hour by pouring on more alcohol. Another method is to paint with a 2 per cent solution of mercurochrome. Sterile gauze in sealed packets may be purchased at drug stores. Purchase a tube of boric acid ointment. Later keep wound covered with boric acid ointment on sterile gauze but do not plug a sinus with the ointment and thus start up a "backfire" infection. (McKittrick.) Change daily until healed.

4. Elevate, and as much as possible until recovery, avoid using the foot.

5. Consult your doctor for any redness, pain, swelling, or other evidence of inflammation.

Buerger[1] has suggested that certain passive exercises may be of value in inducing hyperemia or rubor in the affected limb, and therefore, therapeutically beneficial in increasing the blood supply. If the method is carried out daily for a long period, it is of great value in improving the circulatory conditions and in increasing the blood supply.

Buerger's Passive Exercises.—"The affected limb is elevated with the patient lying in bed, to from 60 degrees or 90 degrees above the horizontal, being allowed to rest upon a support for thirty seconds to three minutes, the period of time being the minimum amount necessary to produce blanching or ischemia. As soon as blanching is established, the patient allows the foot to hang down over the edge of the bed for from two to five minutes, until reactionary hyperemia or rubor sets in, the total period of time being about one minute longer than that necessary to establish a good red color. The limb is then placed in the horizontal position for about three to five minutes, during which time an electric heating pad or hot-water bag is applied, care being taken to prevent the occurrence of a burn. The placing of the limb in these three successive positions constitutes a cycle, the duration of which is usually from six to ten minutes. These cycles are repeated over a period of about one hour, some six to seven cycles constituting a seance."

The Buerger boards as used at the Deaconess Hospital consist of two boards, each $\frac{3}{4}$ inch thick, 30 inches long, and 11 inches wide, hinged at one end. In the middle of one board is a hinged tongue with a cleat on the other board so that the boards can be opened at an angle of 30 degrees, 45 degrees or 60 degrees as desired.

"It is well to begin with about 3 seances daily, that is, 3 treatments daily, gradually increasing the number of seances until the patient allows the seances to occupy at least six or seven hours a day, that is every alternate hour during the daytime. During the hours of rest, heat is applied continuously in the form of an electric pad, hot-water bag, hot-air apparatus or electric lamp.

"In the opinion of the author, this method does far more to improve the circulation than either the application of superheated air (so-called baking treatment), or the diathermic treatment.

"The length of time of its application may in some cases depend upon the pain which may be induced by elevation of the foot. In some cases the symptoms may necessitate a diminution in the period of elevation." This method was used first and most successfully by Brigham, in 1923, in my pathetic case, Case No. 1934, which had resisted many other forms of treatment. This patient eventually gave up morphine, became able to walk and died a sudden

[1] Buerger: Surgical Diagnosis and Treatment by American Authors, ed. by Ochsner, A. J., Lea & Febiger, Philadelphia, 1920, **4**, 810.

cardiac death in December, 1927. So convincing was the effect of treatment that her nurse was later put in charge of the care of the feet of all the surgical diabetics at the Deaconess and also supervises the "Beauty Parlor for Diabetic Feet" given the hospital by Mr. and Mrs. William L. Shearer in which Dr. Kelly and Dr. Kenison are the Chiropodists.

Gangrene in an upper extremity appears in the list but 3 times. A most pathetic instance, just before the advent of insulin, occurred in one of my most faithful patients, Case No. 600, a lady, aged fifty-seven years, eleven years after the onset of diabetes developed a paronychia of the left thumb. This was incised by a surgeon of considerable experience. The wound grew worse, sugar appeared in the urine and the patient radically restricted her diet to become sugar-free, but without success, because of the infection. Several days later I learned that she was doing badly and she entered the New England Deaconess Hospital. Neither surgical nor medical treatment was of avail. The infection spread into the hand and eventually gangrene appeared. By this time the patient had a septicemia from which she died without coma in April, 1922. A fourth case of gangrene in the arm entered the hospital in January, 1928. It was embolic in origin and the patient recovered after amputation.

TABLE 281. DIABETIC GANGRENE WITH AMPUTATION OF BOTH LEGS. 1898–1922.

Individual case numbers.	Onset of diabetes, age.	Amputations.		Results to July 1, 1927.	
		Age at first.	Age at second.	Dead at age.	Alive at age.
343	58	62	64	65	
355	58	73	74	79	
895	55	67	71	76	
1509	35	48	49	55	
1932	67	61	63	68	
2339	63	70	71	71	
2727	53	62	62	63	
	1923 to AUGUST 1, 1926.				
3280	52	64	67	..	68
3519	63	63	64	..	67
3745	58	58	64	67	
3834	68	68	74	..	74
3866	30	53	64	64	
5186	46	59	60	..	61
5250	57	60	60	..	62
5334	58	28	64	64	

Gangrene of the skin of a large portion of the abdomen I saw with Dr. Winnett of Des Moines. Gangrene of the nose is pictured by von Noorden and Isaacs.[1] Gangrene of the nose in 3 children under ten years of age has been reported by Bowers.[2] He con-

[1] Von Noorden and Isaacs: Loc. cit., p. 295.
[2] Bowers: Jour. Am. Med. Assn., 1924, **82**, 1325.

sidered thrombo-angiitis obliterans as the cause. Ardeslier[1] successfully operated upon such a case in a child of eight years.

Amputation of Both Legs.—Both lower extremities were affected with gangrene in 15 instances, and amputation of each leg was required, 7 cases before and 8 cases since January 1, 1923. (See Table 281.) Case No. 343, with onset at fifty-eight years of age, lost one leg from gangrene when sixty-two years of age, and the other leg two years later, death resulting at the age of sixty-five years. Case No. 355 died of angina pectoris four years and eight months after the second operation, sugar remaining absent from the urine during nearly the whole of this period. An amputation of both legs is not necessarily of bad prognosis, because but 3 of 15 such patients have succumbed within a twelfth-month. In 2 instances this was fatal in less than six days, in another case, Case No. 4108, not counted in the series, death occurred at the first few whiffs of the anesthetic, which was ethylene, and before the operation was begun. Case No. 1509, though legless, conducted a large manufacturing business six years after the second operation. Consider how hopeless he appeared in 1919. (See Table 282.) John writes me of a similar case under his care.

The condition of the arteries and veins of extremities amputated for gangrene has been carefully investigated by Buerger.[2] He writes: "A study of the condition of the arteries and veins in limbs amputated for so-called diabetic gangrene reveals the fact that in each and every instance we are dealing not with a gangrenous process due to the diabetes *per se* but a mortifying process dependent upon extensive arterial disease. . . In short, characteristic for so-called diabetic gangrene is the presence of the typical lesions of athero- or arteriosclerosis. These differ in no way from the lesions of the arteries of the arteriosclerotic or senile gangrene, and justify the conclusion that in diabetic gangrene we are dealing with an atherosclerotic or arteriosclerotic process." I cannot agree with all of these statements. Arteriosclerosis is certainly the basis for gangrene; I have never seen gangrene without it. It may be simply senile sclerosis, but more often I believe it is associated with arteriosclerosis in earlier stages which is especially characterized by deposits of cholesterol in the arterial wall, particularly in the intima. It is overwhelmingly more common in the diabetic sclerotic than in the non-diabetic sclerotic (Rabinowitch).[3] Are the sclerosed vessels of arteriosclerotic diabetic patients the result primarily of cholesterol deposits? I hesitate to be dogmatic or explicit because I

[1] Ardeshir: Lancet, 1926, i, 1256.

[2] Buerger: Arch. Diag., April, 1915. See also articles by Silbert and by Samuels: Jour. Am. Med. Assn., 1927, **89**, 964; 1927, **88**, 1780; 1928, **90**, 831.

[3] Rabinowitch: Loc. cit., p. 27.

know others whose opinions I respect far more than my own expect to report upon this subject within a year. I realize that Achard[1] says, "There is a gangrene in the diabetic, but not a diabetic gangrene."

TABLE 282.—CASE NO. 1509. ONSET OF DIABETES AT THIRTY-FIVE YEARS. OPERATION FOR GANGRENE OF ONE LEG, AT FORTY-EIGHT YEARS, BY R. C. COCHRANE; OF REMAINING LEG, AT FORTY-NINE YEARS, BY J. C. O'CONNELL.

Date.	Diacetic acid.	Nitrogen, gms.	Ammonia, total gms.	Sugar in urine, total gms.	Diet in grams.				Carbohydrate balance, gm.	Bloor's blood fat, per cent.	Blood sugar, per cent.	Blood CO_2, vol. per cent.	Alveolar air, CO_2, mm. Hg.
					Carbohydrate.	Protein.	Fat.	Calories.					
1919													
June													
19–20	++++	..	3.2	67									
20–21	++++	16.0	2.8	75	20	27	22	495	−55	..	..	..	26
													24
21–22[2]	+++	18.4	2.6	82	34	18	5	253	−48	1.588	0.197	..	28
													27
23–24	+++	17.8	4.4	101	33	42	13	417	−68	..	..	..	24
24–25[3]	++	13.0	3.2	52	33	28	11	343	−19	0.890	0.182	..	24
26–27	++	20.0	3.1	77	33	57	10	450	−44		0.250	41	29
28–29	+++	22.8	4.0	87	29	45	14	422	−58				25
29–30	+++	22.0	3.1	56	29	41	13	397	−27				29
July													
30– 1	+++	18.2	3.3	42	0	0	0	0	−42				25
1– 2	+++	16.0	3.7	46	0	0	0	0	−46	0.600	0.210	33	29
3– 4	++	15.6	3.6	30	0	0	0	0	−30				32
4– 5	++	15.0	2.7	20	5	14	0	76	−15	0.780	0.194	..	31
5– 6[4]	++	..	3.1	20	0	8	3	59	−20				
7– 8	++	15.0	3.1	38	15	29	10	316	−23				31
11–12	++	..	2.7	49	20	60	22	623	−29				29
12–13	++	..	2.1	47	22	44	15	495	−25				27
14–15	++	..	1.5	25	23	60	18	599	− 2				28
15–16	++	..	1.5	24	18	66	25	666	− 6				26
18–19	..	..	1.5	13	23	58	32	717	+10				
19–20	0	..	1.4	12	23	59	29	694	+11				
23–24	Slt +	..	..	0	41	73	46	888	+41				27
1920.													
June,	amputation of second leg (gas-oxygen anesthesia).												
1926													
Feb.,	death—cerebral hemorrhage.												

If one needs to be convinced of the *uselessness of attempting to save most gangrenous legs*, the specimens removed at operation

[1] Achard: Rev. gén. de Clin. e. d. thér. Jour. d. Pract., 1924, p. 545.
[2] First operation.
[3] Second operation.
[4] Amputation (Spinal anesthesia).

should be injected and studied. These show how hopeless it is to expect the arteries to regain their function. Regret is felt, not for the removal of the leg at the time, but rather that it had not been removed earlier. Extensive thrombosis of a leg precludes healing.

The value of the roentgen-ray in reaching a conclusion as to the desirability of operation is considerable. One obtains in this way both an idea of the condition of the arteries, but also of the presence of necrosed or necrosing bone. The latter of the two conditions is the important factor. The inspection of roentgen-ray plates of the lower extremities for arteriosclerosis is not simple because one may err by considering visible vessels arteriosclerotic, or by not using a magnifying glass and so failing to notice punctate deposits of calcium.

Treatment.—*Diet.*—The dietetic treatment of cases with gangrene is simple and along the lines already described for surgical cases in general. (See p. 772.) The diabetes of these patients is essentially mild, as is almost invariably the case in those over sixty years of age. The chief object is not to make it worse by rigid curtailment of carbohydrate and calories on the one hand, or by overnutrition on the other. Geyelin has told me of a patient whose foot had resisted treatment for months under the care of an excellent physician. When he raised the carbohydrate of the diet from about 75 grams to 225 grams healing promptly took place. All dietetic changes should be gradually made. Already on p. 774 occasion was taken to show how the convalescence from an operation could be utilized to benefit the diabetes. This is still more strikingly shown in Table 283 in which my associate, H. F. Root,[1] has tabulated the changes back toward the normal of the blood sugar before operation and in successive weeks thereafter of 7 patients. Before operation the average blood-sugar percentage was 0.23 and at discharge 0.13.

TABLE 283.—BLOOD SUGAR PERCENTAGES OF 7 CASES OF DIABETIC GANGRENE PRIOR TO INSULIN. (ROOT.)

	(Before Breakfast.)	After operation.			
Case.	Before operation.	First week.	Second week.	Third week.	At discharge.
I	0.30–0.29.	0.37–0.30	0.25	0.24	0.15
II	0.35	0.32	0.22	0.19	0.16
III	0.36	0.36	. .	0.20	0.15
IV	0.23	. . . .	0.20	0.17	0.11
V	0.26–0.13	0.24	0.16	0.13	0.13
VI	. . . .	0.17	0.19	0.10	0.10
VII	0.12–0.14	0.15	0.13	0.11	0.14
Total 7 . Average:	**0.27**	**0.26**	**0.19**	**0.19**	**0.13**

[1] Root: Boston Med. and Surg. Jour., 1922, **187**, 875.

Examples of the composition of the diets of the 7 cases of gangrene prior to insulin whose blood sugars have been set forth in Table 283 can be seen in Table 284. The total calories eventually were low, and I should feed more carbohydrate today with the help of insulin, but these patients were old and immediately after the operation were bedridden and so required little food. In fact, one is anxious to prevent gain in weight in order to protect the stump when the artificial leg is worn. I consider Table 283 of great importance. It has taught me that persistence in a moderately low diet will prove an apparently severe diabetic to be mild. It is also notable because it shows that healing took place in the presence of a high blood sugar. Just as in diabetics with coronary disease one is cautious about lowering the blood sugar, so too should one be with gangrene with its arteriosclerotic basis. Likewise freedom from glycosuria is not essential to healing, although it is desirable provided it is secured without a low carbohydrate diet or excessive insulin dosage. One patient was operated upon by McKittrick with a non-protein nitrogen of 95 mg. per 100 cc. and a blood sugar of 0.50 per cent. He writes, "She now (six days after operation) has a non-protein nitrogen of 43 mg. and a blood sugar of 0.19 per cent and her stump is healing as satisfactorily as any stump possibly could." Ercklertz[1] writing from Umber's Clinic in Berlin takes the opposite point of view.

Insulin.—The use of insulin with cases of gangrene is the same as with any elderly arteriosclerotic diabetic of long duration having an infection.

Exercise.—Exercise both before and after operation, except in the presence of an active infection, is essential. The muscles burn sugar. They must be utilized to maintain the diabetes in a mild state. Bed gymnastics therefore are carried out under the supervision of a trained technician. These exercises lessen pain and, incidentally, are at the same time a good prevention against pneumonia as they improve not only the local circulation but the pulmonary circulation as well.

Ultra-violet Ray.—Light treatments are similarly employed. They exert a favorable action locally, but perhaps are more important as a general tonic.

Surgery.—The treatment of actual gangrene demands the closest coöperation between a physician and a real surgeon. Undoubtedly the writer sees the bad more often than the favorable cases and his views may be guided somewhat by this circumstance. Nevertheless, *it is heart-rending to listen to the histories told.* I will cite three instances. A patient developed gangrene in November, was

[1] Ercklertz: Inaug. Dissert., Breslau, 1926.

treated by her local physician and the surgeons of two well-known hospitals, who advised her to wait until the affected part dropped off. She entered the hospital penniless in June at 7 P.M. The leg was so foul smelling that by 9 P.M. all were glad to have it removed and the patient after a good night, smilingly met a group of visiting doctors in the morning. Think of those months of suffering! (Incidentally this old lady showed a positive Wassermann reaction.) Another patient entered with fever and glycosuria and was immediately operated upon to give him his only chance, though the surgeon was protected by a previous blood culture which ultimately proved positive. He had been having medical treatment, though on inquiry it was learned that gangrene had been present for two months and fever present for a week, during which latter period he had not seen his physician! The third case was that of a woman, Case No. 1759, who entered the hospital with the leg red and swollen and the foot a mass of purulent inflammation and gangrene. There was also a beginning gangrene of the middle toe of the left foot. The diabetes was comparatively mild, but the pulse was 120. A high thigh amputation was performed under spinal anesthesia without shock to the patient, but she died three days later with a gas bacillus infection. The patient was aged fifty-seven years, the diabetes of six months' duration; the infection of the leg had been present two months, and in all she had dieted two days.

TABLE 284.—AVERAGE DAILY DIETS OF 7 CASES OF DIABETIC GANGRENE TREATED PRIOR TO INSULIN. (ROOT.[1])

Case.	Before operation.	After operation.															
	Time in hospital.	Diet.			First week.			Second week.			Third week.			At discharge.		
		C. Gr	P. ams	F. s.	C. Gr	P. ams	F. s.	C. Gr	P. ams	F. s.	C. Gr	P. ams	F s	C. Gr	P. ams	F. s
I . . .	7 days	78	52	10	58	44	24	50	58	38	59	62	47	75	71	54
II . . .	1 meal	20	23	0	77	43	20	58	40	33	63	51	44	96	67	54
III . . .	Immediate operation	..	..	..	114	51	10	69	42	34	68	47	35	114	59	65
IV . . .	1 day	32	34	45	38	23	34	33	35	48	30	33	57	45	41	70
V . . .	8 days	41	25	24	75	33	33	58	43	69	69	54	82	86	64	86
VI . . .	Immediate operation	..	..	..	71	45	43	70	65	80	..	..	..	60	68	72
VII . . .	17 days	51	42	46	32	44	33	35	44	50	41	50	73	65	55	75
Total 7 . .	Averages:	**44**	**35**	**25**	**66**	**40**	**28**	**53**	**47**	**50**	**55**	**50**	**56**	**77**	**61**	**68**
	Calories:	543			681			838			923			1164		

[1] C = carbohydrate. P = protein. F = fat.

NOTE.—Root and I would give carbohydrate 100 grams or more now with the help of insulin.

Gangrene deserves aggressive treatment on the part of physician and surgeon from start to finish. This does not mean that all gangrenous infected legs should be immediately amputated or partially amputated, but it does mean first that their inherent possibilities for causing a fatal issue shall be appreciated and second that the lesions shall have expert surgical care. It is easy to understand why Stetten[1] and Bernheim[2] were successful in many of their cases and avoided operation. Bernheim's treatment as described was energetic and planned to combat the ischemia of the part, by rest in bed, exercises of the bloodvessels by promoting their contraction and dilatation with hot and cold plunges three times a day, heat for an hour at a time, the electric vibrator and the use of bromide and codein, with the expectation that eventually after weeks of treatment the circulation would improve. So long as the consulting surgeon agrees that satisfactory progress is taking place, well and good, but, if this referee is in doubt, operate immediately.

Indications for Operation in Gangrene.—The question continually arises whether the patient shall be operated upon for gangrene. Many factors must be taken into account, but the most important is the evident improvement or non-improvement of the patient. In an individual who has the dry type of gangrene which is plainly becoming localized, it is easy to decide to defer operation. It is quite as easy to decide to advise immediate operation when there is a history of rapidly progressing moist gangrene in the course of a few days. If the condition is remaining stationary, an operation favors safety, because so often in the course of a day or two an old focus, quiescent for weeks, can light up and lead to septicemia. Such flare ups occur more frequently with vessels which are moderately sclerotic than extremely sclerotic. In general the younger the patient the more radical the surgical treatment.

To the mere presence of sugar or acid in the urine I attach little importance, because these can be controlled with or without operation by diet and insulin, but only effectively provided the infection is subsiding. On the other hand, I do believe it important to utilize the common sense measures necessary in preparing a surgical patient for an operation, such as adequate provision for sleep, nutrition and the circulation.

Procrastinating medical methods do more damage than prompt surgical intervention. The chief task of the medical or surgical consultant is to bring to an end dangerous delays and to secure action.

Pain is an indication for operation, and I have been thankful that the operation was performed for this reason in certain diabetics

[1] Stetten: Loc. cit., p. 639.
[2] Bernheim: Loc. cit., p. 639.

whose gangrene was comparatively slight. The pain attendant on the marked arteriosclerosis in the leg was too great to witness, much more to bear, and it was a relief to see the change in the comfort of these elderly people after the leg had been removed. It led one Jewish patient to return to have his remaining leg removed while the beginning gangrene was at a still earlier stage of development.

The financial aspect of gangrene is a serious factor. The medical treatment of gangrene during weeks and months in home or hospital is far more expensive than early surgery. It is likewise far more wearing on the patient's nerves. Subsequently patients regret the postponement of their operation and returning to the hospital advise other patients to be operated upon earlier. So many of these late cases come to me in financial straights and so few pay my surgical colleagues anything that I am almost ashamed to look the latter in the face. An infected or gangrenous foot before it is healed costs, in my opinion, at least $300, quite apart from medical, surgical or special nursing fees or loss of wages.

Convalescence is often prolonged, but since the amputated stumps have been closed tight and without drainage has been much shortened. Extraordinary precautions have been taken to protect the sound leg after operation. A woolen sock is placed on it before the patient leaves the operating table to guard it against undue pressure and for the same purpose a frame with supports by which the patient can lift himself is put over the bed.

The intracutaneous salt solution test for approaching gangrene has not been employed with my cases.[1]

TABLE 285.—DURATION OF LIFE OF DIABETIC PATIENTS AFTER ONSET OF GANGRENE.

Cases.		Years of life after onset of gangrene.												
Condition.	No.	Under 1	1	2	3	4	5	6	7	8	11	12	13	Uncertain.
Living	41	6	10	6	6	5	2	3	1	0	1	2	0	0
Fatal	125	71	8	11	10	5	3	3	2	5	0	1	1	4

Results of Treatment for Gangrene.—The duration of life of diabetic patients after the onset of gangrene has varied in my 166 cases from less than one year to thirteen years. The details for the entire series are shown in Table 285.

Among the 125 fatal cases, 71 succumbed to the disease within the first year, whereas among the 41 living cases 35 are known to have survived it. It is evident that if the patients pass the first

[1] Cohen, *et al.*: Jour. Am. Med. Assn., 1926, **86**, 1677.

year, they can look forward to a considerable period of life. Of the 61 cases treated by amputation at the Deaconess Hospital between May 1, 1923 and January 1, 1927, 34 are still alive, while 7 or 11 per cent died during the first year and 15 cases died without recovery from the operation. Restricting the number of cases to those operated upon at the Corey Hill and New England Deaconess Hospitals between April 1, 1919, and 1923, there have been 25 cases and 7 deaths.

The total amputations upon 52 patients in the recent period are recorded in Table 286. These figures show that a more radical and presumably an earlier decision should be reached in such cases. These data may well be cited in discussions with patients and friends upon the seriousness of delay and to persuade them to sacrifice a limb in order to save a life. Death took place within one month in 15 cases among 56 patients following operation. Nine of these deaths were due to septicemia and these 9 deaths together with 6 other deaths from septicemia constitute nearly one-half of the total surgical deaths from all causes during the three and a half years.

TABLE 286.—DIABETIC GANGRENE—DURATION OF LIFE AFTER AMPUTATIONS OF LEGS.

Year.	Amputations,[1] total.	Death.		Alive, August, 1926.	
		No. cases.	Years of life.	No. cases.	Years since operation.
1923	10[2]	4	0.9	5	2.8
1924	16	8	0.5	8	2.0
1925	15	7	0.2	8	0.9
To Aug. 1, 1926	15	5	0.1	10	0.3

All cases dying within a few days of operation died because operation was performed too late. Undoubtedly the debility of the patient was a large factor. One cause of this debility was the interval between the beginning of the lesion and the date of operation which averaged sixteen weeks. This average includes one exceptionally long case. Without this case the average would be six weeks. Another explanation was the duration of the diabetes, eleven years, and its evident lack of treatment as shown in 6 cases. To reduce mortality from septicemia, therefore, we must (*a*) prevent lesions of the feet and (*b*) if they occur (1) educate the patient to report them at once, (2) reach an earlier decision, as to when to operate, (3) perform a more radical operation and (4) build up more energetically the vitality of the patient by dietetic and other means.

Gangrene is frequently far less serious than a mild infection with

[1] Including 4 second amputations. Of the 52 persons who underwent amputation, 28 are alive on August 1, 1926.

[2] Case No. 3269 had a reamputation of the stump within a month of the first operation.

hardly more than a pin-point discharge due to an osteomyelitis. The former it is true may necessitate the loss of the foot and the latter merely the loss of a toe or two, but the danger arises because the gangrene extends slowly and tends more to localization whereas the osteomyelitis although quiescent for long periods may suddenly flare up and cause septicemia.

It is inappropriate here to discuss in detail the surgical treatment of gangrene. My observation of the surgeons who operate on my cases shows that constant improvements are taking place in their methods of treatment. There has been a tendency to exact localization of treatment to the area involved, to dry dressings in preference to wet dressings, to the use of the war antiseptics, and to the least possible manipulation of the part. Increasingly often amputation is done below rather than above the knee and in many of the recent cases, so sure are these operators of their technique that the wounds are closed without drainage. The Gritti-Stokes operation which preserves the patella is preferred if the infection has not extended too high. A guillotine operation has been employed with effect in certain cases of early septicemia and subsequently the stump has been reamputated and closed. So technical are the details of surgical procedures in diabetics that I welcome the Monograph of McKittrick and Root[1] upon this phase of treatment. It is two years since any anesthetics save spinal anesthesia or gas and oxygen have been employed.

The thigh was amputated in 12 cases with 5 fatalities, the leg was amputated in 25 cases with 7 fatalities. There were 14 operations upon the foot with 4 deaths and the fatal operation upon the hand has been mentioned. Healing, following amputation of one of the central toes, was formerly most uncommon and still is rare and a long drawn out process.

If the diabetic kept his feet as clean as his face, gangrene would seldom occur. Gangrene is responsible for one-fifth of all diabetic deaths, and all diabetics above fifty years of age should be taught to avoid it.

If the beginning of gangrene were as noisily ushered in as an attack of biliary or renal colic the results of treatment would be far different. Death from gangrene today is usually the result of procrastination on the part of the physician and patient, and in the past was often associated with the inauguration of a fat-protein diet and ether anesthesia. Surgery often receives, but seldom deserves, the blame of a fatal issue.

Cursory mention will be made of other surgical lesions which are frequently encountered in diabetes, although not dependent upon it, because of certain peculiarities.

[1] Soon to be published, Lea and Febiger.

10. **Appendicitis.**—In the diabetic patient appendicitis is as insidious as coma and may simulate it. Case No. 3679 was convalescing in the ward from a septic arm, developed a temperature of 100° F., did not complain and denied symptoms until the gangrenous appendix ruptured. Despite operation he died in 1924 under our very eyes. Second, my associate, H. F. Root, was summoned to a suburb to see a case of diabetic coma, Case No. 5385, and found moderate acidosis, but diagnosed appendicitis and six hours later at midnight D. F. Jones took out a gangrenous appendix and Mrs. B. was discharged from the Deaconess Hospital in eighteen days. Third, the reverse of the above. A Turk, Case No. 4740,[1] came to my office with pain in his abdomen. I suspected an approaching rupture of a gall-bladder or duodenal ulcer rather than an appendix, and told him to go to the hospital at once. He refused and I then warned him he might die in a day or two. My diagnosis was wrong, but my advice was sound. Though I had treated over 5000 diabetics I did not weigh the significance of my technician's report of a positive diacetic acid reaction in the Turk's urine. Incipient coma commonly, in fact usually, begins with indigestion, vomiting and distress in the epigastrium and as I might have expected he developed coma and was brought back to my office from Providence, the next day, so ill that his interpreter, fearing death in his car, insisted that my secretary get an ambulance to take him to the hospital a mile away. When he came out of his full fledged coma, blood CO_2 12 volumes per cent, with 140 units of insulin, lavage of the stomach, salt solution and caffeine each subcutaneously, he became one of my best patients.[2] The fourth case, Case No. 4135, was a woman from whom Dr. Lahey removed a goiter three years ago. One day she telephoned me that her abdomen felt uncomfortable. I insisted she have a doctor, and as her own was dead, she took the first she could find who fortunately proved to be Dr. John J. Elliott. He was at once suspicious of trouble and evidently warned her for she came into the hospital during the evening. When the house officer made his rounds she was sound asleep and he did not waken her. In the morning the abdomen was soft with slight but definite localized tenderness, temperature 99° F. but with the white count 23,000. Drs. Root, McKittrick and Clute saw her and largely for safety's sake H. M. Clute operated that afternoon. The gangrenous and ruptured appendix was removed, the local peritonitis drained, while the courageous but feeble patient sat erect for two days, without food save glucose intravenously, the assimilation of which was favored with insulin. Discharged well in eighteen days. Fifth, a little girl, Case No. 5461, aged twelve years, arrived over the road from

[1] Joslin: Boston Med. and Surg. Jour., 1927, **196**, 127.
[2] See Vsadel: Zentralbl. f. Chir., 1927, **54**, 1364.

100 miles away. She had diabetes according to her doctor, but upon arrival was sugar-free in our laboratory. Her grumbling appendix was removed the same evening. After the operation the sugar appeared reaching 5 per cent, thus vindicating her doctor who had treated her well. Prompt surgery saved a tedious convalescence. There is a sixth example, Case No. 2128. He remained in the hospital many days recovery from a general peritonititis, presumably of appendicular origin with which he entered and for which he was operated upon three hours after admission. After several days of intravenous glucose feeding plus subcutaneous insulin I noticed one forenoon that he looked weak, exhausted and was sweating. A blood-sugar test showed this to be due to hypoglycemia, 0.04 per cent, plainly an insulin reaction resulting from an overdose of insulin. Ten days after operation he developed intestinal obstruction which Dr. McKittrick diagnosed and relieved with an ileostomy and though temporarily he had a fistula it did him good rather than harm, because his tolerance rose and nearly quadrupled reaching 200 grams. If one could only explain this phenomenon it would greatly advance our knoweldge of diabetes. I have noted 3 somewhat similar cases in diarrhea and it makes one recall Guelpa's method of treating diabetes with fasting and Epsom salts. Let us therefore remember that an intestinal fistula in a diabetic, like diarrhea, may raise his tolerance. The patient recovered.

Summary upon Appendicitis in Diabetes.—Appendicitis in the diabetic is insidious, almost symptomless, may simulate coma or conversely coma may simulate it, can be successfully operated upon even though acidosis and peritonitis are present and the weakness and sweating of a protracted recovery may be due to an insulin reaction rather than to shock or pocketed pus. Do not sacrifice a patient to appendicitis just because he has diabetes and approaching coma. If in doubt, operate, although you may make an occasional mistake.

11. **Gall Stones.**—If you, who are fat and chance to hear or read these lines, could only choose the form of diabetes you are likely to acquire, I would recommend the gall-stone variety. It is the best of all the types of diabetes.

The average duration of the diabetes in the 35 diabetics with gall stones who have now died was 7.7 years and of the 164 diabetics still living has already reached 7.6 years. This would tend to confirm my statement that gall-stone diabetes is the desirable diabetes. The duration of life after onset of diabetes of the 88 patients who were operated upon for gall stones is 6.8 years and of the remainder the duration is 8.4 years. Of the 10 who have died subsequent to the operation the duration of the diabetes was 9.3 years.

[1] In March and April, 1928, Jones and McKittrick successfully operated upon 3 of our diabetic children for gangrenous appendices. Perhaps their recovery is partly due to the medical education of their families.

The possible prevention of diabetes by the early removal of gall stones is a strong reason for operation upon gall stones in the non-diabetic.[1] Therefore I recommend removal of gall stones both in diabetic and non-diabetics when the danger of operation is slight, first for the prevention of diabetes and second because if diabetes is present an operation may alleviate it. Of 13 diabetics operated upon for gall stones under my care during 1922–1926 there have been no deaths and there were but 2 deaths in the 53 cases reported by Judd, Wilder and Adams.[2] (See p. 767.)

12. **Disease of the Thyroid Gland.**—Here again surgery gives good results not only for the symptoms due to the gland, but frequently for the diabetes. This subject is reported in detail in association with F. H. Lahey[3] elsewhere. Certain features deserve emphasis here. (See also p. 878.)

1. The increased metabolism of hyperthyroidism is just as harmful to the diabetic as overeating of food and is even more apt to lead to coma, because the endogenous overeating of the thyroid case goes on day and night while the exogenous overeating of the diabetic is usually confined to three meals. You can reduce the diet of a diabetic and thus save his life, but you cannot reduce the diet of a hyperthyroid diabetic unless you remove a part of his thyroid.

2. Surgery in the hyperthyroid diabetic is the best sort of a game, because it is exciting and if you know and follow all the rules you are pretty sure to win. At one moment you are confronted with coma, the next confused with thyroid toxicity, and in the following the possibility of an insulin reaction looms up and all in the presence of a fibrillating heart, dehydrated tissues and a non-retentive stomach. No wonder seven doctors united during one day in the treatment of a single case. This circumstance and the considerable number of cases of coma referred to us have led to the introduction at the Deaconess of a special chart arranged with a line for each hour to cover such emergencies. Fortunately diabetes and goiter are now sufficiently mathematical in character and their symptoms so clear that they can be controlled by science rather than empiricism and with good records one doctor can proceed with treatment where the other has left off.

3. Mark the similarity of goiter and diabetes. Each leads to overeating and in turn to emaciation. Red cheeks and weakness are strangely associated, yet now the former are explained by the excessively high-protein diet. Uncontrolled, the metabolism of each is high, overcontrolled by removal of too much thyroid or extreme

[1] Gilchrist of Toronto goes a step further and suggests a possible cure. (Personal communication.)

[2] Judd, Wilder and Adams: Loc. cit., p. 1107.

[3] Joslin and Lahey: Am. Jour. Med. Sci., 1928, **175**. To be published.

undernutrition the metabolism of each falls too low. No wonder before insulin and before modern surgical technique and Lugol's solution the combination of the two was a catastrophe.

4. Surgeon and physician alike must be alert in diagnosis. I think Dr. Lahey will agree that some of his best thyroid cases, often of the thyro-cardiac type, came to him from me and I know that I can reciprocate that many of my most satisfactory diabetics first fed in his fields.

5. A little glycosuria in a thyroid case does not spell diabetes any more than when a little sugar is found in the urine of a patient with gall stones or in the course of pregnancy. The percentage of sugar in the blood clears the diagnosis and this is most essential. Otherwise the diet of a patient with a transitory glycosuria may be unduly restricted and greatly to his detriment. See p. 880.

13. **Prostatectomy.**—Ten cases were operated upon and all recovered. This is all the more noteworthy because an operation for removal of a prostate is a two-stage operation; there is a tedious convalescence and the urine, besides being infected, often contains sugar. Case No. 348 caused considerable apprehension after the operation because of the development of acidosis, undoubtedly due to the use of ether as an anesthetic. (See p. 776.) Case No. 559, with onset of diabetes at seventy-three years, was operated upon at seventy-four years, January 14, 1913. Spinal anesthesia was employed. Case No. 341 was the first prostatic case to take advantage of insulin. He had been under my care for thirteen years and his tolerance had gradually fallen. Glycosuria persisted after operation with carbohydrate 80 grams, protein 43 grams and fat 87 grams, despite 15 units insulin daily, explained by the slight infection which accompanies such an operation, rather than by the 80 grams of carbohydrate. Eventually he became sugar-free with 23 units daily and thirty-seven days after operation remained so with 5 units and a month later with none. Case No. 2765 was a successful case so far as hospital records go, but he actually died a few days later. Contrary to entreaty and against advice he left the hospital twelve days after operation. It was learned later that the retention catheter became clogged, urinary retention resulted and his death occurred from uremia. Until discharge his recovery had been uninterrupted. None of these cases have shown the remarkable increase in tolerance for carbohydrate following the operation which has sometimes been observed by others, if we exclude Case No. 341 who received insulin. In this instance the regaining of tolerance may be ascribed to the persistent and consistent treatment following operation and it may be that the noted gains in tolerance observed by others can be attributed to the same cause.

14. **Removal of Uterine Fibroids.**—Six cases have been operated upon with 1 death. This occurred in Case No. 721. The age of the patient at onset of the diabetes was forty-five years and at operation forty-nine years. Operation was forced because of repeated hemorrhages. On entrance to the hospital April 21, 1914 the glycosuria was 3 per cent and diacetic acid was present. The patient became sugar-free on May 7, with a tolerance for 15 grams carbohydrate, but shortly after grew worse and acidosis reappeared. The hemorrhage left no alternative and operation was performed (anesthetic, nitrous oxide) with a fatal issue forty-eight hours later. Today with transfusion, insulin and an appropriate diet, it is probable that even this patient might be saved.

Glycosuria disappeared for years following the operation upon Case No. 127 for fibroid of the uterus, the only instance of this type in my series. The age at onset of the diabetes was thirty-nine years and at the time of operation, forty-seven years. Following the operation, performed by M. H. Richardson in 1906, there was marked suppuration so extensive in character that drainage was established through the abdomen, the vagina and rectum. The patient at length recovered and nine years after operation was in good health and I thought the sugar had disappeared permanently, but twelve months later a specimen of this patient's urine contained, 104 grams sugar. On February 27, 1922, the blood sugar was 0.26 per cent and the non-protein nitrogen 40.8 mg. per 100 cc. blood. The urine contained a slight trace of albumin and 0.1 per cent sugar, but the patient was wretched with headaches and failing vision due to hemorrhagic retinitis. In August, 1923, she developed coronary thrombosis, and died November 5, 1923.

Hysterectomy for fibroids does not always affect the diabetes favorably. Case No. 2174 came through the operation most satisfactorily, but her tolerance for carbohydrate, which was 173 grams before the operation, fell to less than 61 grams of carbohydrate even with the help of 10 units of insulin. Gradually, however, insulin has saved the day and she is now, July, 1927, in good condition. Perhaps latent infections (teeth) may have had something to do with the loss of tolerance. At any rate the patient has shown a rheumatoid arthritis.

15. **Cancer of the Pancreas.**—Cancer of the pancreas seems far more frequent today than in the past. A search of my records only in part confirms this, but perhaps it will be confirmed when as many of my recent diabetics are dead as of the old. The cancer may develop ten years after the onset of the diabetes, or perhaps may usher in the disease itself. Case No. 896 began in so orthodox a fashion that no one suspected its presence. Insulin is less effective if there is cancer of the pancreas, but it helps to control the diabetic

symptoms. So far as my observation goes the development of cancer of the pancreas, unless diabetes is already present, never leads to frank diabetes. My one case in which it apparently ushered in diabetes has not yet come to autopsy. Here is a good opportunity awaiting the joint investigations of clinician and pathologist.

The roentgen-ray helps greatly in the diagnosis of cancer of the head of the pancreas. Dr. Morrison has taught us at the Deaconess that the wide sweep of the duodenum around the region of the head of the pancreas is distinctive if present.

Continued loss of weight in an adult diabetic who is under reasonably good treatment with diet and insulin means cancer, tuberculosis or pus. Cancer and tuberculosis are becoming equally rare in those diabetics who are under thirty years of age. Perhaps cancer is more common in a diabetic than in a non-diabetic.

When a surgical diabetic is not doing well, do not blame the diabetes. The treatment of diabetes now rests upon so sure a scientific foundation that if the course of the patient is not favorable one must suspect a complication. Where is the pus? Was the poor old man exposed to tuberculosis in his youth and has it now come to the fore? Has the frail old lady a carcinoma of the pancreas, which you could not detect when, forced by emergency, you removed her gall stones under novocaine? Remember that diabetes is a good disease, but has bad companions and these have injured her reputation. Attack them, not her.

Diabetic surgery reflects the surgery of the future in that it is largely preventive. We hear much of preventive medicine, we should hear more of preventive surgery. According to diabetic law an infection makes a diabetic worse, but it is the surgical procedure which removes the infected teeth and tonsils, appendix or kidney and brings to an end infections of the feet. According to another diabetic law an increased metabolism transforms a mild diabetes into a severe, but the surgeon intervenes in hyperthyroidism and transforms the diabetic into his original and usually benign state when he removes the thyroid. Gall stones, and they signify cholecystitis, frequently precede diabetes. They, too, vanish at the hands of the surgeon, who little knows, when he removes them how often he actually prevents the later development of diabetes.

SECTION XIII.

DIABETES IN CHILDHOOD.

By Elliott P. Joslin, M.D. and Alexander Marble, M.D.

Introduction.—The data about to be recorded are based upon children under fifteen years of age having true diabetes mellitus. They do not include the 68 children sent to us because of suspected diabetes. Of the 395 true diabetics all have been traced to July, 1927; of the 68 non-diabetics the condition of 3 was unknown in September, 1926. The status of the true diabetics will be presented first, next certain facts relating to diabetes in childhood will be discussed, and at the conclusion of the section will be recorded our experience with the non-diabetics composed of 5 renal glycosurics, 14 potential diabetics, and 48 still remaining in an "unclassified" group despite the occasional presence of sugar in the urine. There was one stray case of diabetes insipidus who purloined a diabetic case number.

A. PRESENT STATUS OF 395 DIABETIC CHILDREN.[1]

Prior to insulin the exceptional diabetic child eluded the accidents of coma and malnutrition for more than a decade. This was nearly five times the average duration of the diabetic child's companions at that time and proved our treatment of them to have been wrong. W. B. S., Case No. 295, lived twelve years. He was married in the seventh year of his diabetes, and his wife gave birth to a healthy baby. His case is reported in detail on p. 849. Sarah W., Case No. 1360, lived 15.3 years and went into coma. Then there was Alice P., Case No. 887, who contracted diabetes at eight years, lived twenty-nine years, and died in consequence of my ignorant treatment. She died in coma, but her death did more than any of my preceding cases to prolong the lives of the remainder. She taught me: (1) Never to institute fasting suddenly or to prolong it for many days; (2) never, *never*, in coma or out of coma to treat a

[1] Since these statistics were compiled (September, 1926), 40 more children with true diabetes have come for diagnosis and treatment. Their data are not included in these figures.

diabetic symptom, acidosis, with alkalies, but rather to treat the disease diabetes. The remaining 9 of the 12 cases who have survived a decade are alive: Cases No. 203, 825, 1254, 1484, 1609, 1753, 2432, 2997, 5301. Case No. 1469 became a ten-year case in December, 1927.

Inquiry among confreres in the United States who treat many diabetics has disclosed but 4 cases of a similar duration. In all instances, however, these confreres have been in practice for a shorter period and thus have not had the opportunity to follow cases so long. Furthermore, of my own 9 cases there are 4 who have been treated jointly with Woodyatt, Allen, Burgess and J. R. Williams. Most reports upon diabetic children are based upon cases of short duration. Any doctor who has a case of ten years' duration should publish the same for the encouragement of all diabetic children as well as their physicians.[1]

"The child diabetic is the pure diabetic, the diabetic in whom the diagnosis is not in doubt. He sets the standard for all other diabetics. Moreover, he is the desirable diabetic and deserves intensive study because of the light he throws upon the problems of treatment, prognosis, regeneration of the pancreas, and the so-called diabetic complications of the skin, the eyes, and the arteries, and also of diabetic surgery and ultimately of the diabetic causes of death if such exist. He is the best for end-results. It is fortunate that children constitute not more than 7 or 8 per cent of all diabetics, because the number is not overwhelming, and fortunate, too, that they are of all diabetics the most readily traced."

For convenience the diabetic children have been divided according to onset into three epochs: (1) The Epoch of Naunyn; (2) the Epoch of Allen, Woodyatt, Shaffer, Pétren, and Newburgh and Marsh; (3) the Epoch of Banting and Best, Macleod and Collip. The living and the dead appear in Table 287.

TABLE 287.—SHOWING THE NUMBER AND PERCENTAGE OF BOTH FATAL AND LIVING CASES, CLASSIFIED ACCORDING TO PERIOD WHEN FIRST SEEN. COMPILED TO SEPTEMBER, 1926.

Period.	Total No. cases first seen in period.	Status, September, 1926.		Status, July 1, 1927.	
		Dead.	Living.	Dead.	Living.
Naunyn (Aug., 1898 to Jan., 1914)	61	60 (98.4%)	1 (1.6%)	60 (98.4%)	1 (1.6%)
Allen (Jan., 1914 to Aug., 1922)	169	117 (69.2%)	52 (30.8%)	118 (69.8%)	51 (30.2%)
Banting (Aug., 1922 to Sept., 1926)	165	18 (10.9%)	147 (89.1%)	19 (11.5%)	146 (88.5%)
Totals and averages	395	195 (49.4%)	200 (50.6%)	197 (49.9%)	198 (50.1%)

[1] Certain sentences and paragraphs which follow appeared first in the Jour. Am. Med. Assn., 1927, **88**, 28.

From the Naunyn period just 1 patient is alive of the 61 cases treated, and he is an hereditary diabetic. His survival is no mere accident, because he is the son of my diabetic, Case No. 155, page 188.

"From the Allen Epoch with 169 cases there are 51 cases, 30.2 per cent, still living. Allen had the courage to starve a child to make it live, and the other investigators mentioned with him explained acidosis and the place of fat in the diet. These 51 children are cheerful witnesses of their faithful labors, and we should acknowledge these labors to have been performed in a laboratory as well as in a ward. Furthermore, each of these children is alive today, because his or her own doctor in his daily care of the patient has made use of modern diabetic tests in his own office laboratory."

The Banting period so far as statistics are concerned includes 165 cases and is of five years' duration. This is time enough at least with children to show comparative results, even if not end-results. Therefore, note that of 165 children with onset since August 7, 1922, there are 146, or 88.5 per cent, who are known to be alive. Since September, 1926, there are other children, numbering 40, who have come for treatment, but the period of observation is too short for them to be chronicled here.

Combining the present living cases in all periods, the total number of diabetic children with onset under fifteen years who are still under observation is 198. Before entering into a discussion of their health and their future, let us seek evidence upon end-results from fatal cases and first of all from 8 children of my group upon whom autopsies were performed and 2 others placed at my disposal by Dr. John of Cleveland and Dr. Stansfield and Dr. Sparrow of Worcester.

1. **Fatal Cases.—Pathological Evidence Upon Prognosis.**—Shields Warren has had the kindness to study anew the protocols of these 8 patients, as well as those of the two others mentioned, review the conclusions of the pathologists who originally made the postmortems and finally to reëxamine the specimens themselves, which in 7 instances have been preserved. "In each case he found sufficient pancreas, and specifically, an ample number of islands of Langerhans, to allow a longer life. He expresses the hope that through treatment, which permits the element of time to act, irreversible changes in the pancreas may be avoided. Thus pathology puts up no bars against the continued improvement of the diabetic."

Reports of autopsies upon diabetic children have also been published by Boyd and Robinson,[1] Heiberg,[2] Ambard,[3] Kochman,[4]

[1] Boyd and Robinson: Am. Jour. Pathol., 1925, **1**, 135.
[2] Heiberg: Arch. f. Kinderheilk., 1911, **56**, 403.
[3] Ambard, *et al.*: Bull. et mém. Soc. méd. d. hôp. de Paris, 1925, **49**, 547.
[4] Kochmann: Jahrb. f. Kinderheilk., 1922, **99**, 20.

Schippers,[1] and Poynton,[2] but in no instance has a pancreas been reported which was devoid of islands of Langerhans. In other words, as elsewhere mentioned, page 39, there is no proof pathologically of complete diabetes.

Clinical Evidence Upon Prognosis.—The durations of life of my fatal diabetic children are shown in Tables 288 and 289. In Table 288 the cases are listed according to the epoch in which the children died, and in Table 289 according to the epoch in which they came for treatment. Case No. 887 has been omitted from both tables in the averages, because the unusual duration of twenty-nine years for this patient would distort the figures.

TABLE 288.—DIABETIC CHILDREN. FATAL CASES CLASSIFIED ACCORDING TO PERIOD OF DEATH.

Period.	Compiled to September, 1926.				Compiled to July, 1927.			
	Total cases dying in period.	Age at onset, years.	Duration, years.	Death in coma, per cent.	Total cases dying in period.	Age at onset, years.	Duration, years.	Death in coma, per cent.
Naunyn	51	9.7	2.1	95	51	9.7	2.1	95
Allen	110	8.8	2.4	88	110	8.8	2.4	88
Banting	34	9.8	2.6	94	36	10.0	2.7	92
Totals and averages	195	9.2	2.4	91	197	9.2	2.4	91

TABLE 289.—DIABETIC CHILDREN. FATAL CASES AND THEIR DURATION.

Period when first seen.	Total cases.	September 1, 1926.		July 1, 1927.	
		Dead.	Duration, years.	Dead.	Duration, years.
Naunyn	61	60	2.2	60	2.2
Allen	169	117	2.5	118	2.6
Banting	165	18	1.7	19	1.6
Totals and averages	395	195	2.4	197	2.4

During the Naunyn period 51 children died at the end of 2.1 years and in 1914 I had only 10 living diabetic children despite sixteen years of practice. All but 1 of these succumbed so soon that the final average duration of life of the 60 children was raised to but 2.2 years.

By the end of the Allen period the duration of life of the fatal cases had scarcely changed, being 2.4 years, but there was this great difference, that more than one-third of the patients remained

[1] Schippers: Am. Jour. Dis. Child., 1925, **30**, 336.
[2] Poynton: British Med. Jour., 1923, i, 277.

alive and of these 69 patients there are but 17 who have since died. By their deaths the duration has been raised to 2.6 years. Should we reckon the living with the dead, the score of duration for the Allen period would double that of the Naunyn period. There is no reason to suspect that the diabetes in the first period was more severe than that of the second. On the contrary the causes of death in the two periods demonstrate their similarity for they were essentially the same. In the first group 95 per cent died of coma and in the second group 88 per cent.

Coma deferred sums up the achievment of the Allen Epoch over that of the Naunyn if we limit our comparisons to fatal cases, and one cannot escape the conviction that coma should not have arrived so quickly.

"The Banting Epoch, in contrast to the Allen Epoch, began with 70 survivors, and to these were annexed 165 new cases up to September 1, 1926. Of these 235 patients there have been 36 deaths, 15 per cent of those treated. Note the difference. In 1916 my statistics show there were 10 per cent of all my cases, old as well as young, who died during that one year. Now during four years the percentage of deaths even among children is 15 per cent. The average duration of the 19 fatal cases of the 165 first seen in the Banting period is 1.6 years. For the true results of this period, however, reference must be made to living cases. The 17 deaths of these beginning treatment in the Allen Period and the 19 deaths of those whose onset was in the Banting Period require comment. Two of this total of 36 fatalities occurred at the Deaconess Hospital. Tommy D., Case No. 1305, was my first child treated with insulin. He accidentally omitted it, developed an infection, returned to the hospital in October, 1922, and died in seven and a half hours. The other patient, Case No. 3240, entered in the afternoon after two days of coma and a 100-mile ride in an automobile and died about six hours later. None of the remaining 34 patients were seen by me within seven days of death, and in fact in 1 case the interval between the last visit and the date of death was forty-five months."

The decrease in percentage of deaths from diabetes in children to total deaths from diabetes in Massachusetts is suggested by the Mortality Statistics collected by Angeline Hamblen.[1] (See p. 119.) I am indebted to Miss Hamblen for the actual proof which is furnished by Table 290.

Confirmation of improved prognosis is afforded also by Priesel and Wagner[2] who report 43 cases treated since the beginning of 1923 without a death and by Geyelin[3] who had in 1926 treated 51 children

[1] Hamblen: Jour. Am. Med. Assn., 1927, **88**, 243.
[2] Priesel and Wagner: Egeb. d. inn. Med. u. Kinderheilk., 1926, **30**, 535.
[3] Geyelin: Atlantic Med. Jour., 1926, **29**, 825.

since the advent of insulin with only 4 deaths, 3 of which were not in coma, while the fourth died of circulatory failure though acidosis had been successfully overcome. One should not infer that diabetic children do not contract coma. Thirty-eight per cent of Boyd's[1] cases have already had it.

TABLE 290.—PER CENT OF TOTAL DEATHS FROM DIABETES IN MASSACHUSETTS FOUND IN THE AGE GROUP UNDER FIFTEEN. (ANGELINE D. HAMBLEN.)

Year.	Total deaths from diabetes.	No. deaths under 15 years.	Total deaths under 15 years. per cent.
1900	330	23	7.0
1910	575	38	6.6
1920	796	40	5.0
1923	852	23	2.7
1924	772	20	2.6
1925	806	18	2.2

2. **Living Cases.—Clinical Evidence Upon Prognosis.**—"Sufficient has been said of the single survivor of the Naunyn Epoch with eighteen years to his credit, whom all will hope for diabetes' sake had true diabetes. (See p. 188.) The 51 survivors of the Allen period, some of whom joined the diabetic army at the early age of three years, have earned my respect for they have fought diabetes on the average for 7.4 years. Their present state of health indicates they will give a good account of themselves in years to come. Recently I presented a score of children diabetics, a few from the Allen period and the rest from the Banting period, to a group of pediatric societies, and I think the impression conveyed was that diabetic children looked quite as healthy as normal boys and girls. The living cases of the Banting period are so numerous (146) and the diabetes so recent in origin that one would anticipate little in the statistical show, yet it is true that the average living Banting diabetic has already exceeded the average duration of life of all fatal diabetic children in my series heretofore."

TABLE 291.—DIABETIC CHILDREN. LIVING CASES AND THEIR DURATION.

Period when seen.	Total cases.	September 1, 1926. Alive.	September 1, 1926. Duration, years.	July 1, 1927. Alive.	July 1, 1927. Duration, years.
Naunyn	61	1	18.4	1	19.2
Allen	169	52	6.6	51	7.4
Banting	165	147	2.8	146	3.7
Totals and averages	395	200	3.8	198	4.6

[1] Boyd: Canad. Med. Assn. Jour., 1927, **17**, 1167.

TABLE 292.—DURATION OF DIABETES IN FATAL AND LIVING CASES COMPILED TO JULY 1, 1927.

A. *Dead.*

Period.	Total cases.	Dead.	Under 1 yr.	1 yr.	2 yrs.	3 yrs.	4 yrs.	5 yrs.	6 yrs.	7 yrs.	8 yrs.	9 yrs.	10 yrs.	11 yrs.	12 yrs.	13 yrs.	14 yrs.	15 yrs.	Over 15 yrs.
Naunyn	61	60	18	19	9	7	1	2	1	...	...	2	...	...	1				
Allen	169	51	25	32	25	12	8	7	2	2	3	...	...	...	...	...	...	1	1
Banting	165	18	6	8	2	2	1												
Totals	395	197	49	59	36	21	10	9	3	2	3	2	...	...	1	...	...	1	1

B. *Alive.*

Period.	Total cases.	Living.	Under 1 yr.	1 yr.	2 yrs.	3 yrs.	4 yrs.	5 yrs.	6 yrs.	7 yrs.	8 yrs.	9 yrs.	10 yrs.	11 yrs.	12 yrs.	13 yrs.	14 yrs.	15 yrs.	Over 15 yrs.
Naunyn	61	1	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	1
Allen	169	51	...	...	...	...	...	7	21	9	5	3	3	1	1	...	1		
Banting	165	146	1	24	25	40	34	12	6	3	...	...	...	...	1				
Totals	395	198	1	24	25	40	34	19	27	12	5	3	3	1	2	...	1	...	1

B. PROGNOSIS OF DIABETES IN CHILDREN.

The prognosis of a child with diabetes is serious under any circumstances, even though insulin has been discovered, yet it is certainly unfair to base the prognosis upon the unfavorable records of the past. There are but few cures of diabetes, but the few which are on record have most often occurred in children, and there is always the possibility that the present child is the exceptional case which may recover. While the parents are told the usual outcome of such cases, they should be given hope. Think of the number of children whose lives were prolonged by routine treatment and were rewarded by the discovery of insulin. Evidence that parents appreciate this attitude and that they do not resent follow-up letters is afforded by the last sentence of a response to such a letter regarding a fatal case— "I do thank you for writing and asking about my boy," and by the Christmas cards I prize most, those from the parents of my former little patients.

The prognosis is not invalidated by a high blood sugar. In Williams'[1] case a blood sugar of 0.53 per cent fell to 0.11 per cent and he considered the case mild. In a patient, Case No. 2870, treated by John and myself, he found the blood sugar four and a half hours after a meal on August 15, 1922, to be 0.638 per cent. This boy did extraordinarily well with a tolerance for 180 grams carbohydrate, which gradually fell to 86 grams. With insulin he also did well when he adhered to his diet and is alive in February, 1928. The children with high percentages of urinary sugar generally do well. It is my hope that by keeping children alive for a considerable period of years, time will be afforded for the pancreas to regenerate sufficiently to allow of a reasonably comfortable life. I realize the seriousness of intercurrent infections, but they do not appear to cause diabetes, (see p. 539) and seldom more than temporarily damage the pancreas or interfere with the action of insulin, whether endogenous or exogenous.

The more remote so-called complications of diabetes, such as those of the skin and eyes, are most infrequent in children. D. Crosby Greene is responsible for the statement that my diabetic children withstand operations upon the throat better than normal children. Lyman Richards said the same at the time of the successful recovery of Stanley L., Case No. 2680, at the age of 13.1 years, 7.6 years after the onset of his diabetes. At the time of operation he was taking 60 to 65 units of insulin and the blood-sugar tests varied between 0.09 per cent and 0.44 per cent. This may mean that the extra care given a surgical diabetic child offsets the added risk from

[1] Williams: Arch. Int. Med., 1923, **23**, 546. Personal communication regarding his case, No. 1936.

the anesthesia. Eventual arteriosclerosis in its various manifestations is a real danger, but with diets approaching 100 grams of carbohydrate before the end of ten years of diabetes, with better arteries of children to begin with, and with the child's better reparative powers, my apprehension is somewhat allayed; it is all the more so, now that I know that 60 per cent of the cholesterol determinations are not above normal.

The aptitude with which the general practitioner has taken to insulin is not only a credit to his intelligence, but a guarantee of better health to the child Improved technique in treatment is daily bettering our results. Micro-blood-sugar tests (see p. 444) will familiarize all doctors with modern methods of blood analyses.

The favorable influence of heredity is undoubted (see pp. 145 and 821), but I cannot attach great importance to different types of diabetes until I have more cases who have lived a decade. An early detection of the disease is helpful, but a late diagnosis and no previous treatment is better than an early diagnosis with an ill-advised diet.

At present I believe that the younger a diabetic the greater his expectation of life, but few doctors can expect to live long enough to prove this. There is always this favorable aspect with an infant: that the disease could not have lasted very long before being diagnosed. I do not believe with Priesel and Wagner[1] that "Der Diabetes im Kindesalter ist eine dauernd progrediente Krankheit. . . . Der Kinderdiabetes muss am Schlusse ein totaler Diabetes werden," because pathological, p. 811, chemical, p. 830, and clinical, p. 814, evidence of the existence of complete diabetes is not convincing. A later article shows they have modified their views.

C. INCIDENCE.[2]

There are two to three times as many diabetic children in the country today as a decade ago, yet the mortality chart and table of Angeline Hamblen would lead one to believe that the disease was disappearing in childhood. (See Fig. 37, Table 294.) Such is not the case. These divergent views are reconciled in the statement that diabetic children live much longer than heretofore. Statistics upon diabetic children, and adults for that matter, therefore differ widely according to whether they are based on living or fatal cases.

The incidence of diabetes based on the age at onset in the first decade of life to the total incidence ranged around 1 per cent in the past. (See Table 50.) Even in 1910 von Noorden[3] records but

[1] Priesel and Wagner: Loc. cit., p. 677.

[2] A comprehensive study of diabetic children in Norway by Toverud has appeared too late for inclusion in the text. Toverud: British Jour. Child. Dis., 1927, **24**, 185, 257.

[3] Von Noorden: Pfaundler u. Schlossmann: Diseases of Children, Lippincott, 1912, **2**, 225.

2.8 per cent among 3000 cases, but in the author's series of 2611 supposed diabetics first coming for treatment it was 5.7 per cent; among the 2440 of this number who have been classified as true diabetics it was also 5.7 per cent.

In Table 293 the incidence is presented in another form and is based not upon the children with onset in the first decade but in the first fourteen years and thus includes *all* the children. The table is so arranged that one can see the percentage of children in successive thousands. The decrease in number of children in the later thousands may be attributed in part to the shorter interval of time which the later series of 500 cases represents, but it is in part because doctors formerly despaired more of diabetic children and sought consultations frequently, but now find the disease in children more amenable to treatment.

TABLE 293.—DIABETIC CHILDREN UNDER FIFTEEN YEARS OF AGE GROUPED AS CHRONOLOGICALLY SEEN.

Actual dates.	No. of supposed diabetics.	True diabetics.	True diabetic children. Number.	True diabetic children. Per cent of total diabetics.
Aug. 1898 to Feb. 1916	1000	906	87	9.6
Feb. 1916 to Sept. 1920	1000	865	83	9.2
Sept. 1920 to Jan. 1923	1000	839	86	10.3
Jan. 1923 to July, 1924	1000	843	49	5.8
July 1924 to Jan. 1926	1000	809	59	7.3
Jan. 1926 to Sept. 1926	500	417	31	7.4
Total	5500	4679	395	8.4

If the series be studied from the standpoint of five-year-age groups and a fourth group, fifteen to twenty years, added for youth, it is evident that nearly as many cases occurred in the third quinquennium, ten to fifteen years, as in the first two quinquennia combined. This difference is accentuated when one relates it to the living population in the three periods. It would then be four times as great more or less. Our data show that the incidence of true diabetics in the fourth quinquennium was practically the same as in the third. The evidence therefore points to the third and fourth quinquennia as of chief significance in diabetes until the age of twenty years. Somewhat similar data are shown in Table 290.

TABLE 294.—AGE AT ONSET OF DIABETES IN VARIOUS AGE GROUPS IN CHILDREN.

Epoch	Total cases.	0 to 5 years.	5 to 10 years.	10 to 15 years.	15 to 20 years.
Naunyn (1898–1914)	61	7	22	32	
Allen (1914–1922)	169	38	52	79	
Banting (1922–1926)	165	37	55	73	
Totals	395	82	129	184	185

In the Naunyn Epoch my cases in the first five years of life constituted one-third of the children for the third quinquennium, but in the Allen and Banting Epochs they amounted to one-half.

Eighty-two cases had an onset under five years of age and 211 cases had an onset under ten years of age. I doubt if at present

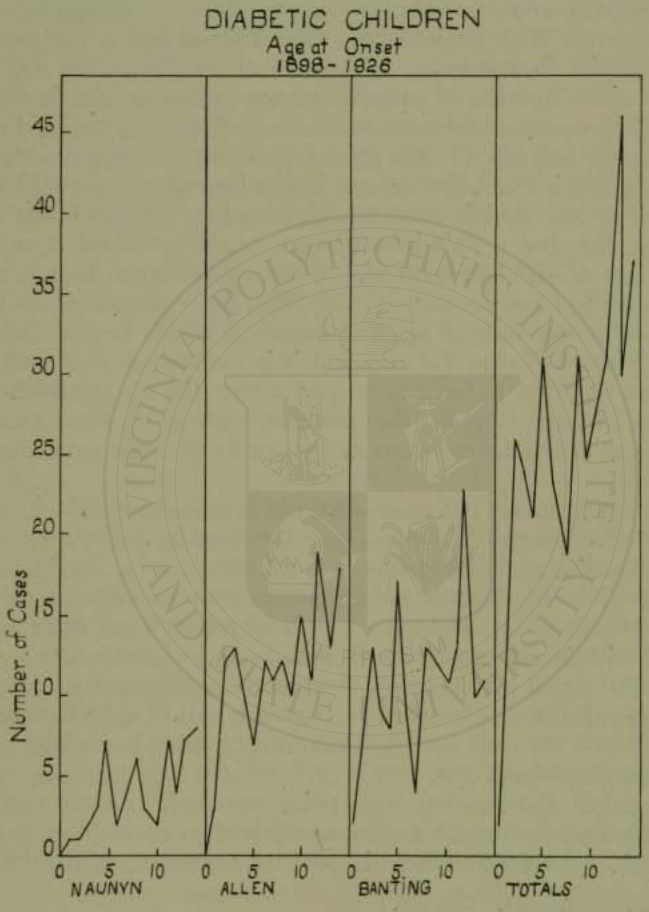

FIG. 38.

diabetes in children under five years is overlooked, but it would appear from Table 294 that it was at the beginning of this century.

Two peaks of age incidence of onset of diabetes are fairly apparent in childhood, the first occurring at about five years and the second and more important at twelve years. This is shown graphically in Fig. 38 in which are represented my cases plotted according to

epochs—Naunyn, Allen, Banting. It is easy to attribute the second peak to the rapid growth at twelve years, but this makes all the more difficult the explanation of the earlier rise in frequency. Priesel and Wagner[1] also call attention to the first maximum in the sixth year and the second in the eleventh to twelfth year. John's[2] series also show peaks at six years and eleven years.

The relation of sex to the age of onset is shown in Table 295.

1. **Diabetes With Onset Under One Year of Age.**—The youngest diabetic child in my series, Richard S., Case No. 5459, was eight months old. Any list of cases under one year must be incomplete and perhaps somewhat incorrect, because of the cases missed in the past, though less often in the present, and because of unsatisfactory data supplied in the older reports in the literature. In 1913 Knox[3] reported a case which came under his observation at the Johns Hopkins Hospital. This infant began to show diabetic symptoms at the age of eight months and a few weeks later died in coma. Knox searched the literature (1852–1913) for reported cases with an onset under one year of age and found 15 which he considered as probably cases of true diabetes, but it is remarkable that 3 of these cases are reported to have recovered under dietary treatment. In addition to these 15 cases with his own, making 16, Knox found 11 other cases which he regarded as not surely diabetic from the data presented.

So far as we know the cases have not been collected since, but we can add a few others. There is a case described by Ashby,[4] with onset at five months, who had gangrene of the toes; another by Major and Curran[5] with cataracts at eleven months; a case with 9.1 per cent sugar described by Schippers,[6] with onset at four months, was treated with insulin and died of pneumonia and coma at 2.1 years; one by DeLange[7] with onset at eight months and death at 2.2 years. There are also cases described by Bowcock and Wood,[8] Kochmann,[9] Lasalle[10] and my own case, Case No. 5459, already mentioned and later described on p. 838.

Congenital diabetes has been twice reported. I have had none such, nor had Naunyn,[11] and he recognized no authentic case in the literature. Ambard's[12] case is that of a woman, aged thirty-five

[1] Priesel and Wagner: Loc. cit., p. 552.
[2] John: Personal communication.
[3] Knox: Bull. Johns Hopkins Hosp., 1913, **24**, 274.
[4] Ashby: Lancet, 1923, i, 22.
[5] Major and Curran: Jour. Am. Med. Assn., 1925, **84**, 674.
[6] Schippers: Ned. Tydschr. v. Geneesk., Amsterdam, 1925, **1**, 2206.
[7] De Lange: Am. Jour. Dis. Child., 1926, **31**, 840.
[8] Bowcock and Wood: Jour. Am. Med. Assn., 1926, **86**, 104.
[9] Kochmann: Jahrb. f. Kinderhelk., 1922, **99**, 20.
[10] Lasalle: Arch. d. Méd. des Enfants, 1923, **26**, 423.
[11] Naunyn: Der Diabetes Mellitus, Wien., 1906, p. 234.
[12] Ambard, *et al.*: Bull. et mém. de la soc. méd. des hôp., Paris, 1925, **94**, 547.

years, with severe diabetes who gave birth in the eighth month to an infant whose urine contained 1.2 per cent sugar. The mother died in a few hours and the child died in twenty-three hours. Necropsy showed lesions in both maternal and fetal pancreas. Morrison's[1] case is even less conclusive. He found it when searching the Boston Mortality Statistics from 1895 to 1913. It was the case of a new-born infant who was said to have died from diabetes. The mother, a diabetic, also died.

2. **Sex.**—Contrary to the impression gained from the literature, there was not a notable preponderance of males among the 395 diabetic children, although it did exist in each of the three quinquennia. There were 206 males as against 189 females, but the actual percentage difference, 4.8 per cent, is slight, as may be seen from Table 295. The males exceed the females by 9 per cent.

TABLE 295.—SEX IN DIABETIC CHILDREN.

	Age groups, years.			Total.	
	0 to 5.	5 to 10.	10 to15.	Number.	Per cent.
Males . . .	43	67	96	206	52.4
Females . . .	39	62	88	189	47.6
Total . . .	82	129	184	395	100.0

3. **Race.**—Jewish children constituted 6.1 per cent of all my children. This is quite in contrast to the 13 per cent of Jews among my 5086 diabetics. It confirms my impression that diabetes which is so common in the later life of the Jew is an acquired rather that a congenital characteristic and hence much more easily avoidable. Abt[2] had likewise seen 7 to 8 Gentile children with diabetes to 1 Jewish child. Priesel and Wagner[3] report among their 58 children 10 Jewish and 1 of mixed race, *i. e.*, 17 per cent. The character of the Jewish children is usually more stable than that of their parents. I have profound respect for one Jewish child, eleven years of age, who for over a year has administered her own insulin.

In the special group of 100 children of my series studied by Priscilla White it was found that all of the children were American born. As a group they represent an average racial mixture. Fifty-six per cent were of American parentage, 17 per cent Irish, 11 per cent Swedish, 7 per cent Hebrew, 5 per cent French, 2 per cent German, and there was a Scotch and Italian parentage in 1 per cent each.

4. **Heredity.**—An hereditary or familial history in the family of a diabetic child is as favorable as in an adult. Elsewhere this has

[1] Morrison: Boston Med. and Surg. Jour., 1916, **175**, 54.
[2] Abt: Endocrinology, 1919, **3**, 273.
[3] Priessel and Wagner: Loc. cit., p. 552.

been discussed in some detail, p. 145, but it may be repeated here that of the 12 diabetic children who have lived more than ten years there was an hereditary or familial element or both in 84.9 per cent, that in the 200 living cases this is present in 31.5 per cent, whereas in the 195 fatal cases this was found in only 21 per cent, essentially the same per cent as for the entire series of diabetics. The data for the children are recorded in Table 296.

TABLE 296.—HEREDITY IN DIABETIC CHILDREN.

Groups of cases.	Heredity.				
	No. of cases.	Hereditary tendency, per cent.	Familial tendency, per cent.	Both hereditary and familial, per cent.	Total per cent.
Duration over 10 years (total)	12	59.2	9.1	16.6	84.9
Living cases from Allen Epoch	52	25.0	3.8	3.8	32.6
Living cases (total)	200	26.0	1.5	4.0	31.5
Fatal cases (total)	195	12.3	5.1	3.6	21.0

Heredity was observed by Priesel and Wagner[1] in 10, or 17 per cent, of their 58 cases, and they discuss in considerable detail the observations of the others. A progressively earlier onset of diabetes in succeeding generations has been commented upon by various writers, see p. 146. The earlier it appears, they reason, the greater must be the congenital insufficiency of the pancreas. Among my own cases, both in children and adults, there are data sufficiently accurate about the onset in two generations to allow the construction of Table 297.[2]

Priesel and Wagner report an instance of a child, aged seven years, whose father, grandmother, and great grandmother on the father's side and grandfather on the mother's side had diabetes. The father developed the disease at thirty-five years, the grandmother is living, and the great grandmother died at fifty-six years.

Kückens[3] records the appearance of diabetes in twins who were so similar that only with difficulty could they be told apart. The color of hair and eyes was the same. Diabetes developed with one at fifteen years and he died in twelve weeks of coma; the other twin showed sugar shortly before his brother's death but under treatment with insulin lives. The simultaneous appearance of diabetes of almost the same severity and character in twins extremely similar and of the same sex makes a complete identity of the hereditary tendency

[1] Priesel and Wagner: Loc. cit., p. 553.
[2] Special studies in the heredity of 1000 cases will be made soon.
[3] Kückens: Klin. Wchnschr., 1925, **4**, 2289.

in these two individuals probable. One is dealing with a single ovum, homologous twins. Priesel and Wagner comment upon the necessity of attributing these cases of Kückens to a congenital minderwertigkeit or to a failure of development (bildungsfehler). There was said to be only two instances similar to the above in the literature. I had no record of diabetes in twins until July 27, 1927, when Earl I., Case No. 4768, brought in his brother in whose urine he had found sugar. Jane T., Case No. 5301, whose age at onset was thirteen years, had an identical twin sister who died of diabetes at the age of three years.

TABLE 297.—DIABETES IN THE CHILD AND PARENT COMPARED. ONSET IN CHILD BEFORE PARENT.

Case No.	Child, age at onset years.	Duration, July 1, 1927 years.	Condition.	Case No.	Parent, age at onset years.	Duration, July 1, 1927 years.	Condition.
105	15	3.8	Dead	339	47	5.7	Dead
....	14	1.4	Dead	473	48	0.2	Dead
503	30	15.2	Alive	711	54	13.8	Alive
....	2	1.0	Dead	954	49	3.0	Dead
....	12	0.2	Dead				
1285	27	....	Untraced	....	55	....	.....
....	23	2.5	Dead	1421	74	1.0	Dead
....	..	....[1]	Dead	4656	48	3.1	Alive
....	..	....[2]	Dead	4719	45	2.0	Alive
....	..	....	Dead	5017	55	1.6	Alive
2300	7	7.0	Alive	....	42	2.3	Alive
2856	10	5.4	Alive	6229	40	1.1	Alive

Langaker[3] reports the existence of diabetes in 4 children, all of whom died within four years, out of a family of 8. Three of these 4 children were less than five years old at death; subsequently a fifth child contracted the disease and died in his seventh year.

Labbé[4] speaks of heredity as being unusual in his 30 cases, but points out the frequency of the simultaneous appearance of diabetes in several children. Among 166 of my children there were 15 who had a brother or a sister with the disease; 23 had parents or grandparents with diabetes.

The subject of heredity will also be taken up in the consideration of the children with non-diabetic glycosuria, see p. 856, since in these children it is even more marked.

Of the children with true diabetes there were 26, or 12 per cent, who had no brothers or sisters. This might seem of significance as evidence of defective germ plasm were it not for the fact that 24 per cent of the non-diabetic glycosurias were "only children" as well.

[1] Died, aged twenty-two months.
[2] Died, aged one and a half years.
[3] Langaker: Deutsch. med. Wchnschr., 1911, **37**, 217.
[4] Labbé: Presse méd., 1922, **12**, 371.

D. ETIOLOGY.

Still less is known about the etiology of diabetes in children than in adults. It is more prudent to record the above facts which may have a bearing upon the subject than to theorize, particularly with reference to race and heredity.

I know of but one case on record in which a diabetic mother gave birth to a diabetic child. Although an hereditary and familial tendency to diabetes is present in 24.6 per cent of all true diabetics and in a slightly greater percentage of diabetic children, I happen to have encountered but one instance where a diabetic patient I had seen had the misfortune to have a child later develop the disease. Of course in time this must happen. I confess I harbor the hope that the instruction given the diabetic patient upon the danger of obesity, particularly in the children of diabetics, may lead to the prevention of the disease in many a child or young adult. In at least 3 instances, Cases No. 105, 2856 and 4147, I have cared for a diabetic child whose parent later developed diabetes.

1. **Marriage.**—"Should these diabetic children later marry? The boys can and will at twenty-one years of age or over; the girls should have diabetes ten years before they assume so much responsibility. Let me cite Case No. 436 who was a trifle older than a child, nineteen years, when her diabetes developed with 8 per cent of sugar in the urine. She was then pronounced hopeless by an eminent German clinician. Subsequently she married and seven years after the onset of diabetes gave birth to a beautiful boy who is now ten years old and the picture of health and her joy today."

2. **Overheight in Diabetic Children.**—Overheight in the past history of the diabetic child, according to Priscilla White,[1] is more common than overweight in the diabetic adult. Previous to insulin therapy, surviving diabetic children soon fell far below height as well as weight, and the fact that the diabetic child was originally tall for his age escaped notice. The proof of overheight is furnished by the records of the heights at onset of the diabetes as well as the maximum weights preceding onset in 100 diabetic children for whom she found these data sufficiently explicit in my series. Furthermore, Morrison and Bogan[2] utilizing the roentgen-ray, found in a series of 68 of my children that bone development was in advance of the chronologic age in diabetes of recent onset, but was below the chronologic age in children with diabetes of long standing. They did not find bone atrophy in children who developed the disease after the ninth year. Transverse striæ of the bones are more common in diabetic than in normal children.

[1] White: Jour. Am. Med. Assn., 1927, **88**, 170.
[2] Morrison and Bogan: Am. Jour. Med. Sci., 1927, **174**, 313.

Ninety per cent of the 100 diabetic children were overheight in contrast to 62 per cent of the 925 adults above the age of twenty years, see Table 67, who were overweight prior to the disease. It is generally admitted that overweight is a precursor of diabetes in an adult, and now we have even more striking evidence of overheight in the child. This deviation of height from the normal average, when based on Wood's[1] table, amounts to an excess of 2.7 inches.

3. **Overweight in Diabetic Children.**—Obesity was the exception in the 100 cases studied by Priscilla White. There were but 5 who were as much as 10 per cent overweight for height and but 2 reached the obese class of 20 per cent overweight. Compared with Gray's[2] standard they weigh for their height 0.9 pound less than the slender private school child. Dr. White attributed significance to the fact that so striking a precursor of the disease as is obesity in the adult should be so rare in the child. It would seem to indicate that overweight in and of itself is not the real factor which leads to the development of diabetes in the adult any more than overheight in and of itself leads to the development of diabetes in the young. Overweight and overheight must be secondary to other determining causes, and one cannot help surmising that there must be a close interaction between the pancreas, gonads, thymus, and hypophysis and the thyroid and adrenal. Ladd and Day[3] find in a careful study of 34 diabetic children compared with the Bardeen standard that all but 4 of the 30 were overweight or overgrown or both at onset.

4. **Influence of Activity of Sex Glands.**—The influence of the internal secretion of the glands of sex on skeletal growth and body weight is best shown at two periods of life—puberty and menopause. Precocious sexual maturity is associated with dwarfism; with delayed maturity there is excessive growth in height. Normally early maturity signifies that growth in height is near its completion, cessation of growth in height indicates sex maturity. As for body weight, the menopause is often followed by obesity.

A striking parallel exists between the beginning and the end of sexual activity and the onset of diabetes. Thus the onset in 47 per cent of our 395 children occurred at the age of puberty ten to fifteen years, and there were more cases in the twelfth year than in any other year of childhood. Similarly in adults the fifth decade shows the greatest morbidity of diabetes and the sixth stands next to it, these two decades comprising nearly one-half of all the patients one sees. In statistics based upon mortality and not upon morbidity

[1] Wood: Ninth yearbook of the National Society for the Study of Education, Part I, Health and Education, Chicago, 1910, p. 34.
[2] Gray and Fraley: Am. Jour. Dis. Child., 1926, **32**, 554.
[3] Ladd: Am. Jour. Dis. Child., 1926, **32**, 812.

at onset these significant data are obscured. *The quinquennium for females which has the highest number of diabetics is that between the forty-ninth and fifty-third year; that for males is the same.* The year of age which contains the greatest number of females reckoned by onset among my true female diabetics is the fiftieth year and the years for the males are the fifty-first to fifty-third. (See Fig. 19.)

Among 34 girls between the ages of twelve and fifteen for whom information is available, catamenia had become established before onset of the diabetes in 15 per cent.[1] In 6 per cent onset of diabetes and menstruation were coincident, while in 79 per cent catamenia had not begun. Priesel and Wagner[2] with illustrations portray the sexual development of children. They noted the temporary loss of tolerance before and during menstruation. Diabetic boys likewise mature according to their data as well as girls. The normal sexual development of a diabetic child at puberty may soon be considered as an index of good or bad treatment. Priesel and Wagner[3] in a later publication and also Boyd record proper sexual development and the former confirm their original statements about development in height and weight.

5. **Influence of Thymus.**—The diabetic child closely resembles in some respects the thymic child, who is likewise superior in height, mentally precocious, sexually immature, and has a profuse growth of lanugo hair. Postmortem examinations of diabetic children are few, so we have little anatomical evidence of any subinvolution of the thymus in diabetes. Dr. Ralph Major, however, in a personal communication described a case of fatal diabetic coma in a child in whom the autopsy revealed an unrecognized status lymphaticus. Bertnard Smith of Los Angeles told me that he had observed an enlarged thymus in 7 cases among his large group of diabetic children.

6. **The Influence of the Hypophysis.**—The possible relationship of the pituitary gland to diabetes has become more convincing through the work of Davidoff and Cushing.[4] They have demonstrated in their studies of acromegaly the frequent association of hyperactivity of the pituitary gland and a depressed function of the internal secretion of the pancreas by the frequency of hyperglycemia and glycosuria in 100 of Cushing's acromegalic patients. "The excessive growth of our prediabetic children may well be a 'secondary reaction' on the part of the hypophysis which mildly stimulates growth. Of course, under these circumstances growth would be purely in the direction of gigantism and would show no acromegalic characteristics as the epiphyses of these young people are all open.

[1] Priesel and Wagner: Loc. cit., p. 700.

[2] Case No. 2802 developed diabetes at the age of 14.5 years in February, 1922, and catamenia began six years later.

[3] Priesel and Wagner: Klin. Wchnschr., 1927, **6**, 1892.

[4] Davidoff and Cushing: Arch. Int. Med., 1927, **39**, 673.

I would consequently regard it as secondary gigantism of a mild grade." (Cushing.) Whatever the explanation may prove to be it is significant that preceding the onset of diabetes in the child it is the rule to find for the age an excess of height.

This evidence of unusual growth in children led to the sending of one of our cases (Case No. 5036) to Dr. Cushing, see page 875.

In the above patient as in certain others following the use of insulin the appearance of the child has changed to that of the companions of his own age. He now remains nearly sugar-free in contrast to his former 5 per cent and takes 12 units of insulin. The blood sugar two hours after lunch on September 1, 1927 was 0.23 per cent. The father, Case No. 5049, of the boy is 5 feet 11½ inches tall, his greatest weight 252 pounds, and my preliminary classification of potential diabetes made in February, 1926, was changed on July 15, 1926, to true diabetes because of a blood sugar of 0.2 per cent after a meal and 0.1 per cent of sugar in the urine.

7. **The Influence of the Thyroid.**—At the Deaconess Hospital our attention is daily drawn to diseases of the thyroid gland, because of the many patients undergoing treatment under the direction of our associates, Lahey and Clute. It is notable, therefore, that but 6 of the carefully selected 100 children showed thyroid enlargement, and in none of these were symptoms present of disturbed thyroid function. In fact of the entire group of 395 children there was but 1 case of hyperthyroidism, Case No. 377.

The occurrence of hypothyroidism and diabetes in the same child speaks for a related origin according to Priesel and Wagner.[1] Wilder[2] describes a boy with onset of diabetes at fifteen months who developed myxedema which was diagnosed at three years. (See page 891.)

8. **The Influence of Infections.**—It is as difficult in children as in adults to associate an infection with the onset of diabetes, see p. 539, not because infections are rare, but rather because they are so abundant. Thus Dr. White could find but 6 suggestive instances among the 100 children studied with especial detail from the entire group of children. Yet the evidences of infection presented by the children upon their first examination were appalling. Four had abscessed teeth, 44 showed or gave a history of infections of the tonsils in the previous eighteen months, and 64 had general adenopathy. It would be of value to know if private school children, who are presumably more free from such physical defects as diseased teeth and tonsils, have a lower incidence of diabetes. Their superior growth, however, would somewhat complicate the problem.

During the year preceding the onset of diabetes 40 of the 100 children gave a history of one or more infections. Since the result

[1] Priesel and Wagner: Klin. Wchnschr., 1925, **4**, 1055.
[2] Wilder: Arch. Int. Med., 1926, **38**, 736.

of an infection may be latent and the harmful sequence may not appear for a period of years, Dr. White collected all known infections which had occurred in the lives of 100 children prior to the onset of the diabetes. (Table 71.) In only 2 of the children were infections absent. During the year preceding onset of diabetes, 60 showed no infections whatsoever, and even in the remainder the association of the infection with diabetes appeared incidental rather than causal.

Priesel and Wagner evidently share my view of the difficulty of associating the onset of diabetes with an infection. It is true that during an infection the diabetes of a child or adult becomes more severe and formerly a permanent loss of tolerance appeared to result. (Geyelin.[1]) With insulin available during an infection the harmful effect is less apparent.

In connection with mumps Neurath[2] has shown that the pancreas can be affected. Other writers also have noticed diabetes in association with mumps. I found no such case until September, 1916, Case No. 1139. Long before insulin one of my children, Case No. 105, survived an intercurrent attack of mumps, and in 1907 his recovery was thought to be unusual. See page 823.

9. **The Influence of Syphilis.**—Among my 395 diabetic children there has not been one who requires, so far as I could determine, treatment for any symptom of syphilis. There is no record of a syphilitic child in the group. Wassermann reactions are recorded as having been performed upon 121 of my 200 living children, and in 119 cases were negative, 1 was doubtful, and 1 was positive. S. Strouse[3] has never seen a case of diabetes in a syphilitic child. He adds that the records of syphilitic children do not show that glycosuria is common.

10. **Emotional Excitement.**—I cannot attach much importance to emotional excitement or fright in a child. If these were of significance there would certainly be a thousand cases in children for each one diagnosed today.

11. **Tuberculosis.**—Pulmonary tuberculosis has been diagnosed but once in any child which has come under my supervision. In no instance has a death from this cause been reported subsequently, and I recall no instance in American medical literature. Case No. 2279 developed pulmonary tuberculosis at his home and lives, and Case No. 2007 had a cervical tuberculous gland break down. The results of a series of von Pirquet skin tests are not yet sufficiently numerous to report, but the procedure is now being made a part of the routine examination of all children.

[1] Geyelin: Cecil: Text-book of Medicine, W. B. Saunders Company, Philadelphia, 1927, p. 568.
[2] Neurath: Wien. med. Wchnschr., 1911, **61**, 1218.
[3] Strouse: Abt, Pediatrics, W. B. Saunders Company, Philadelphia, 1923, **2**, 770.

E. SYMPTOMS.

The symptoms of onset of diabetes are often so slight that I am convinced the disease will never be diagnosed early unless frequent routine examinations of the urine are made. The only safe method for a physician at present is to examine the urine whenever a patient is seen. This should be done invariably not only during, but also subsequently to, an infectious disease, though in this latter instance the purpose is more to detect albumin than sugar. The characteristic symptoms of diabetes have been discussed on p. 553, such as polydipsia, polyuria, polyphagia, with loss of strength and weight and change in disposition are usually noted. It is not uncommon to elicit a history of enuresis nocturna in children long before the diabetes could have possibly begun, just as with adults one often hears that they have been water drinkers all their lives.

1. **Type of Onset of Diabetes in Children.**—The onset may be sudden or slow, but as with adults is usually indefinite. Reference has been made to Case No. 129 which remained latent for four years, and another patient, Miss L., Case No. 5731, is still more in point. This patient illustrates not only the difficulties of determining the onset, but the diagnosis as well. At five years of age she showed sugar in the urine, but not in a second specimen a few days later. At ten years she was sugar-free. Now at 16.8 years during four days she shows sugar in 14 out of 15 specimens in varying quantity up to 1.8 per cent while an analysis of the blood sugar is 0.07 per cent fasting and 6 analyses after meals range from 0.08 per cent to 0.13 per cent. It would be easy to dismiss thought of diabetes and of renal glycosuria as well, the urinary specimen without sugar ruling that out, and in fact I actually classify the case only as a potential diabetic and therefore do not include her in my children's series, but some doubt arises for two reasons: (1) Her brother, Case No. 2615, thirteen years older than herself, in 1922 showed 0.2 per cent of sugar in the urine with 0.18 per cent of sugar in the blood after a meal, and in 1926, 2.3 per cent in the urine and 0.18 per cent in the blood three hours after food. This brother has an enlarged thyroid gland. (2) Two years before her birth a younger brother died in 1907 at the age of ten years of diabetic coma after two years of diabetes. One cannot help wonder, (1) if this younger brother was not originally just as mild a case as his brother and sister and, (2) whether this girl now seventeen years of age can be prevented from developing true diabetes. Instead of a glucose tolerance test I have prescribed the best of hygiene with freedom from overwork in any line and a diet consisting of carbohydrate 150 to 200 grams and protein and fat as desired providing the weight is held between normal and 10 per cent below normal.

An attempt to classify the type of onset in 60 living children with true diabetes has resulted in the following table, Table 298. The term "gradual" indicates the probable onset in the course of

TABLE 298.—TYPE OF ONSET OF DIABETES IN 60 LIVING CHILDREN.

Type of onset.	No. of cases.	Per cent.
Indefinite	20	33.3
Gradual	27	45.0
Rapid	9	15.0
Sudden	4	6.7

one to eight weeks; "rapid" indicates within one week, save for those cases to whom the term "sudden" can be applied in which the onset was thought by the family to have taken place in the course of twenty-four hours.

TABLE 299.—AVERAGE BLOOD SUGARS IN DIABETIC CHILDREN DURING SEVEN YEARS.

Case No.		1920.	1921.	1922.	1923.	1924.	1925.	1926.	1927.	Average.
1469	F.	0.09	0.13	0.13	0.22	....	0.13	0.10	....	0.13
	P. C.	....	....	....	....	....	0.17	0.14	0.19	0.17
1616	F.	....	....	0.15	....	0.37	0.16	0.37	0.08	0.22
	P. C.	....	....	0.06	....	....	....	0.17	....	0.11
1895	F.	0.11	0.19	0.21	0.27	0.15	....	0.11	....	0.14
	P. C.	....	0.27	0.08	0.15	....	0.13	0.14	....	0.15
2256	F.	....	0.26	0.25	0.19	0.15	....	0.25	....	0.22
	P. C.	....	....	0.23	....	....	....	0.22	....	0.23
2366	F.	....	0.28	0.26	0.14	....	....	....	....	0.23
	P. C.	....	....	....	....	....	....	....	....	....
2419	F.	....	....	0.15	....	....	0.11	0.10	0.10	0.12
	P. C.	....	....	....	....	0.17	....	....	....	0.17
2560	F.	....	....	0.20	....	....	0.07	0.30	....	0.19
	P. C.	....	....	0.22	....	....	....	....	0.27	0.25
2877	F.	....	0.10	....	0.21	0.18	....	0.14	....	0.16
	P. C.	....	....	....	....	....	....	0.10	....	0.10
2979	F.	....	....	....	....	....	0.10			0.10
	P. C.	....	....	....	....	....	....	....	0.06	0.06

F = Fasting; P. C. = After a meal.

2. **The Blood Sugar in Diabetic Children.**—The percentage of sugar in the blood of a diabetic child during the course of twenty-four hours rivals, in its variations, the moods of the child itself. This is still more the case since the introduction of insulin, because so many more severe cases are now kept alive. The highest blood sugar reported in a child of my series, apart from coma, or to be more arbitrary in a child with a blood CO_2 of 20 volumes per cent or

above, is 0.89 per cent in Case No. 5413. Petrén[1] records a blood sugar of 1 per cent. At the other extreme is Millard Smith's case of the child who recovered from insulin hypoglycemia when the blood sugar was zero as has been described on p. 46. The highest blood sugar in the presence of coma has been 0.77 per cent three hours after 60 units of insulin, Case No. 3877. Smyth[2] mentions a blood sugar of 0.76 per cent.

Children furnish an excellent opportunity for the study of the effect of the duration of the disease upon the percentage of sugar in the blood. (See p. 830.) The records of the blood sugar so far as the average values are concerned in 9 of the 10 cases recorded in Table 311 are given in Table 299. The data are unsatisfactory to this extent: that in successive years they were not always taken under similar conditions.

3. **Manifestations in the Nervous System.**—Severe psychoses, melancholia, hypochondriasis, and neurasthenia occur in diabetic children, but less frequently than one would expect. These complications did not occur in Priesel and Wagner's series, largely I believe because their cases have been treated since the advent of insulin. Children formerly sensed the atmosphere of depression around them, though they rarely gave way to it. Occupation, responsibility, good reasons for hope, and above all an actual feeling of health, are the best antidotes. Yet I can add with much seriousness that one should never allow a diabetic child to become melancholy.

Organic nerve diseases are rare. Neuritis is almost unknown although blood-sugar tests have shown high values for years and years.

A sure diagnosis of epilepsy has not been made in my children, or for that matter in my adults, though an atypical instance is presented by John C., Case No. 3019. He is an only child, developed diabetes at 1.6 years of age with diabetic heredity on the father's side: to wit, a great grandfather, two greataunts, and one greatuncle. With insulin he did beautifully and was successfully operated upon for removal of tonsils. He had severe insulin reactions after 0.8 year of diabetes, and on account of his vivacity it was hard to anticipate or prevent them despite adjustments of diet and insulin. After 1.3 years of diabetes, he developed literally the "falling sickness" and would drop so suddenly as to be injured rather seriously. He shows a negative Wassermann reaction. Even after study with the help of specialists in children, in nervous diseases of children, in ophthalmology, and in brain surgery, a diagnosis cannot be reached. He is worse when the diabetes is poorly controlled. His mental development is not only retarded, but has

[1] Petrén: Ergeb. d. inn. Med. v. Kinderheilk., 1925, **28**, 92.
[2] Smyth: California and Western Med., 1926, **25**, 629.

retrograded. He takes insulin four times a day, 10, 10, 5 and 10 units, and his diet is carbohydrate 131 grams, protein 56 grams, fat 83 grams. His weight was 44.5 pounds at the age of 5.4 years, July, 1927. The mother is a former nurse and keeps the urine either sugar-free or on the verge of being sugar-free. Recently the patient has been given desiccated thyroid beginning with 0.1 grain daily. This has been raised to 15 grains and there has been some improvement, which however, has not been permanent. His highest dose has been 30 grains. Luminal has been of some benefit.

4. **The Skin of Diabetic Children.**—Children prove that the so-called complications of the skin in diabetes are not related to the blood sugar, because in children the blood sugar is often high and complications of the skin are rare. Pruritus either general or local does not exist, and eczema, intertrigo, psoriasis, and purulent skin infections are most uncommon. On the other hand, the skin of an untreated diabetic child almost suggests the diagnosis of the disease. It is very dry with a localized dryness about the chin which verges into eczema.

Xanthoma is common. There is a peculiar canary-yellow tint of the skin about the naso-labio fold, under surface of the foot, and palm of the hand which is striking. This varies with the season, being more common in summer, and may be due to the pigment carrotin. Xanthoma (see p. 725) may be localized or generalized. It may disappear with treatment.

Xanthosis one must connect with lipemia in certain cases. For example, the diabetic diet contains substances which are rich in lipochromes, such as butter, eggs, and above all the green vegetables. During the World War when extra vegetables were taken in Germany this color was more apparent. As untreated diabetics never take as many vegetables as the treated diabetics, it is only the latter who show the yellow color to a marked degree. The high color of butter (grass butter) in the spring when the cows get much green food is common knowledge. No pathological or prognostic importance is attached to this yellow color by Priesel and Wagner.

Lanugo hair was a characteristic sign on the arms, legs, and backs of debilitated diabetic children undergoing treatment by undernutrition. This disappeared with improvement.

Rubeosis diabeticus is said by Priesel and Wagner to be also characteristic of diabetic children. The patient presents a rose-red, cherry-red injection of the mucous membrane which is not identical with the redness which one sees as a result of heat, alcohol, or of certain poisons. It is pathognomic enough to be of value in differential diagnosis. The color is most apparent on the cheeks, hands, and feet. It was common years ago with patients showing chronic acidosis, but the younger assistants do not see it today.

5. **Arteriosclerosis.**—See p. 675. Arteriosclerosis was found at the autopsy upon Case No. 1305, a boy with diabetes of 5.5 years' duration. It was also found by roentgen-ray in Cases Nos. 1616, 2007, 2353, and 3620 with ages at onset of diabetes at 5.5 years, 5.8 years, 8.8 years, and 11.1 years respectively. One of my living ten-year diabetic children, Case No. 2432, shows arteriosclerosis by roentgen-ray.

6. **Eyes.**—Cataracts in diabetic children are rare, but they are so pathetic and so striking a complication that they are reported frequently and one is compelled to associate them with the disease. Strouse and Gradle[1] describe a girl, aged ten years with a cataract, who was successfully operated upon and is now taking insulin. Sherrill[2] published an account of a boy, aged fifteen years, with bilateral cataracts, and Major and Curran[3] had an infant aged eleven months with a cataract. This last case is especially discouraging, because it suggests that the cataracts did not arise from the prolonged duration of the disease or improper treatment which might be corrected in another patient.

Among my own cases in childhood, cataracts have been recognized 16 times. Case No. 1898, with onset of diabetes at 1.9 years, was the daughter of an ophthalmologist who made the diagnosis of diabetes upon finding a cararact in each of his own child's eyes. (See p. 738.)

7. **Other Signs of Degeneration.**—Signs of degeneration and signs of abnormal development were common in the diabetic children of Priesel and Wagner. Cataracts may fall into this class. Other phenomena which they noted were contractures of the fingers of both hands similar to Dupuytren's contracture, a softening defect in the distal ends of incisors which suggests Hutchinson's teeth, even when the Wassermann reaction is negative, and a malformation of the external ear. In a child, aged twelve years, the uvula was absent and there was a difference in the vision of the two eyes. In still another there were congenital cataracts with "mikrophthalmos and nystagmus" in the same eye. Two children showed on the posterior surface of the ear a warty growth or a cartilaginous development the size of a grain of rice (not a Darwinian tubercle). Lordosis and lordotic albuminuria were present in certain children. Obesity was seen in 2 children, a dwarf-like appearance in another, and undeveloped genitals in still another. Infantalism was present in 1 case, and 1 child had an enlarged thyroid with symptoms suggestive of hypothyroidism. Physical anomalies and malformations such as these have not been common in my series and I cannot believe it

[1] Strouse and Gradle: Jour. Am. Med. Assn., 1924, **82**, 546.
[2] Sherrill: Jour. Metab. Res., 1922, **1**, 667.
[3] Major and Curran: Jour. Am. Med. Assn., 1925, **84**, 674.

wholly due to lack of observation, but my cases in the future will be studied more intensively along these lines. Diabetes is such a broadening disease that one longs to be a specialist in every branch of medicine and surgery.

8. **Complete Diabetes.**—If diabetes is ever complete, one might expect those diabetic children who have survived the disease long to show this. Anyone will acknowledge that in 1922 I must have given insulin to those children, and in fact to those adults, who were the most nearly complete. They were the most severe cases culled from about 1000 of my living diabetics at that date. There survive today 13 of these first 18 cases in children. I have again carefully examined the protocols of the children who died, and I am sure that these cases succumbed not because of complete diabetes but for other reasons. Of the living the largest quantity of insulin being taken by any case is 60 units by Case No. 3739. The course of 10 of the children with long duration is shown in Table 311. In Table 300 the twelve fatal and living cases with duration over ten years are summarized and most of them have been described in detail elsewhere in this book. Ten years should be enough for the diabetes to become complete. See Case Index p. 971.

TABLE 300.—TWELVE CASES OF DIABETES IN CHILDREN WITH DURATION OVER A DECADE.

Number.	Name.	Heredity.	Onset of D. M.		Death.		Living Duration, July, 1927, years.	Diet, C., gms.	Insulin, units.
			Date.	Age, years.	Date.	Duration, years.			
203	Howard	Mother	4-'08	9.1	..	...	19.4	[1]	0
295	W. B.	Father Brother	5-'00	14.0	5'12	12.0			
825	James	G. Aunt and her daughter	11-'14	14.8	..	...	12.7	82	50
887	Alice	M. G'mother	7-'86	8.0	8'15	29.1			
1254	Graves	0	2-'17	11.8	..	...	10.4	..	40
1360	Sarah	0	12-'03	13.7	3'19	15.3			
1484	Jeannette	0	4-'17	9.9	..	...	10.3	..	0
1609	Edmund	P. G'mother	4-'17	10.4	..	...	10.3	36	55
1753	Eleanor	0	1-'16	8.8	..	...	11.5	..	50
2432	Elwyn	0	1-'13	15.0	..	...	14.5	..	10
2997	Hermione	G'mother	4-'15	5.8	..	...	12.3	34	45
5301	Jane	P. Uncle and twin sister	9-'16	13.5	..	...	10.8	100	45

Case No. 203, see p. 188.

Case No. 295, see p. 849.

Case No. 825 I was fortunate to see with Dr. John R. Williams of Rochester, New York. His diabetes began two months prior

[1] Free diet.

to his fifteenth birthday with the customary symptoms. A great-aunt and her daughter had diabetes, and also a half cousin. The quantity of urine was 5000 cc., the blood sugar varied from 0.11 per cent to 0.28 per cent, even on a restricted diet. The quantity of sugar in the urine while dieting was low, 1.6 per cent. In 1919, the percentage of sugar was 3.3 and acetone abundant. In May, 1922, the body weight was 76 pounds and insulin was begun by Dr. Williams, and by 1925 the weight had risen to 124 pounds. In May, 1926, he weighed 121¾ pounds, net. Insulin dosage was 35–0–20, carbohydrate 65 grams, protein 63 grams, fat 115 grams, and the patient in good condition and working.

Case No. 887, see p. 600.

Case No. 1254, a bright boy aged eleven years and eleven months, began treatment within a month of onset in February, 1917, was one of the earliest to take insulin, has outgrown a doctor's care for 4.5 years taking a moderately restricted diet and 20 units of insulin twice a day. Weight, 150 pounds, dressed.

Case No. 1360, a girl, developed diabetes at 9.1 years of age in December, 1903, and died March 28, 1919, of diabetic coma. I saw her first in August, 1917, when the urine contained 7.8 per cent of sugar with much diacetic acid. She gave a history of having been thin until eight years of age when on account of enlarged glands she was fed with emulsions and began getting fat. During 1916, under treatment with undernutrition she lost 20 pounds. However, her condition so far as strength was concerned was excellent. Her weight was 151 pounds dressed. She reported having driven an automobile from Baltimore to New York in a day, and previously had undergone strenuous exercise.

Case No. 1484, see p. 223.

Case No. 1609, see pp. 107, 112.

Case No. 1753 has been treated by many physicians in the country interested in diabetes, and I saw her first in 1920. She developed the disease in January, 1916, at the age of 8.7 years when the urine contained 6 per cent of sugar, and it was only possible for her to keep sugar-free on a low diet. In January, 1920, her urine contained 2 per cent, the blood-sugar fasting was 0.22 per cent, and the weight 25 kilograms. She became sugar-free on carbohydrate 21 grams, protein 55 grams, fat 54 grams, and the blood-sugar fasting fell to 0.13 per cent. Xanthoma diabeticorum was present to a marked degree. The usefulness of an undernutrition diet is disclosed by the fact that in May, 1926, the condition of the patient is reported excellent and catamenia present.

Case No. 2432 developed diabetes in 1913 at fifteen years of age or less, not more. No diabetic heredity. His use of candy and cake had been excessive. Seven per cent of sugar was present at the

first visit in December, 1921, and presumably large quantities of sugar had been present for years. His blood sugar at that time was 0.4 per cent. In 1923 diarrhea began, for which the patient took opium in one form or another, largely in the form of patent medicines. With diet and 10 units of insulin in 1924 he became sugar-free on carbohydrate 76, protein 71, fat 118, calories 1650. Weight 45 kilograms. Condition at this time was fair. Lungs, heart, and abdomen were negative, though there was a very little edema of the ankles. The lanugo hair was prominent in 1921. In 1926 the patient came under supervision again, taking 15 units of insulin, and before leaving the hospital on 10 units of insulin a day, was sugar-free with carbohydrate 93 grams, protein 50 grams, fat 126 grams, and 1706 calories. Weight 49 kilograms. Blood sugar was 0.1 per cent fasting, 0.18 per cent at one and a half hours after a meal. At this latter visit the palpable radial arteries were clearly manifest. There was distinct calcification of the blood-vessels of the legs and pelvis. No sclerosed patches were seen in the aorta. At the last visit the movements of the bowels had decreased from seven to three a day.

This patient reports having had gangrene in the middle toe in April, 1922.

A little girl, Case No. 2997, developed diabetes in April, 1915, at the age of 5.8 years with 4 per cent of sugar and was referred to me by Dr. Alexander Burgess in January, 1923, for treatment with insulin. She then showed 5.8 per cent of sugar with acidosis, but became sugar-free in the course of eight days with a restricted diet and 12 units of insulin. Dr. Burgess reports on August 29, 1925, her weight 108 pounds with light clothes, height without shoes 60½ inches. Menstruated July, 1925. Insulin 13 units three times a day.

Case No. 5301, whom I saw with B. H. Ragle, developed diabetes in 1916 at the age of thirteen years with sudden onset in the course of twenty-four hours, having previously lost an "identical" twin sister of diabetes. While at school in Boston in 1926 her tonsils were successfully removed by D. C. Greene.

9. **A Single Type of Diabetes in Children.**—There is but one type of true diabetes in children. How can I say otherwise with only 12 cases of true diabetes out of 395 remaining alive for more than ten years? Little evidence exists to suggest any great difference in the severity of the disease. Except for the cases in which heredity is a marked element and apparently in consequence somewhat milder and the rare cases with a pituitary element and showing marked overgrowth, the cases are much the same in character unless their course is disturbed by poor treatment. Potential diabetics, renal glycosurics, and a group of cases with an occasional glycosuria

must be considered separately and not be confused with true diabetes. Priesel and Wagner, who have studied so diligently their own series of cases as well as those of others, have reached the same conclusion and have given up distinctions in severity after their four years' experience. The early detected case with good treatment is apt to do so well that it blinds the doctor to the dangers ahead; the case early diagnosed, but who unfortunately for the patient is suddenly placed on a low-carbohydrate, high-protein and high-fat diet, reacts so promptly to its deleterious influence that it conveys the impression of extreme severity. I find it safer to draw conclusions about types of severity at the end of a decade. For another point of view consult Wieland,[1] Solomon,[2] and even Geyelin.[3]

F. TREATMENT.

Never ask a child if he has broken his diet any more than you would ask your friend if he has been dishonest. Teach him how to keep sugar-free and to use the Benedict test, but most of all develop his character and preserve his morale. Place responsibility upon him and trust him. Often the parents are more difficult to treat than the children; often the mothers are exhausted and one can secure the child's help to give them a rest and at the same time improve the health of the child. Diabetic children must understand their disease so well that they will have sufficient confidence to teach others about it. They love to do this. They can become real doctors' helpers. Be most charitable toward dietetic indiscretions Remember how crude are our ideas upon diet, and how often inadequate to meet Nature's demands.

Diabetic children are proverbially precocious and therefore should be treated with the respect one would have for an individual five years more advanced in age or, in other words, as if on a par with the average diabetic adult. I have not seen more than 1 stupid diabetic child per 100 diabetic children. Twenty-two are known to have led their classes or to have been distinguished to some unusual degree at school before onset of diabetes. Priesel and Wagner had no child who was poor at school; all were talented. I fear for the child who leads his class. Overgrowth in mind is not as common as overgrowth in stature in the previous history of the diabetic child, but it is certainly the rule.

The inauguration of treatment by a brief stay in a hospital or treatment at home with the aid of a nurse, exceptionally qualified

[1] Wieland: Klin. Wchnschr., 1923, **2**, 736.
[2] Solomon: Deut. med. Wchnschr., 1914, **40**, 217.
[3] Geyelin: Atlantic Med. Jour., 1926, **29**, 825.

by diabetic training, tact, and character yields the best results. No doctor in active practice can devote to a diabetic child the time which his education needs. Following the above rules, I suspect, accounts for my not having found the treatment of diabetic children "notoriously difficult." Indeed children make exceptionally good patients. This may be due to an earlier discovery of the disease and to a greater insistence on vigorous treatment.

I like to send diabetic children to hospitals, because in hospitals almost no children die of coma. During the years July 1, 1925, to July 1, 1927, 6 of my children died in coma outside of hospitals in various parts of the country, and these were the only children in my series to die of coma. If a child goes to a hospital once, he is the more ready to go again. Parents should acquire the habit of taking their diabetic children to the hospital when ill, and perhaps this is the safest rule for all illnesses and all ages.

Diabetic children must be kept under supervision if they are to live. In one way or another they should report to their physicians each month. In Vienna, Priesel and Wagner perform a von Pirquet test twice yearly.

The treatment of diabetes in infancy is a simple problem and far easier than is supposed. There are good reasons for this statement. (1) The diagnosis is made early and it is a maxim of diabetic treatment that the case promptly diagnosed does the best. In an infant the duration prior to diagnosis must of necessity be short, and, if the disease is recognized at all, it is probably earlier diagnosed in infancy than in any other period of life. (2) The infant is not even tempted to take food surreptitiously. Treatment is therefore placed on a purely scientific basis and if the results are not satisfactory the doctor has himself to blame. (3) The diet is of the simplest nature, consisting of milk, cream, cereal, orange juice and a taste of a 5 per cent vegetable. (4) The normal infant's diet is proportionately low in carbohydrate and rich in protein and fat and can be adjusted to a diabetic diet with less changes than a diet at any other period of life. Take milk, for example: One quart of milk contains carbohydrate 48 grams, protein 32 grams, fat 32 grams. (5) There are no worries about hours for meals or insulin reactions, because babies eat so frequently that it is comparatively easy to adjust diet and insulin. (6) Finally babies are not annoyed by subcutaneous injections of insulin.

In illustration of the ease of treatment of a diabetic baby note the diet of Case No. 5459, Richard, with a maternal diabetic grandmother and aunt, who developed diabetes at eight months and came under my observation two months later taking 23 units of insulin. (Table 301.) For comparison is placed alongside the diet of Mary S. O. who happened to be residing at my house.

TABLE 301.—SIMILARITY OF DIETS IN HEALTH AND DIABETES IN INFANCY.

Food.	Mary S. O. Normal child—11 months, weight 9 kilograms. Quantity.	C.	P.	F.	Richard S. Diabetic child—12 months, weight 8 kilograms. Quantity.	C.	P.	F.
Milk	960	48	32	32	750	37	25	25
Cereal	20	15	2	0	15	10	3	1
Bread	20	12	2	0				
Zwieback	...	..	..	..	1	7	1	1
Orange	100	10	0	0	110	11	0	0
Banana	25	5	0	0				
5 per cent vegetables	30	1	0	0	100	4	2	0
10 per cent vegetables					55	4	1	0
Egg					1	0	6	6
Cod-liver oil					5	0	0	5
		91	36	32		73	38	38
	Total calories, 796; calories per kilogram, 88.				Total calories, 786; Calories per kilogram, 98.			

The diet of Richard for the first week at the hospital and for a day of each of the next four weeks and his diet for various dates during the first year of his diabetes together with insulin dosage and urinary findings is given in Table 302.

TABLE 302.—DIET OF RICHARD, CASE NO. 5459, FOR ONE YEAR. ONSET AT AGE OF EIGHT MONTHS.

Date.	Diet. C.	P.	F.	Cals.	Insulin.	Urine sugar, per cent.	Weight, pounds.
1926							
Aug. 15–16	69	37	41	793	4–0–4	3.5	15¼
16–17	71	37	41	803	4–0–4	2.3	
17–18	73	37	41	809	4–4–4	1.30 A.M. yellow	
						5.30 A.M. red	
						9.30 A.M. 0	
						10.50 A.M. 0	
						11.00 A.M. 0	
						1.20 P.M. 0	
						6.00 P.M. 0	
						10.00 P.M. 0	
Aug. 18–19	70	38	41	801	4–4–4	3.30 A.M. red	16
						5.00 A.M. red	
						7.00 A.M. red	
						8.20 A.M. red-brown	
						8.30 A.M. 0	
						2.00 P.M. 0	
						4.00 P.M. 0	
						9.30 P.M. 0	
						11.35 P.M. 0	
						2.30 A.M. green	
						4.50 A.M. green	
Aug. 19–20	72	39	47	867	4–4–4	1.0	16¼
20–21	72	39	47	867	4–4–4	1.0	16½
21–22	72	39	47	867	4–4–4	0.1	16¼
28–29	77	39	47	887	4–2–4	0	16¾
Sept. 4	72	39	47	867	4–2–4	0	17¼
11	72	39	47	867	4–2–4	0	17½
18	71	35	41	793	4–2–4	0	17⅞
Dec. 21	75	38	39	803	6–5–5	0	19¾
1927							
Mar. 22	88.5	40	41	883	5–4–5		20¼
June 27	93.5	46.5	47.5	987	4–3–3	0	21¾
Jan., 1928	101.5	49	59	1133	5–7–6	0	26¼

The high percentage of sugar and the large number of units which the chart showed when the patient came here for treatment may have been due to an unusually large quantity of food and perhaps in part to the presence of a slight infectious diarrhea. Fortunately I was able to show this patient at a clinic at the Washington meeting of the American Medical Association in June, 1927.

TABLE 303.—CASE NO. 2007. AGE AT ONSET, FIVE YEARS, NINE MONTHS. DECEMBER, 1920.

Date.	Urine.			Blood sugar, per cent.	Diet in grams.				Weight pounds.	Insulin.
	Diacetic acid.	Sugar.								
		Per cent.	Gms.		C.	P.	F.	Cals.		
Dec. 2, 1920	0	4.4	51							
5, 1920	0	0.5	5	....	91	55	40	944	45	
6, 1920	0	0.3	3	....	102	58	0	640		
7, 1920	0	0	0	....	64	33	0	388		
11, 1920	0	0	0	....	64	40	12	524		
Jan. 18, 1921	0	0	0	....	128	55	33	1029	45	
July 27, 1921	0	0	0	....	152	68	42	1258	46½	
Nov. 28, 1921	0	0	0	....	155	70	44	1296	48¼	
June 8, 1922	0	0	0	0.09[1]	165	70	44	1336		
Aug. 10, 1922	0	0	0	....	175	75	44	1396		
Oct. 31, 1922	0	0	0	0.13[1]						
Jan. 20, 1923	0	0	0	0.21[2]	175	75	44	1396		
Mar. 19, 1923	0	0	0	0.15[3]	178	75	44	1408	50	
Aug. 1, 1923	0	0	0	0.11	160	68	59	1443	51	
Sept. 20, 1923	0	0	0	....	100	68	69	1293	53½	2
Oct. 11, 1923	0	0	0	....	135	60	80	1500	54	7
May 10, 1924	0	0	0	0.16[2]	135	76	80	1564	60½	6
Oct. 30, 1924	0	0	0	0.15[4]	139	72	75	1519	69	14
Apr. 23, 1925	0	0	0	0.09[2]	139	72	75	1519	70	15¾
Nov. 16, 1925	0	0.7	..	....	130	53	66	1326	76½	29
June 16, 1926	0	0	0	0.14[2]	141	79	94	1726	82½	32
Oct. 13, 1927[5]	0	3.2	..	....	141	79	94	1726	93½	48
Jan. 7, 1928	0	0.3	..	0.11	141	79	94	1726	94	75

The favorable effect of an early diagnosis, presumably within fifteen days to ninety days of onset, is shown by 2 children whose diabetes was discovered at this early period, none will be surprised to learn, by Dr. John Lovett Morse, Emeritus Professor of Pediatrics at the Harvard Medical School. The first case illustrates also the favorable influence on prognosis of a high percentage of sugar in the urine of a child at onset, which can be explained by its previous non-exposure to the baneful influence of an excess of fat and a minimum of carbohydrate.

[1] 3° after dinner.
[2] 1° after lunch.
[3] 1½° after lunch.
[4] 4° after lunch.
[5] Tuberculous gland opened on the following day.

George B., Case No. 2007, see p. 591, showed 4.4 per cent sugar in December, 1920, at the age of five years and eight months. On August 1, 1923, he was sugar-free and the fasting blood sugar was 0.11 per cent on a diet of carbohydrate 150 grams, protein 68 grams, fat 59 grams, without ever having taken insulin. He had gained 5 pounds in weight. This boy has two diabetic grandparents, and this circumstance may be a very important factor in his improvement.

On August 5, 1923, this child, although sugar-free in a twenty-four-hour specimen, would show urinary sugar if the carbohydrate for breakfast exceeded 33 grams, but after twice the quantity at noon and night the Benedict test remained clear.

On September 19, 1923, insulin was begun and has been continued as is shown by Table 303. The tonsils were removed September 15, 1925, and in June, 1927, a tuberculous cervical gland was opened. During the summer of 1926 he won a silver cup with his yacht, the "Red," which he sailed alone. At school he stands near the top of his class and played football successfully in 1927.

Ethel C., Case No. 5724, 5.5 years at onset, is the other patient of Dr. Morse. She showed 7 per cent sugar in the urine three months after onset with 0.19 per cent sugar in the blood. Her course is shown in Table 304.

TABLE 304.—ETHEL C., CASE NO. 5724, AGE AT ONSET 5.5 YEARS IN 1926. AN ILLUSTRATION OF A FAVORABLE PROGNOSIS ACCOMPANYING A HIGH PERCENTAGE OF GLYCOSURIA.

Date	Urine.			Blood sugar, per cent.	Diet.				Wgt., lbs.	Insulin, units.
	Diacetic.	Sugar.								
		%	Gms.		C.	P.	F.	Cals.		
1926										
Dec. 13	0	7.0								
Dec. 14	0					Two	meals			
	0	2.5	5	0.19	54	26	26	554	35	5
	0	0								
	0	0								
Dec. 19	0	0	0	0.16	119	40	38	978	35¾	6
Dec. 20	0	st[1]	0	0.10	129	40	38	1018		6
Dec. 31	0	0	0	0.16	119	40	38	978	37[2]	7
1927										
Feb. 12	0	0	0	0.05	113	40	42	990	35½	7
Mar. 25	0	1	0	0.12	113	44	42	...	...	5
Aug. 4	0	0	0	..	...	...	...	...	37¾[2]	6
1928										
Feb.	0	1.7	...	0.19	84	48	82	1266	42½[2]	21

[1] Slight trace.

[2] Dressed.

TABLE 305.—CASE NO. 1469. DIABETES OF 9.7 YEARS IN A GIRL WITHOUT DIABETIC HEREDITY AGE AT ONSET 10.7 YEARS IN 1917.

Date.	Volume.	Urine.			Blood sugar, per cent.	Height, inches.	Weight naked, pounds.	Diet in grams.				Insulin. units per day.	Remarks.
		Diacetic.	Sugar.					C.	P.	F.	Cals.		
			Per cent.	Total grams.									
1918													
Jan. 7	*	+	4.0										
8	620	sl +	0.2	1	0.19	..	82⅛	25	5	0	120		
26	1180	0	0	0	...	..	78¾	63	60	65	1077		
1919.													
Dec. 15	930	0	0	0	0.07	68	98¼	38	13	3	231		
19	1680	0	0	0	0.12	..	97¾	91	73	31	935		
1920.													
Dec. 11	....	...	0.1	...	0.10	..	91¾[1]	82	85	78	1370		
1921.													
Apr. 4	2600	0	0	0	0.11	..	84½	46	74	56	984		
Oct. 13	2800	0	0	0	0.11	..	80	38	42	41	699		
1922.													
Mar. 1	3040	0	0.2	6	0.13	..	78¾	63	49	69	1049		
Aug. 18	2700	0	0	0	0.13	..	81¼	30	37	75	943		
Dec. 19	4500	0	0.1	5	0.14	68	85	27	55	119	1399	2	Insulin begun
1923.													
Jan. 1	2500	0	0.2	...	...	..	83¾	42	53	120	1460	12	
Aug. 21	2800	0	0.3	8	0.20	68½	101	40	41	118	1386	30	
1924.													
June	....	...	0.1	...	0.17	..	115[1]	45	46	123	1471	30	Catamenia established
1925.													
Feb. 25	....	0	0.3	8	0.13	..	124¼	60	46	118	1486	45	
1926.													
June 10	....	...	...	...	0.35	..	...	..	..	...	....	130	Measles and coma, $CO_2$13
June 19	1700	0	0.3	5	0.17	68½	141¼	66	61	117	1561	30	Catamenia regular
July 27	....	...	...	...	0.038	..	...	..	..	...	....	..	Hypoglycemia following exercise
Nov. 1	....	...	...	...	0.12	..	...	70	72	100	....	50	
1927.													
Feb.	....	...	...	...	0.19	..	152[1]	80	65	130	....	60	
1928.													
Jan.		0	2.4		0.34	68¾	159¾	152	71	93	1729	64	

* Admission specimen.

[1] Dressed.

The course of diabetes in a child, see Frontispiece, who has had the disease for ten years, is that of Eleanor, Case No. 1469. The onset was gradual at 10.7 years in December, 1917, when her weight was 80 to 90 pounds. There was no known diabetic tendency in her family. During the five years before insulin she and her mother kept their courage and adhered to the low nutrition diet. In the subsequent five years of insulin she has developed normally and is now a junior in a well-known college. She weighs 140 pounds and is 5 feet $8\frac{3}{4}$ inches tall. When she had measles at the age of nineteen years, Dr. Root helped bring her out of coma. In July, 1926, after severe exercise she was given insulin instead of food on the wrong diagnosis that her somnolence was due to coma instead of to insulin, and five hours were required for her to recover from the severe hypoglycemia induced. This was accomplished with the aid of epinephrin, sugar by rectum, 250 cc. of orange juice by mouth, and 20 cc. of 50 per cent glucose intravenously. The local physician when called sensed the situation, but the diagnosis was puzzling. The error in diagnosis on the part of her mother came from obtaining a positive test for urinary sugar, due to the fact that the bladder contained residual urine. This situation illustrates well the necessity, in the treatment of hypoglycemia or diabetic coma, of securing complete evacuation of the bladder.

The condition of the living children cited in the third edition of this book is recorded in Table 306.

TABLE 306.—STATUS OF CHILDREN CITED IN AUTHOR'S THIRD EDITION, 1928.

Case.	Date.	Age.	Weight, pounds.		Height, inches.		Urine sugar, per cent, 1928.	Carbohydrates, gms., 1928.	Insulin units, 1928.
			First.	1928.	First.	1928.			
1616	Aug., 1919	5.5	35½	73	42¾	51½	3.4	101	22
2007	Nov., 1920	5.7	49d	96½	46	60½	5.0	141	42
2084	June, 1919	3.2	27d	59½	39½	47½	0	70	28
2508	July, 1921	4.5	34½	70	. .	49½	0	72	24
2560	June, 1921	5.9	46¼d	70	47½	56½	0.4	100	24
2802	Feb., 1922	14.4	67½	116¾	59½	61½	0	34	24
2870	Aug., 1922	8.8	65	88½	53½	62	0	. . .	40
2962	Dec., 1922	12.3	97¾d	151	61	62½	6.0	75	55
3078	Jan., 1923	13.3	81	103	61	63½	1.7	96	40

1. **Growth in Height and Weight of Diabetic Children Without Insulin.**—This was slight, though Case No. 2007, aged five years, added 2.5 inches to his stature and 5 pounds to his weight in two and a quarter years. Rexane, Case No. 894, grew 6.5 inches and gained 14.2 pounds in the eight years of diabetes before her death at the

age of ten years. Her height was then 45.5 inches without shoes and her weight 47.4 pounds without clothes. She was, therefore, about 7 inches underheight and about 20 pounds underweight for the average child. From the age of two years she was kept alive by faithfulness and cheerfulness, only to die in coma December 28, 1922, just a few days before she was to begin insulin. As a rule without insulin many of these tiny diabetics became pathetic feeble beings, old in facial aspect and in manner but dwarfs in size. Not so with Rexane!

When growth is retarded it is encouraging to remember that Osborne and Mendel[1] state, as a result of their experiments upon animals, that "after periods of suppression of growth even without loss of body weight, growth may proceed at an exaggerated rate for a considerable period. This is regarded as something apart from the rapid gains of weight in the repair or recuperation of tissue actually lost. Despite failure to grow for some time, the average normal size may thus be regained before the usual period of growth is ended. Gain in weight can be kept in abeyance for months. This has been shown for small animals in the Philippines and for steers by Benedict[2] who found that steers when subjected to a 50 per cent reduction in rations . . . went through the winter of one hundred and forty days with a loss of 1300 grams of nitrogen and approximately 52 kilograms of fat, and this loss was not inimical to the subsequent development of the steers . . ."

2. **Growth in Height and Weight With Insulin.**—The growth with insulin may be excessive as with Alice, Case No. 2802. The peculiar nephritic, myxedematous aspect of such children is now generally recognized. Priesel and Wagner[3] give 31 excellent pictures of the gradual change of diabetic children under the influence of insulin, illustrating both healthy and abnormal growth. I wonder if retention of cholesterol as well as of carbohydrate in the form of glycogen contributes to this abnormal edema.

How many pounds should be gained in one year by a diabetic child? Normal boys up to the age of ten should average an increase of about 6 pounds a year and thereafter up to sixteen years about 8 pounds; the girls, a trifle less. Consequently, if a diabetic child gains 1 pound a month, or even ¾ pound a month, until he is within 10 per cent of his standard weight, that should suffice.

The growth in weight and height of the living 31 children remaining from the Allen Epoch is shown in Table 307.

[1] Osborne and Mendel: Am. Jour. Physiol., 1916, **40**, 16.
[2] Benedict: Record of Proceedings, American Society of Animal Production, Annual Meeting, 1923.
[3] Priesel and Wagner: Loc. cit., p. 700.

TABLE 307.—GROWTH IN WEIGHT AND HEIGHT OF CHILDREN IN ALLEN ERA. ALIVE JULY 1, 1927.

Case No.	Onset.			Last report.				Gain in		Duration, years.
	Age, yrs.	Wght, lbs.	Hght, inch.	Date.	Age.	Wght, lbs.	Hght, inch.	Wght, lbs.	Hght, inch.	
1254	11.9	91	62½	July, 1927	22.4	152½	69	61½	6½	10.5
1469	10.7	82½	66	Jan., 1928	20.8	159¾	68¾	93¾	2¼	10.1
1484	9.9	84½	60½	July, 1927	20.2	115	64¼	30½	3¾	10.3
1616	5.6	35½	42¾	Jan., 1928	13.8	73½	51½	38	8¾	8.4
1779	3.6	38	48	July, 1927	11.1	72½	53½	34½	5½	7.3
1895	14.8	130	67½	July, 1927	22.3	168	70¾	38	3¼	7.0
1949	6.8	48	49	Jan., 1928	13.5	89	54¼	41	5¼	7.8
1997	12.5	91	60?	Jan., 1928	19.2	129¾	63¼	38¾	3¼	8.3
2007	5.8	43½	46	Jan., 1928	12.8	96¼	60½	52½	14½	7.2
2024	10.9	84	59½	Jan., 1928	18.2	112	62	28	2½	7.3
2063	14.3	100?	60	Sept., 1927	23.2	109	61½	9	1½	8.9
2084	3.2	34	39¼	Nov., 1928	11.6	60	46¾	26	7½	8.4
2105	10.0	88	63	July, 1927	16.6	146	64¾	58	1¾	6.7
2124	14.3	97	62	July, 1927	20.9	130	64	25	2	6.6
2256	14.6	103½	65	Oct., 1927	23.3	117	65	13½	0	8.7
2274	6.0	50½	47	April, 1927	12.3	69½	54⅛	19½	7⅛	6.3
2300	7.1	43	50	July, 1927	14.2	87	59	44	9	7.1
2353	8.8	48	48½	Jan., 1928	15.3	106¾	59½	58¾	11	6.5
2364	10.8	83	56½	Aug., 1927	18.4	125	67½	42	11	6.7
2366	14.2	89	63¼	July, 1927	20.8	155	65½	66	2¼	6.7
2388	11.1	83	57	July, 1927	17.8	127	64	44	7	6.7
2417	10.9	63½	58½	July, 1927	17.0	110	63	46½	4½	6.0
2419	14.6	115	68¾	July, 1927	11.9	142	72¾	27	4	7.2
2528	8.4	74	53	Jan., 1928	16.1	92	60¾	18	7¾	6.7
2560	5.9	45	47½	Dec., 1927	12.4	70½	56¼	25½	8¾	6.5
2568	7.7	47½	55½	July, 1927	11.9	78	58½	30	3	6.2
2589	8.2	70	59	July, 1927	15.9	116	63½	46	4½	7.5
2617	14.0	107	61½	Jan., 1928	19.9	90½	62	−16½	½	5.8
2679	7.3	51	50½	July, 1927	12.5	67	53	16	2½	5.3
2726	13.6	28	44¾	July, 1927	12.1	65	48	37	3¼	6.7
2757	10.6	57	55¼	Jan., 1928	16.6	90	63½	43	8¼	5.0

The food requirements of normal boys and girls are given by Holt. These values appear extraordinarily high to one accustomed to the diets of diabetic children.

A comparison is made in Table 309, of the diet in grams of carbohydrate, protein, and fat per kilogram body weight which a normal child should receive according to Holt with the diet of two diabetic children. This method was first used for carbohydrate in diabetics, I believe, by Root and Miles.[1] One of the patients was under the care of Newburgh,[2] the other under that of one of my associates. Attention is directed to the protein which the Ann Arbor writer actually gave his child as well as to the high-fat and low-

[1] Root and Miles: Jour. Metab. Research, 1923, **2**, 173.
[2] Newburgh: Personal communication.

carbohydrate in his diet compared with the normal fat and attempt at normal carbohydrate in the diet of the other child. The future careers of these two children the profession will watch with interest.

TABLE 308.—SUGGESTED TOTAL DAILY CALORIES (FROM DR. HOLT'S PAPER ON "THE FOOD REQUIREMENTS OF CHILDREN.")[1]

Age, years.	Boys.					Girls.				
	Average weight.		Calories per		Total daily calories.	Average weight.		Calories per		Total daily calories.
	Kilos.	Pounds.	Kilo.	Pound.		Kilos.	Pounds.	Kilo.	Pound.	
1	9.5	22	100	45	950	9.3	21	101	45	940
2	12.2	27	93	42	1135	11.8	26	94	43	1110
3	14.5	32	88	40	1275	14.1	31	87	40	1230
4	16.4	36	84	38	1380	15.9	35	82	37	1300
5	18.2	40	82	37	1490	18.2	40	78	36	1410
6	20.0	44	80	36	1600	20.0	44	76	34	1520
7	21.8	48	80	36	1745	21.8	48	76	34	1660
8	24.0	53	80	36	1920	23.9	53	76	34	1815
9	26.4	58	80	36	2110	26.2	58	76	34	1990
10	29.1	64	80	36	2330	28.5	63	77	35	2195
11	31.4	69	80	36	2510	31.5	69	80	36	2520
12	34.2	75	80	36	2735	35.8	79	80	36	2864
13	38.0	84	80	36	3040	40.6	89	79	36	3210
14	42.5	94	80	36	3400	45.0	99	74	34	3330
15	48.2	106	80	36	3855	48.3	106	67	30	3235
16	54.5	120	75	34	4090	51.0	112	62	28	3160
17	57.5	127	69	31	3945	52.6	116	58	26	3060
18	59.8	132	62	28	3730	52.8	117	56	25	2950
Adult	68.0	150	48	22	3265	60.0	132	44	20	2640

TABLE 309.—DIETS OF NORMAL AND DIABETIC CHILDREN COMPARED IN GRAMS OF FOOD PER KILOGRAM BODY WEIGHT.

Observer.	Age.	Carb.	Prot.	Fat.	Cals. per kilo.	Weight in per cent of normal for age.
Holt and Fales[2] . .	4 yrs., 5 mos.	10.1	3.3	3.2	83	
Newburgh[3] . . .	4 " 5 "	1.1	2.1	7.8	83	+6
Horace Gray . .	4 " 5 "	7.8	2.9	3.3	73	−6

In a later publication Gray[4] also tabulated 140 diabetic children and showed the carbohydrate varied between 1.9 to 3.3 grams per kilogram, the protein 1.6 to 3.1 grams, and the fat 3.4 to 5.1 grams. The calories ranged from 49 to 73 per kilogram.

[1] Holt and Fales: Am. Jour. Dis. Children, 1921, **21**, 1.
[2] Holt and Fales: Loc. cit.
[3] Personal communication.
[4] Gray: Jour. Am. Med. Assn., 1925, **84**, 14.

3. **Diet.**—The diet for diabetes has been discussed on pp. 488-532 and here but a few notes will be added.

Parents occasionally renounce regulation treatment and adopt quack methods. In not a single instance has the child done as well as before the change was made. Later on the parents repent, but the harm is done and the child as well as my statistics pay the penalty.

The diet of children with diabetes from the age of two years upward requires surprisingly few modifications from that of an adult. Especial care should be taken in the preparation of the vegetables, for children eat fast and occasionally diarrhea results. Strange to say, more frequently the complaint is of constipation. Children's specialists, accustomed to dealing with children of delicate digestions, sometimes err in making the diet too simple.

The quantity of protein required by the child is proportionately more than that of an adult. Three grams of protein per kilogram body weight is the amount which the normal child of about four years requires. As age advances this gradually decreases to the 1 to 1.5 grams required by an adult. Table 310 shows the nitrogenous urinary excretion of 4 healthy children selected for their health and size from among the playmates of some of my diabetic children.

TABLE 310.—THE NITROGEN AND SALT IN THE URINES OF FOUR HEALTHY CHILDREN.

Date.	Name.	Age.	Height, inches.	Weight.	Volume, cc.	Specific gravity.	NaCl, gms.	Nitrogen, gms.	Calculated protein per kilogram body weight.[1]
1916.									
Oct. 18–19	C. P.	2 yrs. 10 mos.	38½	33 lb.	670	1015	3.4	6.2	2.8
19–20	..	...	..	...	960	1013	5.9	5.5	2.5
20–21	..	...	..	...	560	1015	3.2	4.3	2.0
20–21	R. B.	4 yrs. 3 wks.	41	34 lb. 14 oz.	590	1016	2.4	6.0	2.6
23–24	..	...	..	...	1135	1016	3.9	7.7	3.3
26–27	..	...	..	...	630	1017	3.8	5.2	2.2
20–21	A. C.	4 yrs. 2 mos.	42	38 lb.	540	1019	5.0	5.4	2.1
21–22	..	...	..	...	350	1030	3.3	5.6	2.2
22–23	..	...	..	...	452	1022	3.3	5.0	2.0
24–25	D. J., Jr.	3 yrs. 6 mos.	40¾	41 lb. 13 oz.	870	1014	3.5	6.9	2.5
25–26	..	...	..	...	890	1013	3.2	6.6	2.4
26–27	..	...	..	...	730	1014	3.1	6.4	2.3

[1] (Urinary nitrogen + 10 per cent) × 6.25.

The quantity of protein in broth must be considered in planning the diet of children. One specimen of broth showed 36 grams to the liter, computed from the content of nitrogen and thus not accurate.

As low a quantity of protein as 0.6 to 1 gram per kilogram of body weight will allow growth in stature and gain in weight and normal development if caloric requirements are fulfilled and the diet adequately chosen from foods rich in vitamines, according to Bartlett.[1] The protein requirement of children he considers from his investigations a function of the ingested calories, varying inversely with the caloric intake. It bears no relation to the fatty acid glucose ratio provided it is compatible with a persistent absence of ketosis. The protein requirement varies inversely with the age and is directly proportional to the rate of growth. Therefore it is possible to feed to children diets much lower in nitrogen than normal provided they are rich in vitamines and adequately chosen from vegetable and animal sources.

The quantity of carbohydrate is determined by the same methods as in adults. Tolerance tests are demoralizing, because the child cannot reason out why so much food of the character he enjoys should be good for him one day and not the next. It is better policy to keep the carbohydrate low rather than near the toleration limit. The Eskimo children have little carbohydrate and thrive, and so should diabetic children with practice. New tests in treatment should be worked out upon adults: a colt needs a steady rein. In giving carbohydrate to a child do not forget that the addition of 5 grams carbohydrate to the diet of a child weighing 15 kilograms is proportionately equal to the addition of 15 to 25 grams to that of an adult.

The quantity of fat is regulated by the weight, now that with insulin there is no need to worry about acidosis. Attention is called to Case No. 1895, Table 313, who reduced the fat in his diet and thus his weight and as a result was able to increase his carbohydrate. I still give far less fat and less calories than most authors and have given less fat for years. Now it would appear as if the reward for this was coming, in that these patients can now tolerate more carbohydrate. The principle that overfeeding is harmful to a diabetic can not be wrong.

The restricted diet of children may conceivably conceal dangers due to the absence of salts of one kind or another. To avoid such a contingency raw vegetables are prescribed freely, cream and butter, likewise usually 2 to 4 grams of cod-liver oil daily, and liver at least once a week.

It is best not to give children saccharin. Strict dieting must be

[1] Bartlett: Am. Jour. Dis. Child., 1926, **32**, 641.

carried out for such a long period that it is kinder to the child and easier for him to give up the taste of sweets. For this reason various diabetic breads are not to be encouraged. Meat, eggs, cream, butter vegetables, fruit, and oatmeal are the standards.

In addition to the following illustrative cases, other cases in children are described on pp. 834, 852.

Case No. 295 is reported in detail in Publication 136, p. 126 of the Carnegie Institution of Washington, D. C., and also in Publication 176, p. 21. This case and the next, Case No. 304 are inserted here because of the exceptionally long duration, which may be explained by the presence of a diabetic heredity. Case No. 295 was a male; born February 2, 1886; married, chauffeur; came under observation October 25, 1909; onset of diabetes at the age of fourteen years in 1900; death in coma in May, 1912.

Family History.—Father died of diabetes, complicated by appendicitis, at age of fifty-one years, having been ill with the disease for two or three years. One brother died of diabetes at the age of eleven years. The mother had gall stones. Two brothers and one sister well. The patient was married September, 1907, and had one child in fairly good health, five months old.

Past History.—A frail boy; scarlet fever, measles, chicken-pox, whooping-cough. October, 1907, typhoid fever.

Present Illness.—The date of onset is not accurately known, but during 1899 the patient was thirsty and had polyuria. In May, 1902, sugar was found in the urine. Sugar was absent from the urine for a brief period in 1904. Since the onset of the disease the patient had worked steadily, rarely losing time, save during an attack of typhoid fever, and on account of a furuncle on the heel. He began his occupation as chauffeur in April, 1909.

The greatest quantity of urine noted in twenty-four hours was 12 quarts, and upon October 23, 1909, the quantity measured amounted to 10 quarts. Up to October 1, he was in fairly good health, but was then especially upset because he could not get the diet to which he had been accustomed, being forced to live, while upon a visit, chiefly upon sugar and starch. He now "eats any time."

Physical Examination.—The greatest weight, dressed, was 60.8 kilograms; on October 25, 1909, it was 49.5 kilograms. Height, 176 cm. Typical gaunt, flushed, dry appearance. Reflexes normal; eyelids red; teeth in good condition; tip of tongue red and back of tongue slightly dry; lungs and heart normal; pulse, 128, blood-pressure, 100. "Acetone" odor to breath, and whole room filled with it.

An attack of influenza in the spring of 1910 reduced the strength of the patient materially, yet he recovered sufficiently to go into

the poultry business. He did not limit his diet, and it included, among other articles, 2 quarts of milk, 6 oranges, and *10 eggs* daily. In February, 1911, he returned to the hospital on account of diarrhea, which had existed for some time. Under hospital care the number of stools decreased from 12 to 5 daily, and his condition improved. During 1911, the patient's condition did not change. He agreeably passed the early winter in Florida, but in February, 1912, as the diarrhea had returned, again entered the hospital for a few days. Except for emaciation and weakness and the presence of numerous furuncles, his condition had changed but little. Death took place in coma several weeks after his return home in May, 1912.

Case No. 304; female; age at onset thirteen years in 1901; came under observation at the age of twenty-one years on November 24, 1909, and died in coma on January 4, 1910, following restricted diet and unusual exertion.

Family History.—Several of the family died of diabetes, the grandmother at thirty-five, the mother at forty-one, and a brother at twenty-five; another brother had had the disease for six years. One brother well, one brother died of pneumonia at twenty-eight, a sister of diphtheria at four.

Past History.—The only illness observed was measles. Catamenia began at the age of thirteen and continued until the end. Symptoms of diabetes also appeared when the patient was thirteen. When first seen she appeared in far better condition than one would expect. She was nervous, the eyes were prominent and her hair had been falling out, but the thyroid was normal. The pulse was 92, blood-pressure 130; there were scars of tuberculous glands in the neck, but the physical examination otherwise was negative. The diet was restricted, and at first the patient did well, but during the Christmas vacation she grew very tired one night at a dance, returned to Boston for school the next day, and became exhausted with the weight of a heavy bag which she carried a long distance. In a few hours she was in coma.

4. **Exercise.**—Diet, exercise, and insulin control the percentage of sugar in the blood, and it is only when the harmonious action of all three is obtained that treatment is efficacious. The diet can be arranged easily in a hospital, but it is more difficult to provide for exercise, particularly for children. To obviate this defect at the Deaconess Hospital there has been provided simple gymnastic equipment in the solarium on the roof. In this way not only exercise, but sunlight as well, is made available. The latter may be quite important. All know diabetics do better in the summer time. Is this wholly to be explained by more fresh air and exercise or are the sun's rays an important feature?

Exercise has also been beneficial even when it has been violent.

Case No. 785, who took no exercise and made no exertion, improved very slowly as compared with Cases Nos. 925 and 923, who played tennis and walked miles. All the children appear to be better when taking exercise. We must never forget that much of the glycogen in the body is stored in the muscles and that undoubtedly fully as much of the carbohydrate ingested is burned there. A reaction occurred when one boy receiving insulin walked 10 miles in a forenoon, an illustration of the power of exercise to reduce the blood sugar. A similar case was that of Eleanor R., Case No. 1469, described on p. 843.

5. **Insulin.**—Injections of insulin annoy a baby less than the average child and a child less than the average adult. Although more than 200 children have been taking insulin from one to nearly five years, I can recall but one, after the first month's trial, who has asked: "How long must I take it?" Children adjust themselves to routine.

It is the exceptional diabetic child who can afford to do without insulin. If there are but 12 diabetic children who have lived more than ten years, it is reasonable to protect the remainder from the start, and insulin appears to do this. I give insulin at an earlier stage of diabetes today than at any time since its discovery.

The dose of insulin may be exceedingly small. A few units given to a child in a reliable family accomplishes unbelievable results. Even in the course of years the quantity given need not reach large proportions and yet provide for growth in weight and height as well as development. I have no child under my personal supervision taking less than 2 or more than 60 units even among the 51 with a duration of 5.0 to 14.5 years.

The frequency of injections almost invariably becomes twice a day, very frequently three times a day, and occasionally the evening dose is given after supper, but so far as I am aware not as many as four times a day, save in 8 instances. Four injections have been carried out daily by the parents of Case No. 2007. The mother of this child has examined each specimen of his urine since the onset of his disease. Betty E.'s mother prevents reactions by giving small amounts of carbohydrate at 11 A.M. and 8 P.M.

The sites of injection and the systematic distribution of injections over the body have been discussed. All these details are especially important when dealing with children. (See p. 79.)

My experience with insulin in children is best shown in Table 311. Many of these 10 children were mentioned in the third edition of this book in 1923. For this reason the case numbers are given. Already these children had passed the average expectation of life for fatal diabetic children of their time when they began insulin. Their average age at onset of diabetes was 9.5 years, the

duration of the diabetes in 1922 was 2.4 years. In the interval of nearly four years their average weight has increased 40 pounds and the average height of the 7 children whose data can be compared for 1922 and 1926 has risen 3.3 inches. The diet has slowly progressed. In fact, the carbohydrate has doubled, the protein has increased one-half, and the fat about one-third, and a gain in total calories of about 50 per cent has resulted. The figures are as reported to me, but I do not believe they are without some errors. Insulin rose rapidly in amount the first twelve months until it was freely available, but has since risen slowly. It is notable that the gain of 29 grams of carbohydrate, more or less, for the year ending July, 1926, was at the expense of but 2 units of insulin. They are by no means always sugar-free, but the attempt is made to keep sugar-free. They are happy children. If they could have begun insulin earlier, I believe their course would have been still better.

TABLE 311.—TREATMENT OF 10 LIVING DIABETIC CHILDREN WHOSE DIABETES BEGAN IN PRE-INSULIN DAYS. 1922–1926. AVERAGE AGE AT ONSET 9.5 YEARS.

Year.	Duration of diabetes.	Weight in pounds.	Height in inches.	Diet				Insulin.
				C.	P.	F.	Cals.	
1922	2.4	58.0	57.7	39	44	80	1052	9
1923	3.4	67.4	....	45	50	107	1343	23
1924	4.4	80.0	....	58	49	99	1319	28
1925	5.4	92.0	....	53	56	109	1417	30
1926	6.2	98.0	61.0	82	67	103	1523	32

Case Nos. 1469, 1616, 1895, 2256, 2366, 2419, 2560, 2877, 2919, 2979. All are alive in 1928.

The 10 scarred insulin veterans whose records are cited in Table 311 are the sentinels of the diabetic army. Probably their number cannot be triplicated, possibly not duplicated, if age and duration are considered. They are there to protect a million diabetics. One dreads to have them always serve in the advance guard, but if they must so serve, then we should array them with the best armor modern hygiene affords. This includes treatment of teeth and tonsils, postural training, protection against smallpox, tuberculosis, diphtheria, scarlet fever and minor infections, whether general or local, and always adequate sunlight, hours of rest and hours of play. This applies not only to this group of diabetic children, but to all groups.

The severest case in a child in the series treated with insulin was Freddie G., Case No. 1616. He has gained 4½ pounds in eight months, has grown 1¾ inches, and was taking 25 units insulin, January, 1928. He is now slightly overweight for his height.

It is astonishing how small a quantity of insulin is required to furnish sufficient calories for the growth of children with diabetes of two years, more or less duration. Billy B., Case No. 2560, was at the top of his class. He developed diabetes when five years and five months old in June, 1921. In the subsequent eighteen months he lost 6 pounds. He then commenced insulin and in eight months upon 2 units daily regained the weight he had lost or an average of ¾ pound each month. By January, 1928, he had gained 25 pounds in weight and about 8¾ inches in height.

Dorothy Z., Case No. 2508, was 16 pounds overweight when she developed diabetes in July, 1921, at the age of four years and six months. From her highest weight of 48 pounds she lost 21 pounds. She has gained 39½ pounds from her lowest weight and she takes, in 1927, 24 units of insulin. To avoid showing sugar in the forenoon, the breakfast and supper hours were separated by an additional hour. Particularly with children is the mistake made of giving meals too close together.

TABLE 312.—TREATMENT OF A CHILD WITHOUT AND WITH INSULIN DURING EIGHT YEARS AND EIGHT MONTHS. "BUDDY" H.

Case No. 2084. Age at Onset, Three Years and Two Months. June, 1919.

Date.	Diacetic acid.	Urine sugar,		Diet.				Weight, pounds.
		Per cent.	Gms.	Carb.	Prot.	Fat.	Cals.	
Dec. 1, 1920	+	3.0						
2, 1920	0	2.9	17	56	41	32	774	
9, 1920	0	2.4	55	43	39	22	575	24
16, 1920	0	2.0	23	33	36	35	591	24
Jan. 9, 1921	0	2.1	24	24	39	43	639	24
Feb. 10, 1921	0	0	0	15	39	40	576	25
20, 1921	0	0	0	16	37	35	527	24
Mar. 17, 1921	0	0	0	23	38	39	595	
April 2, 1922	0	0	0	26	40	42	642	25
June 2, 1922	0	0	0	24	38	39	599	24
Oct. 3, 1922	0	0	0	27	37	49	697	
Mar. 4, 1923	0	0	0	20	36	37	557	23
Aug. 1, 1923	0	0	0	48	42	78	1062	32
Oct. 1, 1923	0	0	0	50	42	79	1079	34
April 20, 1924	0	0	0	50	42	79	1079	37
Nov. 25, 1924	0	0	0	50	43	85	1137	39
April 11, 1925	0	0	0	56	55	95	1292	43
Sept. 5, 1925	0	0	0	56	63	95	1331	49
Mar. 5, 1926	0	0	0	58	67	100	1400	48½
Nov. 1, 1926	0	0	0	65	71	100	1444	55
June 14, 1927	0	0	0	68	68	100	1444	57½
Jan. 1, 1928	0	0	0	70	71	100	1464	59½

Buddy H., Case No. 2084, first showed diabetic symptoms when three years and three months old in July, 1919. I have no other case of his age or younger now alive who has lived as long

with diabetes. Compare Rexane, p. 843. His weight fell from 34 pounds to 23 pounds. He began insulin in March, 1923, soon contracted scarlet fever, yet despite this infection his weight had increased to 34 pounds by October 1, 1923, to 57½ pounds in 1927, and his height has risen 17½ inches. He takes 25 units of insulin daily. (Table 312.)

The regeneration of the pancreas has been discussed elsewhere but clinical evidences of it are not wanting in children. I cannot otherwise interpret Table 311 in which in the course of four years the value of a unit of insulin has increased. Geyelin[1] evidently has found suggestive evidence of similar character. George C., Case No. 4830, affords an excellent example. He began insulin in October, 1925, at the age of 3.2 years with 0.9 years of diabetes to his credit. His diet was carbohydrate 45, protein 40, fat 53, with 4 units of insulin. In August, 1927, his diet was carbohydrate 91, protein 62, fat 92, with 11 units. This would represent a gain of 3.5 grams of carbohydrate for each additional unit of insulin given during the eleven months under observation or, in terms of glucose, 4.5 grams glucose per unit.

Evidence of regeneration of the pancreas is likewise furnished by Case No. 1895, a boy whose diabetes began in 1920 at the age of 14.8 years. When insulin arrived, his weight had fallen from 122 pounds to 96 pounds net and he could keep sugar-free in December, 1921, with a diet of carbohydrate 55 grams, protein 49 grams, fat 86 grams; and in October, 1922, with carbohydrate 12 grams, protein 28 grams, fat 82 grams. Insulin was begun in October, 1922, and the daily dose in March, 1924, had reached 24 units with a diet of carbohydrate 70 grams, protein 74 grams, fat 158 grams. By 1925 he was taking 30 units, carbohydrate 90 grams, protein 65 grams, fat 140 grams and had gained to 145 pounds. Then by his own intuition he deliberately lowered his weight 10 pounds and by autumn, 1926, was sugar-free upon a diet of carbohydrate 159 grams, protein 83 grams, fat 103 grams, with 44 units of insulin. August, 1927, finds him living on a diet of 2000 calories and insulin 30 units.

6. **Treatment of a Diabetic Child During an Infection.**—The same methods should be employed as under ordinary conditions, but in addition one must be alert to prevent the onset of diabetic coma. Coma can easily occur, because the child is overeating endogenously, due to the fever. To guard against excessive catabolism of body protein and fat continue the carbohydrate and promote its utilization with insulin. The latter can easily be taken in the form of fruit, milk, or oatmeal gruel. A febrile patient does not wish much

[1] Geyelin: Atlantic Med. Jour., 1926, **29**, 825.

protein and fat, and it may be best to allow him to draw on body stores rather than to overburden the digestion. Prevent the mild diabetic becoming even temporarily severe by filling his liver with glycogen.

TABLE 313.—GAIN IN TOLERANCE FOR CARBOHYDRATE. BOY, CASE NO. 1895. AGE AT ONSET 14.9 YEARS IN JULY 1920. HEIGHT, 5 FEET 7½ INCHES NET. WEIGHT 122 POUNDS NET.

Date.	Glycosuria, per cent.	C.	P.	F.	Weight, naked.	Insulin.
1920. July	Onset	...	...	...	122	0
August	3.0	...	...	...	110	0
December	0	94	79	91	...	0
1921. October	6.6	...	...	...	108	0
December	0	55	49	86	103	0
1922. October	0	30	60	109	99	6
1923. June	0	68	65	139	118	35
1924. March	0	70	74	158	130	24
1925. December	0	90	65	140	145	30–40
1926. August	0	150	75[1]	Less	135	44–30[1]
1927. August	0	...[2]	...	...	163	30
1928. Alive						

Do not omit insulin, but rather give it more frequently, adjusting the dose to keep the urine sugar-free or nearly so. Presumably it will be necessary to increase the insulin one-half or even to double it, but if it is given at six- or four-hour intervals there is little danger of an insulin reaction. With care a diabetic child will pass through any sort of infection which a normal child would withstand.

It is difficult to keep diabetic children sugar-free. I try to do it, but by no means always succeed, yet I do persist and often, unexpectedly, all goes well. The real trouble in keeping these children sugar-free is that one is dealing with three variables—diet, exercise, insulin—and it is almost against reason or theory to predict how they will act.

In the index under "Children" will be found references to certain phases of diabetes in childhood which for the sake of avoiding repetition are omitted here.

G. THE NON-DIABETIC GLYCOSURIAS IN CHILDREN. RENAL GLYCOSURIA. POTENTIAL DIABETES. "UNCLASSIFIED" CASES.

Glycosuria may be transitory all will agree. Particularly common is the appearance of sugar in the urine during acute infections, after surgical operations, perhaps because of the anesthesia or perhaps

[1] Varying largely with exercise.

[2] On no fixed diet, 2000 calories.

because of emotional stress, which alone may lead to it; during pregnancy, and in diseases of the thyroid and pituitary glands. To differentiate these transient glycosurias from those of true diabetes is not always an easy matter, even with a knowledge of the percentage of sugar in the blood. A decision often can be reached only with the aid of the element of time. (See Case No. 129, p. 537, a case described by Ohler,[1] Case No. 5724, Ethel, p. 841. See also Case No. 473, p. 557. Similar difficulties are often encountered by others: *e. g.*, Geyelin, Smyth.)

More than one-seventh of all the children referred to me for possible diabetes have proved to be non-diabetic, and Geyelin's[2] experience is like mine.

Glycosuria in infants and children not of pancreatic origin has been studied by Hartmann.[3] He points out errors in diagnosis which may arise from anhydremia, a concentrated urine, renal glycosuria, pentosuria (from apples and cherries), chronic nephritis, cachexia, alimentary (?) glycosuria, and brain injury.

Many of the glycosurias seen in children are known to be "benign," because they have remained so for many years. During the twenty-eight years from 1898 to 1926, 68 children have come for examination in whom no definite proof of diabetes was found. It is easy to understand that an hereditary history, 17.6 per cent, familial, 2.9 per cent, and both combined, 8.8 per cent, was present in these cases, making a total element of heredity of 29.3 per cent. Likewise it is not strange that 16, 24 per cent, of the children were "only children" in contrast to 49, 12 per cent, of the 395 true diabetics. This circumstance would explain the diabetes of the only child on the ground of increased attention by the parents to the health of the single child. It requires tact to protect such a child from too much attention. These 68 children can be divided into four groups.

TABLE 314.—CLASSIFICATION OF CHILDREN REFERRED TO AUTHOR FOR DIABETES.

	Living.	Dead.	Total.
A. True diabetes	200	195	395
B. Not diabetes	66	2	68
Renal glycosuria	4	1	5
Potential diabetes	14	0	14
Diabetes insipidus	1	0	1
Unclassified	47	1	48

Sex.—There are 37 males and 31 females in the series.

Age of Onset.—The average age of onset of the symptoms thought to be diabetic was 7.6 years.

[1] Ohler: Med. Clin. North Am., 1922, **5**, 1465.
[2] Geyelin: Atlantic Med. Jour., 1926, **29**, 825.
[3] Hartmann: Med. Clin. North America, 1925, **9**, 69.

Duration of Life.—The average duration of life to July 1, 1926 of the 64 living cases who have been traced (2 children have died of non-diabetic causes) is 5.2 years. There are 13 of these children who have had a duration of over ten years. The duration of life by periods is as follows: the 4 cases in the Naunyn Epoch have thus far lived an average of 15.5 years; the 21 cases in the Allen Epoch for 7.8 years; the 41 cases of the Banting Epoch 2.9 years. One renal glycosuric, Case No. 2165, has had a duration of 32.3 years to July, 1926.

Compared with the mortality of true diabetics, how strange it is to write that but 2 of these 66 traced cases have died. One can quickly dispose of the 2 fatal cases. The one, an unclassified case, lived only twelve days after the first visit and died of tuberculous meningitis and peritonitis; the other had renal glycosuria and lived 6.5 years after the discovery of his condition until he was killed in a coasting accident.

Summary of Examinations of Urine and Blood.—A study of the urinary and blood-sugar values gives some idea as to the method of classification and the severity of the disease. No test of the blood sugar while under my observation gave a value higher than 0.17 per cent. (See also p. 550 for criteria of classification.)

TABLE 315.—RENAL GLYCOSURIA. FOUR LIVING CASES.

	Findings by	
	Other physicians.	E. P. J.
Highest urinary sugar recorded:		
+, No amount stated	1	0
0.3 per cent or over	3	4
Highest blood sugar recorded:		
0.11 per cent or below	..	3
0.12 to 0.14 per cent	..	1
0.15 per cent or over	1	

TABLE 316.—POTENTIAL DIABETES. FOURTEEN CASES.

	Findings by	
	Other physicians.	E. P. J.
Highest urinary sugar recorded:		
No sugar	..	2
+, No amount stated	9	
Trace	1	4
0.1 to 0.2 per cent	..	3
0.3 per cent or over	4	5
Highest blood sugar recorded:		
0.11 per cent or below	1	5
0.12 to 0.14 per cent	..	1
0.15 per cent or over	..	5

TABLE 317.—UNCLASSIFIED. FORTY-SEVEN LIVING CASES.[1]

	Findings by	
	Other physicians.	E. P. J.
Highest urinary sugar recorded:		
No sugar	1	25
+, No amount stated	31	
Trace	7	5
0.1 to 0.2 per cent	3	13
0.3 per cent or over	5	4
Highest blood sugar recorded:		
0.11 per cent or below	..	28
0.12 to 0.14 per cent	..	3
0.15 per cent or over	1	2

Symptoms.—The presenting symptoms, suggesting diabetes, of these 66 living children are listed below:

	Cases.
Nervousness	24
Weakness and tired feeling	21
Polyuria	16
Polydipsia	12
Polyphagia	11
Enuresis	11
Loss of weight	9

As is evident a diabetic symptomatology was by no means a feature. However, the absence of symptoms should not encourage waiting for classical symptoms before suspecting diabetes in a child. Children often do not complain of the abnormalities which are a source of worry to an adult. It is always best to err on the side of safety and examine the urine.

Treatment.—The advice and treatment have varied with each individual, but in the usual case in which the diagnosis has remained in doubt after a period of hospital stay, the following regime has been outlined:

1. Ordinary diet with sufficient calories to permit normal growth, save for the exclusion of actual sugar and candy, and the substitution of ice cream or fruit for dessert. Bread allowed in reasonable quantities. Fruits and vegetables urged.

2. Normal life with no restrictions save that the general health be protected, obesity avoided, exercise encouraged, and foci of infection removed.

3. Urine to be tested for sugar once a month for a year and every three months thereafter for life. The specimen should be obtained one hour after an ordinary meal.

4. Report for a health examination every six months. A test of the blood sugar at one hour after a meal should be taken at that time.

[1] Diabetes insipidus, 1 case, no sugar ever found in urine.

Present Condition.—Most of the 66 living cases are in good health and have shown no sugar in the urine for many months and in many cases not for years. A tabulated account of their condition follows:

TABLE 318.—TABULATION OF CONDITION OF SIXTY-SIX LIVING CASES OF GLYCOSURIA IN CHILDHOOD.

	Cases.
Good health; no diabetic symptoms; no sugar in urine	36
Alive; presumably well and show no sugar in urine	9
Show sugar in urine rarely or occasionally, though in good health	7
Show sugar constantly, though in good health (renal glycosuria)	4
Classification changed from that of questionable diabetes to true diabetes and now taking insulin	1
Under observation less than a year	7
Untraced	2
Total	66

A great many of the patients who respond to inquiries state that they live on a liberal diet except that they avoid sugar, sweets, cake, and the like. This is more often from force of habit than anything else.

SECTION XIV.

DIABETES IN PREGNANCY.

By Priscilla White, M.D.

Diabetes is more menacing to pregnancy than pregnancy is to diabetes. The accidents of pregnancy occurred three times as frequently as the accidents of diabetes in 89 pregnancies among our series of diabetics. Of these patients 25 were diabetic before the pregnancy and 33 became diabetic during the pregnancy. The tragic end-results of diabetic pregnancies are increasingly infrequent and with proper supervision and coöperation can be largely eliminated.

The theoretical pit-falls endangering such patients are many. The pregnant diabetic like the thyroid diabetic is an unstable organism and even in these days of insulin tests the skill of the physician. Complications of one condition may precipitate accidents of the other. Diabetes with its faulty carbohydrate metabolism may be fertile ground for the development of toxemias. Conversely, pernicious vomiting may result in severe acidosis. Hypoglycemia may occur coincidently with increasing pancreatic tissue of the fetus and coma may follow the withdrawal of this insulin supply. Despite these theoretical pessimisms a study of cases reported in the literature and our own case records show that diabetes is no longer a contraindication to pregnancy.

1. **Glycosuria of Pregnancy.**—The clinical significance of sugar in the urine of a pregnant woman and the point when a benign glycosuria will become true diabetes is difficult to ascertain. Glycosuria may even be diagnostic of pregnancy, recur with repeated pregnancies and disappear later. Case No. 438 seen in conjunction with Dr. Franklin S. Newell is illustrative. Sugar appeared in the first pregnancy, but ceased immediately after confinement. In the summer of 1910 it recurred but a miscarriage took place. In March, 1913, the patient considered herself pregnant, but the urine at the time and at subsequent examinations failed to show sugar and time proved that pregnancy did not exist. Pregnancy did occur in December, 1913, and a trace of sugar showed throughout, only to disappear after confinement. The patient died of influenza in February, 1919, without any sign of diabetes.

That glucose early in pregnancy and lactose in the puerperium are physiological and not the starting point of diabetes is well known. Williams found glycosuria in 13.6 per cent of 500 pregnant women at some time during pregnancy. Although sugar occured in the urine more commonly during the second half of pregnancy, it was always glucose. This glycosuria Williams[1] considers to be a renal glycosuria. These cases resemble the glycosurias of thyroid disease with their low-sugar threshold and disappearance of sugar when normal metabolism is restored.[2]

Many explanations are offered for their occurrence. The sugar may be a manifestation of pleuriglandular changes of pregnancy, overactivity of thyroid, pituitary and adrenals depressing insulin activity, or a disturbance of glycogenolysis, or of sugar storage. John[3] conceives the possibility of hydropic degeneration occurring in the pancreas as in the overstrained partially depancreatized dogs of Copp and Barclay.[4] Complete recovery follows with treatment and removal of the burden.

2. **Onset of Diabetes in Pregnancy.**—That the warning of a glycosuria in pregnancy must not be ignored as a starting point of diabetes is evidenced by the fact that 33 of our 58 pregnant diabetic women developed diabetes during the pregnancy. The danger is even more strikingly illustrated by Springer's[5] case who gave a slightly positive reaction at term and who died a few months later in true diabetic coma. On the other hand Bowcock and Greene[6] followed a case of renal glycosuria of four years' duration through two successful pregnancies without being able to find any indication of diabetes.

These occurrences are important: (1) Because they again are a reminder of the necessity of seriously regarding all glycosurias; (2) because they suggest a good opportunity for preventive medicine in patients of this type. A woman who shows glycosuria in pregnancy should never become fat.

Blood-sugar tests, however, conduce to peace of mind by allowing a differential diagnosis and by safeguarding the future. A blood-sugar test early reveals the grave as well as the benign case.

3. **Conception in Diabetes. — Menstruation.** — Pregnancy contracted during diabetes is less frequent than diabetes contracted during pregnancy. The infrequency of pregnancy in the diabetic is probably due to two reasons, the age incidence of the disease and the con-

[1] Williams: Boston Med. and Surg. Jour., 1925, **192**, 163.

[2] Adlersberg and Porges by means of special dietary conditions utilize the appearance of both acetonuria and glycosuria in the diagnosis of pregnancy. See Adlersberg and Porges: Med. Klinik., 1926, **22**, 1556.

[3] John: Surg., Gynec. and Obst., 1926, **42**, 543.

[4] Copp and Barclay: Jour. Metab. Res., 1923, **4**, 445.

[5] Springer: Zentralbl. f. Gyn., 1924, **48**, 2624.

[6] Bowcock and Greene: Jour. Am. Med. Assn., 1928, **90**, 502.

current sterility associated with diabetes. Formerly sterility was the rule. In 1881 Duncan[1] collected from the literature 22 cases; in 1909 Williams[2] collected 66. Lecorche[3] collected 114 cases with 7 gestations. Von Noorden[4] reported 22 among 427 women; and the Mayo Clinic[5] 285 women of the child-bearing age with 11 gestations since 1922.

Insulin, it is true, has decreased the frequency of sterility among diabetic women, but the return to normalcy is slow. Taking menstruation as an index of ovarian activity, there still is evidence of depressed function. Maturity among diabetic girls occurs, but it is delayed in appearance. Return of menstruation among long-standing diabetics comes only after prolonged insulin treatment. Even in cases treated with insulin at the onset, menses may cease for one or more years. In 2 cases the catamenia returned after an absence of six years and six and a half years.

Pregnancy, however, may occur in a diabetic even though the diabetes has been of years' duration, as in Case No. 1207, who first showed diabetes in 1895 and became pregnant for the eleventh time twenty-three years later and had a healthy baby. In our series the range of duration of diabetes varied from a few weeks to eight years before the first pregnancy during diabetes.

4. **Effect of Pregnancy on Diabetes.**—**Tolerance.**—A gain of tolerance for carbohydrate, reduction of insulin dosage, and the lowering of blood sugar is illustrated to a varying extent by the following 6 cases. This clinical picture is in accordance with the theory of Carlson and Drennan[6] now under dispute.

TABLE 319.—THE CHANGE IN TOLERANCE IN DIABETIC PREGNANCIES.

Case No.	Duration D. M.	Type of onset.	First half of pregnancy.						Last half of pregnancy.					
			C.	P.	F.	Urine.	B. S.	Ins.	C.	P.	F.	Urine.	B. S.	Ins.
3660	4 3	Grad.	68	60	122	0 2	0.21	23	78	64	126	0.5 1.0 3.0	0.19 0.12 0.10	20
3030	3 6	Rapid	153	62	98	0	0.13	0	153	62	98	1.3	0.13	0
3750	2 9	Grad.	88	53	112	..	....	..	78	52	104	0 7	0 20	20
5257	1 6	Grad.	118	69	117	0 2	0.13	0	175	73	112	0	0 08	0
4615[7]	1 6	Grad.	108	66	128	tr.	0.16	0	108	68	128	0 2	0 12	0
5465	0 1	Grad.	86	60	104	0 3	0.17	15	98	69	113	0 4	0 13	12

[1] Duncan: Cited by Cragin, Practical Obstetrics, Lea & Febiger, 1916, p. 487.
[2] Williams: Obstetrics, New York, 1923, p. 561.
[3] Lecorche: Cited by DeLee, The Principles and Practice of Obstetrics, 1918, p. 518.
[4] Von Noorden: Quoted by Wiener, Am. Jour. Obst. and Gynec., 1924, **7**, 710.
[5] Parsons, Randall, Wilder: Med. Clin. North America, 1926, **10**, 679.
[6] Carlson and Drennan: Am. Jour. Physiol., 1911, **28**, 391.
[7] Dead.

A change for the better was observed by Stander and Peckham[1] to take place in the second half of 3 pregnancies.

5. **Effect of Pregnancy on Metabolism.**—Further evidence of this gain in carbohydrate tolerance is shown in studies of the metabolism in Case No. 436. Before the pregnancy the respiratory quotient was 0.78. During the fifth month of pregnancy it rose to 0.82 along with a clinical rise in tolerance for carbohydrate. During the seventh month it rose to 0.84. Six months after confinement the respiratory quotient had fallen to 0.74.

The metabolism of 3 diabetic patients during pregnancy presented no abnormalities, either as compared with normal women in similar condition or with 2 patients compared with themselves at an earlier or later period when not pregnant and yet diabetic. If one allows for the restriction of diet to which these patients were submitted, it is justifiable to conclude that their metabolism may be considered to conform to the conclusions of Carpenter and Murlin,[2] namely, that the metabolism of pregnant women is slightly more than that of women at complete sexual rest.

TABLE 320.—THE METABOLISM OF A DIABETIC BEFORE, DURING, AND AFTER PREGNANCY. CASE NO. 436.

Date.	Body wgt., kg.	Av. pulse.	CO_2, cc. per min.	O_2, cc. per min.	R. Q.	Heat output per 24 hrs.		B.M.R. rate, per cent.	NH_3, gms.	$FeCl_3$	N, urine.	Sugar, gms.
						Total cals.	Cals. per kgs. body wgt.					
1914.												
Dec. 7–8	63.6	66	151	194	0.78	1139	21	− 7	1.6	+++	6.3	4
1916.												
Jan. 13–14	61.3	...	176	214	0.82	1487	24	+ 5	1.2	0	10.9	2
Mar. 21–22	65.8	86	191	228	0.84	1598	24	+10	..	....	11.3	0
1918.												
Nov. 7–8	58.5	...	155	210	0.74	1429	24	+ 3	1.9	....	...	38
1922.												
Oct. 26	58.3	79.0	137	173	0.79	1193	20	−12	0.2	+	9.2	
1927.												
Dec. 16	60.9							−15				0.4%

6. **The Lowering of the Sugar Threshold.**—A lowered threshold has been observed in a few of our cases. Without laboratory facili-

[1] Stander and Peckham: Am. Jour. Obst. and Gynec., 1927, **14**, 313.
[2] Carpenter and Murlin: Arch. Int. Med., 1911, **7**, 184.

ties for the estimations of blood sugars such a condition might cause confusion. Lowering of the threshold for sugar in pregnancy (non-diabetic) has been demonstrated by many workers. Levulose, 100 grams as a test, was used by Gottschalk and Strecker[1] and according to them a positive levulosuria is diagnostic, but a negative result does not exclude pregnancy. Rowe[2] has demonstrated a lowering of the tolerance for galactose in pregnancy. The normal organism will tolerate 40 grams of galactose. The pregnant organism will tolerate only 20 grams. As long ago as 1899 Payer[3] found 50 per cent of his pregnant women had glycosuria after ingestion of 50 grams of glucose.

TABLE 321.—CHANGE IN THRESHOLD FOR SUGAR IN THE PREGNANT DIABETIC.

Case No.	First 3 months.		Second 3 months.		Third 3 months.	
	Urine, sugar, per cent.	B. S.	Urine, sugar, per cent.	B. S.	Urine, sugar, per cent.	B. S.
3030	0	0.11	1.0 0.3 0.3	0.11	0 0.3 0.1	0.14
3750	0.7	0.20	1.4	0.14	1.3	0.13
5257	....	....	0.2	0.13	tr	0.08
2888	0.3	0.10	2.3	0.17	2.0	0.15
3660	....	....	3.0	0.19 0.12	0.5 1.0	0.10 0.16
4631	+++	0.12	++	0.12	++	0.12

The danger of reduction of diet and increase of insulin dosage on urine tests alone cannot therefore be over-emphasized. In 8 examinations in which the sugar in the urine amounted to from 0.5 to 3 per cent 2 cases only had a blood sugar over 0.17 per cent (after a meal) and not once did the blood sugar exceed 0.2 per cent.

7. **Permanent Effect Upon Tolerance.**—Among 38 cases for whom the data were available there were but 3 who may be called severe diabetics. This is contrary to the results of the Mayo Clinic, Bowen,[4] and others who conclude that many of these cases become severe diabetics. De Masa[5] claims there are women who are diabetics only during pregnancy. M. L. Pérez's[6] case is suggestive of recovery with its subsidence of symptoms during the puerperium.

[1] Gottschalk and Strecker: Klin. Wchnschr., 1922, **1**, 2467.
[2] Rowe: Jour. Am. Med. Assn., 1927, **83**, 1403.
[3] Payer: Monatschr. f. Geburt. u. Gynak., 1899, **10**, 559.
[4] Bowen: New York State Jour. of Med., 1927, **27**, 351.
[5] De Masa: Quoted by Strouse and Daly: Med. Clin. North America, 1925, **9**, 1491.
[6] Pérez: Jour. Am. Med. Assn., 1922, **79**, 1965.

The Mayo Clinic writers describe a similar case, but with return of sugar at the time of lactation and reappearance of menstruation. The patients showing subsidence of symptoms after confinement cannot, however, be held above suspicion for 3 such cases in our own series have ultimately developed true diabetes. The circumstances connected with one of these, were most unfortunate, because the patient was followed for some weeks after confinement and tests of urine and blood proved to be normal. Three months after confinement diabetes appeared.

Our results are summarized in Table 322.

TABLE 322.—A SUMMARY OF THE DIET, BLOOD SUGAR AND INSULIN EMPLOYED BY 38 PREGNANT WOMEN AT THE END OF A PERIOD OF ONE TO TWENTY-FOUR YEARS OF DIABETES, AND AT VARIOUS INTERVALS SINCE PREGNANCY.

Case No.	Latest pregnancy date.	C, gms.	P, gms.	F, gms.	Insulin, units.	Latest blood sugar, (Folin-Wu).	Latest urine, sugar, per cent.	Date of latest report.
436	1916	78	....	....	12	0.27	0.3	1927
791	1915	78	45	107	13	0.24	0	1926
812	1914	105	64	120	6	0.17	0	1926
992	1916	158	61	121	13	0.22	0	1927
1975	1916	43	51	154	..	0.13	0	1926
2779	1924	64	51	140	0	0.16	0	1923
2888	1926	108	60+	120+	0	0.17	2.3	1927
3030	1924	88	64	139	15	0.17	..	1926
3124	1921	66	60	135	40	0.27	..	
3161	1921	66	60	142	52	0.14	..	1926
3216	1920	84	64	112	9	0.14	..	1923
3233	1914	68	78	151	14	0.17	..	1923
3259	1923	98	62	126	0	0.08	0	1923
3313	1913	98	72	120	10	....	0	1927
3352	1914	68	64	117	0	0.06	..	1924
3476	1920	100	60	130	0	....	0	1926
3630	1922	..	Liberal	....	..	....	0	1926
3660	1924	76	54	103	15	0.23	2.3	1927
3705	1915	78	45	107	13	0.19	0.3	1924
3750	1926	115	67	117	10	0.17	0.4	1927
3847	1914	88	58	110	10	0.12	..	1927
3938	1918	58	52	111	20	0.23	0.3	1924
4010	1918	64	43	82	..	0.18	0	1926
4132	1918	78	63	125	8	0.17	..	1924
4300	1923	200	60	100	0	0.17	0	1926
4353	1901	78	62	131	10	0.17	0	1926
4449	1923	200	90	80	20	....	0	1926
4615	1924	130	60	120	0	0.13	0.7	1927
4631	1918	68	51	118	33	0.21	0	1926
4664	1910	84	72	117	..	0.16	..	1927
4856	1925	88	54	141	20	0.12	..	1926
4858	1924	74	52	88	25	0.14	0	1926
4859	1920	84	73	159	20	0.22	0.4	1926
4941	1924	88	61	131	10	0.18	0	1926
5063	1922	78	56	140	20	0.12	0	1926
5188	1925	76	55	101	15	0.08	0	1927
5257	1926	212	60 ±	100 ±	0	0.08	0	1926
5465	1926	98	69	113	12	0.13	0.4	1927

8. **Hypoglycemia.**—Hypoglycemia late in pregnancy and the puerperium when either the fetal or maternal pancreas may be responding to increasing demands by an overproduction of insulin is conceivable, but it has not occurred in our series. Among the cases directly under supervision the high-carbohydrate diets and low-insulin dosages minimized this danger. At another clinic where patients are treated with larger amounts of insulin warning against the danger of hypoglycemia is emphasized. It was observed once by Bowen, whose patient was taking at the time 48 grams of carbohydrate and 68 units of insulin.

Macleod[1] emphasizes the possibility of hypoglycemia following delivery due to the passage of sugar from the blood to the breasts at lactation. For this reason at the Mayo Clinic the plan of feeding both mother and baby soon after delivery has been adopted.

The possible danger of insulin shock following delivery is suggested in a few of our patients. Case No. 4631 was sugar-free after delivery. Glycosuria reappeared with a thyroid operation two years later. Case No. 4858 had 9 per cent sugar during pregnancy. This disappeared for eight months after delivery. Ten months later she was admitted to the hospital with sugar 4 per cent, a 3+ diacetic acid reaction and a blood sugar of 0.30 per cent. In Case No. 1975 the sugar disappeared during the last month of pregnancy and remained absent for three months after delivery then reappeared and has persisted during the nine subsequent years. Case No. 2384 was sugar-free for one month after delivery. Case No. 3660 was sugar-free and had normal blood sugars for twenty-four hours and for the subsequent two weeks she had only a trace of sugar with less than one-half the usual amount of insulin. Gradually, however, her insulin requirement rose to the former dosage. Case No. 3161 was sugar-free for ten days after delivery but is now a severe diabetic.

9. **Coma.**—Before insulin coma was the end-result of the pregnant diabetic. No matter what course was adopted the danger was imminent. Surgical intervention with general anesthesia would precipitate it. Fetal death, which occurred in 50 per cent of the cases prior to insulin, was a source of coma. If the patient came successfully to term, labor accompanied by partial starvation and over-exertion would bring it on. Even in the non-diabetic, hyperglycemia due to the anesthesia, asphyxia or involution is the rule. Labbé[2] and others have shown the CO_2 combining power in pregnancy, although non-diabetic, may be as low as 20 volumes per cent without ketosis. Nine of Labbé's 19 non-diabetic pregnancies had

[1] Macleod, Machowitz and Simpson: Trans. Roy. Soc. Canada, 1925, **5**, 71.
[2] Labbé and Couvelaire: Bull. Acad. de Méd., Paris, 1925, **94**, 1016.

a lowered alkali reserve. Yet how easy is it for the CO_2 in the diabetic to fall below 20 volumes per cent and for coma to ensue!

In our own series coma was met infrequently. Prior to insulin there were 2 coma deaths. Since insulin there have been no coma cases in pregnancy and only 1 case with demonstrable acidosis. This reached a 4+ acetone reaction in Case No. 3660 with a blood sugar of 0.10 to 0.16 per cent and a CO_2 combining power of 49 volumes per cent. In contrast to this coma occurred 4 times in Bowen's 10 pregnancy cases.

These latter cases are, with exception of his Case VII, characterized by extremely low CO_2 combining powers with relatively low blood sugars for diabetic coma cases. This same feature was evident in Case No. 3660 as well as in Case No. 1722. The latter started in labor on February 1, 1920, at 3.00 A.M. At 7.10 A.M. February 2 she was delivered of a dead infant, and her condition became rapidly worse. On February 3 she was conscious but had Küssmaul breathing; at 6.30 P.M. she could not be roused; and she died at 2.30 A.M. February 4.

The urine on January 23, showed:

		Grams per liter.					NH_3 expressed as N/10 cc.	Acetone expressed as N/10 cc.
Vol.	Sp. Gr.	N.	NH_3N.	NaCl.	Acetone.	Sugar.		
2580	1.030	6.67	1.14	3.80	3.44	50.00	1075	591

The blood on the same date:

Blood sugar.	Non-protein nitrogen.	Acetone.
0.18 per cent	23.8 mg. per 100 cc.	22.0 mg. per 100 cc.

At this time the question arose whether or not the condition was one of toxemia rather than acidosis (diabetic).

Soler[1] reports a case with acidosis in spite of large doses of insulin. Reveno[2] and Ambard[3] each report a death from coma. Four of Strouse and Daley's[4] 8 patients had severe acidosis. On the other hand Labbé,[5] Peters,[6] Wiener,[7] and the Mayo Clinic report 19 pregnancies without reference to severe acidosis.

10. **Infection.**—Previous to insulin Williams stated that the diabetics who survived coma succumbed to infections. No intercurrent infections have complicated our cases since 1922.

[1] Soler: Jour. Am. Med. Assn., 1927, **87**, 710.
[2] Reveno: Jour. Am. Med. Assn., 1923, **81**, 2101.
[3] Ambard, *et al.*: Bull. et mém. Soc. méd. d. hôp. de Paris, 1925, **49**, 547.
[4] Strouse and Daley: See De Masa: Med. Clin. North America, 1925, **9**, 1491.
[5] Labbé and Couvelaire: Bull. de l'Acad. de méd., Paris, 1925, **94**, 1016.
[6] Peters: California and Western Med., 1925, **23**, 1300.
[7] Wiener: Am. Jour. Obst. and Gynec., 1924, **7**, 710.

11. **Duration of Life Since Pregnancy.**—Among 58 cases 42 were alive in June, 1926.

TABLE 323.—DURATION DIABETES IN WOMEN WHO BECAME PREGNANT CALCULATED TO JUNE, 1926, OR TO DEATH.

Case No.	Duration to June, 1926.	Duration to death.	Case No.	Duration to June, 1926.	Duration to death.
102[1]	....	23.0	3233	11.5	
106[1]	....	9.0	3259	3.3	
306	Untraced		3313	12.7	
436	12.0		3352	13.0	
461[1]	....	1.0	3470	10.5	
604[1]	....	4.0	3476	5.6	
608[2]	....	0.6	3630	4.5	
671[2]	....	2.5	3660	4.5	
729[3]	....	7.6	3705	11.3	
791	11.7		3750	2.1	
812	12.0		3847	13.6	
854[1]	....	9.3	3938	7.9	
992	10.0		4010	13.2	
1018[2]	....	1.4	4132	14.7	
1070	....	1.4	4300	6.8	
1207[1]	....	5.8	4353	24.8	
1389[2]	....	1.2	4449	2.7	
1722[2]	....	1.3	4615	0.5	
1975	9.7		4631	7.7	
2218[1]	....	1.4	4664	7.0	
2384	5.1		4856	1.1	
2779	2.3		4858	1.8	
2888	6.5		4859	5.9	
3010	....	15.0	4941	2.0	
3030	2.1		5063	3.0	
3124	4.7		5122	1.7	
3161	7.3		5188	1.7	
3216	5.6		5257	0.7	

Diabetes developing in pregnancy or pregnancy in diabetes may be serious, but it is perfectly clear that the pregnancy is endangered rather than the diabetes, because the duration of the diabetes is long.

12. **Effect of Diabetes on Pregnancy.**—Abortions and miscarriages are said to be frequent. Cragin states 50 per cent of cases abort as the result of death of the *fetus in utero*. Four miscarriages occurred in the 10 patients observed by the Mayo Clinic. Two occurred in Bowen's series of 10 pregnancies. In our series of 89 pregnancies there were 13 abortions or miscarriages.

Despite the theory that carbohydrate imbalance is a cause of toxemias, the faulty carbohydrate metabolism of diabetes does not seem to be associated with them. Eclampsia occurred once and mild toxemias 3 times in our patients. Among Bowen's cases there was 1 probable eclamptic.

[1] Coma. [2] Miscellaneous. [3] Ether.

13. **Hydramnios.**—Hydramnios was found in 6 out of 26 gestations in Grafe's[1] cases, among whom a high glucose content in the amniotic fluid was found in 5. One case of hydramnios occurred in Bowen's group and 1 in our own.

14. **Effect on Baby.**—The percentage of still-births is high. Fourteen still-births, or 25 per cent, occurred among our 56 pregnancies coming to term. The possible causes for fetal death *in utero* are many. The size of the baby is one of the greatest dangers. Many of the babies reported in the literature are large.[2] This corresponds to the overgrowth of diabetic children. Coloroni[3] found 19.5 per cent of the fetuses of diabetic mothers oversize. In Bowen's series of the 6 babies born at full term, 4 weighed 9 pounds or more and 2 weighed 7 pounds or less. Cortabarria[4] reported a large macerated fetus. One can only speculate as to the cause for this phenomenon. The high glucose content of placental blood in diabetes, in contrast to the normally low content in the placental blood of non-diabetic individuals, is possibly an etiological factor. Of our own 14 still-births 2 of the mothers had diabetic complications, 6 had complications associated with pregnancy, and 4 were uncomplicated. Among our living cases not one mother had a diabetic complication and only 3 had a complication of pregnancy. Controlled diabetes is essential to fetal welfare. Diabetic accidents, coma and hypoglycemia, are preventable. Therefore, the number of fetal deaths from diabetic accidents should now be few.

Besides fetal death it is possible for the usual complications of diabetes and hypoglycemia to occur, but fortunately they do so only rarely. Diabetes simultaneously in the child of a mother diabetic at the time of pregnancy is reported twice in the literature, once by Ambard *et al.*[5] and once by Merklen, Wolf, and Oberling.[6] Diabetes occurred in the child of a diabetic mother, Case No. 4631, when she became five years of age.

Hypoglycemia is more to be feared than diabetes in the new-born. The infant's blood sugar is low according to the studies of Guy.[7] It may be as low as 0.01 per cent, the average being 0.11 per cent in 32 observations by Rowley.[8] There is also the possibility of compensatory hypertrophy of the pancreas as shown by the remarkable case of Gray and Feemster[9] with death of the baby from hypoglycemia.

[1] Grafe: Cited by Cragin: Loc. cit., p. 487.
[2] Fat children born dead suggest the investigation of the parents for diabetes according to Blanco: Archiv. de Endocrin. y nutric., 1926, **4**, 105.
[3] Coloroni: Cited by Springer: Ztschr. f. Gynak., 1924, **48**, 2624.
[4] Cortabarria: Revista Med. del Uraguay, Montevidio, 1922, **25**, 611.
[5] Ambard, *et al.*: Bull. et mém. Soc. méd. d. hôp. de Paris, 1925, **49**, 547.
[6] Merklen, Wolf, and Oberling: Bull. de l'Acad. de Méd., Paris, 1925, **93**, 80.
[7] Guy: Cited by Rowley: Am. Jour. Obst. and Gynec., 1923, **5**, 23.
[8] Rowley: Am. Jour. Obst. and Gynec., 1923, **5**, 23.
[9] Gray and Feemster: Arch. Path. and Lab. Med., 1926, **1**, 348.

TABLE 324.—OUTCOME OF 89 DIABETIC PREGNANCIES.

Case Nos.	Outcome.	Number of pregnancies.
102	Miscarriage	1
	Living child	2
	Still-birth	1
106	Living child	2
	Premature	1
436	Living child	1
	Therapeutic abortion	1
729	Living child	3
	Miscarriage	4
791	Living child	4
854	Living child	1
	Still-birth	2
1018	Living child	2
	Still-birth	1
	Miscarriage	2
2888	Living child	2
	Still-birth	1
3010	Therapeutic abortion	2
3233	Living child	1
	Miscarriage	1
3660	Living child	1
	Still-birth	2
	Therapeutic abortion	1
4010	Living child	1
	Still-birth	1
4300	Still-birth	2
4664	Living child	2
461, 604, 608, 2218	Died undelivered	1
671, 3216	Therapeutic abortion	1
812, 881, 1070, 1975, 2384, 3030, 3124, 3161, 3470, 3630, 3705, 3847, 4449, 4615, 4631, 4858, 5063, 5122, 5257, 5465	Living child	1
1207, 3259, 5188	Miscarriage	1
3750	Miscarriage	2
1722, 3313, 3938, 4941	Still-birth	1
4132	Premature	1
306, 992, 1389, 2779, 3352, 3476, 4353, 4859	Unknown	

TABLE 325.—SUMMARY OF OUTCOME OF 89 DIABETIC PREGNANCIES.

	Number.	Per cent.
Living children	42	47
Still-births	14	16
Miscarriages	13	14
Unknown	8	9
Therapeutic abortions	6	7
Undelivered	4	5
Premature	2	2

15. **Treatment of the Pregnant Diabetic.**—The treatment of diabetes in pregnancy is along the very same lines as the treatment of diabetes apart from pregnancy, simply bearing in mind the sudden transitions which may occur in these individuals and the pains which must be taken to adapt the diet to their dietetic whims. There is no harm in moderate undernutrition until term, because thereby

the mother will be in better diabetic condition and delivery will be made easier because of a smaller baby. The diet in all diabetics should be liberal in calcium because of its favorable action upon fertility.[1] Cod-liver oil is as good for the diabetic mother and the fetus as for the non-diabetic.

Small doses of insulin given frequently if necessary are preferable to large doses given at infrequent intervals and hypoglycemia may thus be avoided.

High-carbohydrate diets not only tend to promote a storage of glycogen in the liver, which is so essential an aid in the avoidance of toxemias, but they are also a protection against acidosis which easily occurs.

Daily examination of specimens of urine, weekly examinations of the blood sugar during pregnancy, hospitalization a week or more before term, four-hourly urine tests during labor and the puerperium will minimize the diabetic dangers.

Operative deliveries are not contraindicated on the grounds of diabetes. The diabetics of today stand operations well. If the size of the baby cannot be controlled by proper diabetic and general dietetic supervision then an induced labor or Cæsarean section may safely be chosen. A short labor with simple operative assistance is far safer than a long exhausting labor.

In general, close and persistent supervision of the patient by both internist and obstretrician is the most important part of the treatment. In this way many of the accidents of diabetic pregnancies may be avoided and an increasing number of diabetic mothers will give birth to living babies.

[1] Macomber: Jour. Am. Med. Assn., 1927, **88**, 6.

SECTION XV.

GLANDS OF INTERNAL SECRETION.

A. THE PITUITARY AND DIABETES.

THIRST with a history of being "a water drinker as long as I can remember" is a symptom not uncommonly volunteered by diabetic patients. This symptom together with the known tendency of diabetic children to be above height for their age at the onset of diabetes, their acknowledged mental precociousness, the proved development of their bones a year in advance of their age, the peak incidence of diabetes in children being at maturity, twelve years for my cases, the occurrence of glycosuria in pregnancy, the general frequency of obesity prior to the onset of diabetes in adults, all suggest that the pituitary is concerned in the development of diabetes.

This view of the connection of the pituitary with the pancreas is strengthened by the fact that in disease of no other organ save the pancreas are glycosuria and diabetes so common. In 100 cases of proved acromegaly Davidoff and Cushing[1] found glycosuria in 25 per cent and diabetes in 12 per cent with the probability that these figures would be increased if the patients had been longer under observation. In fact all the 9 acromegalic cases who were carefully investigated with the glucose tolerance test showed hyperglycemia, and an impairment in tolerance for glucose occurred in 6 cases after operation. Conversely their patients with the reverse condition, hypopituitarism, usually had a high tolerance for sugar and ordinarily showed hypoglycemia.

Transitory glycosuria, only, can be produced by lesions in or about the pituitary or by injections of posterior lobe extract. The diabetes which is found in connection with acromegaly or other pituitary disease does not differ essentially at any given date from ordinary diabetes (see Woodyatt's case reported in Colwell's[2] article, also John[3]), but it varies from time to time according to the activity of the pituitary and in consequence a spontaneous, tem-

[1] Davidoff and Cushing: Arch. Int. Med., 1927, **39**, 673.
[2] Colwell: Medicine, 1927, **6**, 1.
[3] John: Arch. Int. Med., 1926, **37**, 489.

porary or permanent cure of the diabetes may be effected, With the development of hyperthyroidism or myxedema in a diabetic patient the course of the diabetes is markedly altered, but no such clear dependence of the pancreas upon the thyroid is presented as is met with in disease of the pituitary. Allen recognized the importance of undernutrition in the spectacular improvement of the diabetes in my Case No. 344, who had tuberculosis, and utilized it for the treatment of all diabetics. Investigators today are not alert, if they fail to recognize that practically the only temporary or permanent cures of diabetes recorded are those cases in which a pituitary factor has been present. The Davidoff and Cushing article is replete with suggestive evidence and Colwell in his comment upon this temporary or permanent recovery writes "This fact is considered to be highly significant, for if the diabetes of acromegaly is a true diabetes and if it is capable of disappearing, then a knowledge of the mechanism involved might conceivably be employed in a study of the cause or cure of ordinary diabetes."

The hypophysis alone is perhaps never the cause of glycosuria and this appears to take place only by the interaction of the hypophysis upon the islands of Langerhans. An excess of secretion from the posterior lobe of the hypophysis causes glycosuria while a deficiency of this secretion results in an increased tolerance for carbohydrate. A tumor or acidophilic cells of the hypophysis always exists in acromegaly and diabetic states are signally frequent in clinical disorders involving the region of the hypophysis, but though glycosuria is easily produced experimentally in the region of the hypophysis and base of the brain in or about the floor of the third and fourth ventricles it is invariably temporary. One might attempt to be more specific and say that the chromophilic cells of the pituitary exert a partially controlling influence upon the cells of the islands of Langerhans. When there is evidence of hyperpituitarism these chromophilic cells are increased in number, and coincidentally the islands of Langerhans cease to maintain a normal carbohydrate metabolism, as evidenced by hyperglycemia and glycosuria. When hypopituitarism exists, neither hyperglycemia nor glycosuria appear. Acromegaly, hyperpituitarism, is to hypopituitarism as Graves' disease, hyperthyroidism, is to hypothyroidism, myxedema.

The fluctuating character of acromegalic glycosuria is its striking feature. Hyperpituitarism as expressed by acromegaly is not a steadily progressive disorder any more than is hyperthyroidism. "There are distinct waves of what the patient recognizes as more or less intense periods of 'acromegalism.' Some pronounced acromegalics go through a long life very little troubled by these symptoms; others are continually more or less miserable from the toxic effects of the disease. . . . (I am quoting Davidoff and Cushing.)

"Still other patients may never have more than a single primary wave of transient hyperpituitarism, and such evidences of overgrowth as may have been occasioned remain barely discernible. Indeed, the acidophilic adenoma which is unquestionably the underlying lesion may become completely degenerated and cystic, just as may a thyroadenoma, and signs of actual pituitary insufficiency come to be superimposed on the relics of a once active acromegaly. With these peculiarities of acromegaly in mind one can appreciate how it happens that acromegalics may show waves of mellituria, even periods which justify the designation of actual diabetes and yet spontaneously recover from them, irrespective of any dietary restrictions or treatment by insulin. One of our patients, an intelligent and observant woman, who had a transphenoidal operation twelve years ago with marked relief from her pressure symptoms, continues nevertheless to have recurrent periods of acromegalism; and with each wave of the process, which is signalized by a sense of exhaustion, she becomes temporarily highly glycosuric.

"Richard M. (E. P. J.'s Case No. 5036) is a boy aged eight years, who looks easily fourteen years. He is 53 inches tall (5 inches over the average for his age) and weighs 79 pounds (average for his age, 54 pounds). He has been in perfect health, is an exceptional student and the leader in his school. He was accidentally found to have 5 per cent sugar in his urine. This disappeared under treatment with insulin. The question arises whether this is primarily pancreatic or primarily hypophysial diabetes." The roentgen-ray shows a normal sella. The father of this boy is 5 feet, 11½ inches tall in his shoes, has weighed 252 pounds dressed and has a mild diabetes.

The antagonism of pituitrin and insulin was first pointed out by J. H. Burn[1] and confirmed in Cushing's Clinic and Davidoff and he cites the following experiments. In 3 of their patients with acromegalic diabetes who had been shown to respond normally to insulin, 20 units of insulin combined with 1 cc. of pituitrin were injected. The results are given below and show that the expected fall in blood sugar at the end of a two-hour period had not occurred.

TABLE 326.—THE BEHAVIOR OF THE BLOOD SUGAR IN 3 CASES OF ACROMEGALY UPON THE SIMULTANEOUS INJECTION OF INSULIN AND PITUITRIN. (DAVIDOFF AND CUSHING.)

	Case I.	Case II.	Case III.
Fasting . . .	0.33 per cent	0.13 per cent	0.15 per cent
	20 units insulin and 1 cc. pituitrin subcutaneously	20 units insulin and 1 cc. pituitrin subcutaneously	20 units insulin and 1 cc. pituitrin subcutaneously
After two hours .	0.32	0.14	0.142
After four hours .	0.30	0.12	0.112

[1] Burn: Jour. Physiol., 1923, **57**, 318.

Blotner and Fitz[1] have likewise shown that the blood-sugar curves of insulin and pituitrin are almost exactly the reverse of one another.

Case No. 5447 I was allowed to see through the courtesy of Dr. Harvey Cushing. Operations for the pituitary adenoma were performed, either in New York or Boston, in 1921, at the age of forty-three years, and again in 1925, but definite polyphagia, polyuria, and polydipsia with loss of weight were not observed until August, 1924, the presence of diabetes being proved in January, 1925. Between 1924 and 1926 the weight fell from 205 to 160 pounds. In 1926 glycosuria at times rose to 2 per cent on a diet of about 100 grams of carbohydrate, without insulin, but with 30 units of insulin remained in the neighborhood of 0.5 per cent, even when the carbohydrate was 166 grams. Observations during three weeks seemed to show somewhat less constant relation between the intake of carbohydrate, glycosuria, and the use of insulin than one usually sees in diabetes. Moreover, the blood sugar at no time fell below 0.18 per cent even though the sugar in the urine fell to 0.1 per cent and it did not rise above 0.3 per cent. The metabolism averaged on two days +32 per cent. Cammidge[2] likewise noted the difficulty of balancing the insulin with the diet in diabetics with acromegaly and to a less extent with diabetics who "although not presenting the typical clinical features of acromegaly are apparently related to it."

Cammidge's suggestion of a pituitary element in diabetics who do not show frank elements of pituitary disease should receive careful attention. Case No. 1760 at the age of twenty years in 1920 showed various symptoms and signs of glandular disease not characteristic of any one gland but of three glands, the thyroid, pituitary and ovary. To several of us the prognosis appeared so definitely unfavorable that we did not attack the therapeutic problem with sufficient energy. The urine contained 0.7 per cent sugar and the blood sugar was 0.16 per cent at seventy-five minutes after a full meal; the metabolism was —30 per cent. Subsequently, Dr. Timme of New York treated her with thyroid, pituitrin and lutein and in January, 1927, she looked and felt perfectly well, not having taken any medicine for six months. The blood sugar fasting was 0.08 per cent, at one hour after a meal 0.12 per cent, but the urine contained 0.3 per cent of sugar. The metabolism was − 2 per cent. I suspect that in 1920 more detailed blood-sugar analyses after meals would have disclosed a blood sugar above 0.16 per cent and might have allowed a diagnosis of diabetes, although I placed her at that time in the "unclassified" group of glycosurics. She deserves continued observation and especially at a period when taking glandular medication.

[1] Blotner and Fitz: Jour. Clin. Invest., 1927, **5**, 51.
[2] Cammidge: Proc. Royal Soc. Med., (Sect. Med.), 1926, **19**, 37.

Case No. 5520 showed true gigantism (pituitary hyperactivity before growth attained) and in September, 1926, at the age of thirty years was 6 feet 3 inches tall, and weighed 155 pounds naked, in contrast to the highest weight in 1920, 207 pounds dressed. With 20 units of insulin he tolerated carbohydrate 147, protein 81, fat 137, and the blood sugar varied between 0.13 per cent late in the forenoon to 0.2 per cent at two hours after a meal. In November, 1927, his weight had risen a few pounds, but the tolerance for carbohydrate was perhaps a little lowered although the observations were complicated by his being operated upon for hemorrhoids. His general condition, however, seemed better. Three days after the operation his blood sugar was 0.32 per cent after a meal.

Case No. 3620 (hypopituitarism) developed diabetes in August, 1922, at the age of eleven years, and came under my observation in December, 1923 with a history of an uncle and an aunt having had diabetes. The urine contained 5.5 per cent of sugar, acidosis marked, but with only 20 units of insulin the blood sugar dropped to 0.07 per cent, though a few days later on a diet of carbohydrate 45, protein 42, fat 91 grams, it was 0.27 per cent fasting and yet he was sugar-free. By May, 1925, his weight had risen to 75 pounds dressed, and the height was then 4 feet, $3\frac{3}{4}$ inches. Diet evidently was not strictly followed. In November, 1927, he reëntered the hospital and this time with extreme acidosis, which, however, was relieved very promptly with 5 doses of insulin, 10 units each, the blood sugar falling to 0.03 per cent. Marked variations of blood sugar ensued, ranging from 0.54 to 0.03 per cent, although the subsequent doses of insulin did not exceed 35 units in the twenty-four hours, with an approximate diet of carbohydrate 88 grams, protein 53 grams, fat 94 grams. Weight had again fallen to 54 pounds naked and his height without shoes was 4 feet 7 inches. He presented a pathetic object because of his severe headaches for which nothing appeared to give relief. Dr. Percival Bailey, then of the Peter Bent Brigham Hospital, saw him and made the following note on November 10, 1927, when the age of the boy was aged sixteen years. "Undersized, emaciated, skin dry, delicate and hairless. Testes very small, left undescended. No secondary sexual development. Voice childish. Mentally alert. Roentgen-ray shows sella turcica definitely smaller than normal. No supracellar calcification seen. Optic disks pale and sharply outlined. Visual fields normal to rough test, but more careful examination necessary. Doubt whether diabetes can cause this. Probably supracellar cyst."

Two of the conclusions reached by Davidoff and Cushing are as follows:

"Insulin and posterior-lobe extracts have been shown to be, and insulin and anterior-lobe extracts may be presumed to be, counteractive in their effects. Whether in acromegaly the mellituria is due

to an excess of posterior-lobe extract, as the counter-effects on insulin would appear experimentally to indicate, or to an over-activity of the acidophilic cells of the anterior lobe as we are inclined to believe, or possibly to a combination of both, for we know little of the source of the active substance of the posterior lobe, time will surely tell. Hyperpituitarism in any case produces a substance which enters the circulation and counteracts the normal functional activity of the pancreatic islets, glycosuria being the frequent consequence.

"The partial extirpation of the acromegalic adenoma by surgical procedures will apparently render patients with diabetes more amenable to insulin and may promptly lower the tendency to hyperglycemia exhibited by many of these patients even in the absence of active glycosuria. It may be anticipated that more radical procedures than those customarily undertaken, now that the operation has become reasonably safeguarded and perfected, will similarly serve to reduce the hyperpituitarism to such a degree as to check actual acromegalic glycosuria or even acromegalic diabetes more effectively and permanently than would treatment by insulin."

B. THE THYROID AND DIABETES.

1. **Diabetes and Hyperthyroidism.**[1]—During the last few years the writers have been associated on the staff of the Deaconess Hospital, the one having a considerable number of diabetic patients, the other a considerable number of thyroid cases. Not infrequently a patient has come to the hospital to enter upon one service who belonged on the other, and the similarity between the severe, untreated diabetic and the hyperthyroid patients has been forced upon us. Each reports a loss of weight, each is likely to have red cheeks, each has a high metabolism with its accompanying increased pulse-rate, especially high with the hyperthyroid, and yet in both weakness rather than strength comes from the lavish number of calories consumed and an irritable instead of a calm demeanor. The patients remain an equal length of time in the institution and leave with a lowered metabolism, in the one case as a result of aid through altered diet and insulin *to an underfunctioning pancreas*, and in the other as a result of aid through the surgical removal of a portion of the gland *to an overfunctioning thyroid*. And the analogy does not cease here, because following discharge a gradual gain in weight, strength, and restoration of morale can be predicted provided both continue to obey all the rules of the game.

Before insulin and modern surgery the association of two such

[1] A detailed consideration of this topic will appear by Joslin and Lahey: Am. Jour. Med. Sci., 1928, vol, **176**. Dr. Lahey and I preferred to include the name of Richard Middleton as joint contributor, but his modesty forces us to acknowledge his assistance in this place.

dynamic diseases as diabetes and hyperthyroidism was a catastrophe, because each accentuated and accelerated the downward course of the other. Even today, although the combination of diabetes and hyperthyroidism is amenable to treatment, it requires little imagination to perceive that one is dealing with a highly powered, highly geared machine, which is always travelling at an excessive rate of speed. Any trifling defect in the machine soon makes itself apparent and even a slight divergence from the routine pathway of treatment which would be negligible with the diseases apart can promote disaster when they are combined. The dramatic physical improvement noted in the hyperthyroid diabetic a few weeks after operation, if uncontrolled by chemical tests, would be most deceptive. The casual observer would conclude that the large majority of these patients had been cured and it is with some disappointment that one must record that complete recovery has, as yet, not taken place in any case in our experience.

Excellent reviews have been published in this country on this same topic by Fitz[1] and later by Wilder.[2] In the series of the former there were described 39 thyroid diabetics, and in that of the latter 75 cases. John[3] has also contributed a recent article. The present series contains 75 cases. On account of these recent articles scant mention is made here of the earlier literature.

(*a*) **Incidence of Glycosuria in Disease of the Thyroid.**—Hyperthyroidism is the fundamental factor in disease of the thyroid which leads to glycosuria. This is evident from an analysis of 500 cases of disease of the thyroid in the Lahey series. Thus in 38.6 per cent of 228 cases of primary hyperthyroidism, there was 0.1 per cent or more of sugar in the urine before operation or 0.5 per cent or more after operation. Likewise in 27.7 per cent of 83 cases of adenomatous goiter with secondary hyperthyroidism glycosuria of this percentage was present, but in 189 cases of non-toxic goiters it was present in only 14.8 per cent. This last percentage is essentially the same as that among 500 successive surgical cases at the Deaconess Hospital who had neither diabetes nor thyroid disease, because in this series it was found to be 13.6 per cent.

An interesting comparison between the incidence of glycosuria in disease of the thyroid and pituitary is afforded by data in a paper by Davidoff and Cushing.[4] They found that about 25 per cent of their 100 acromegalics showed glycosuria.

Fitz, Wilder, and we found the course of the diabetes in the non-toxic thyroid patient was uninfluenced by the thyroid disease or by the removal of the goiter.

[1] Fitz: Arch. Int. Med., 1921, **27**, 305.
[2] Wilder: Arch. Int. Med., 1926, **38**, 736.
[3] John: Ann. of Surgery, 1928, **87**, 37; Endocrinology, 1927, **11**, 497.
[4] Davidoff and Cushing: Arch. Int. Med., 1927, **39**, 751.

(*b*) **Incidence of Hyperglycemia in Disease of Thyroid.**—In hyperthyroidism the fasting blood sugar may be normal, and indeed is usually normal. Evidently the changes in carbohydrate metabolism occurring in connection with the thyroid gland are concerned more with its function than with its anatomical structure and this suggests that a similar relation may hold with the pancreas. In other words, the removal of nineteen-twentieths of the pancreas is a gross method of producing diabetes. A far more natural method would be a procedure which would influence the function of the gland. This is accompanied temporarily in diabetes by an infection. An infection similarly intensifies hyperthyroidism, but its action in hyperpituitarism is not so generally acknowledged.

(*c*) **The Diagnosis of Diabetes in Thyroid Disease.**—Acknowledging the disturbance of carbohydrate metabolism in hyperthyroidism as shown by the frequency of glycosuria and hyperglycemia, one wonders about the closeness of the relation between the two diseases or symptom complexes, diabetes and hyperthyroidism. Are these totally distinct diseases, fortuitously occurring together on rare occasions. Does one cause the other or is either an etiological factor in the development of the other? Does true diabetes ever occur in hyperthyroidism unless there has been the diabetic "anlage" in the Naunyn sense? Moreover, is the disturbed carbohydrate metabolism of hyperthyroidism any more than one might obtain as a result of increased metabolism from any other cause, such as that which occurs in fever or after exercise? Recognizing the disturbed carbohydrate metabolism in hyperthyroidism, how far can it proceed before one must classify it as diabetes? These questions illustrate the complexity of the problem which is furthermore increased by the circumstance that after operation and cure of the hyperthyroidism a slight disturbance of carbohydrate metabolism may return to normal. It is very evident that one must be very cautious or he will find himself making many diagnoses of diabetes and attaining many cures of a disease in which as yet one hesitates to advance such claims. For this reason the diagnosis of diabetes in hyperthyroidism must rest on a different basis from that usually adopted. Ordinarily a patient is said to have diabetes who has certain characteristic symptoms, a glycosuria varying with the diet and hyperglycemia above 0.13 per cent before or above 0.16 per cent after a meal. *For the present therefore and to avoid premature diabetic cures, we have raised the standard for a diagnosis of diabetes in hyperthyroidism to a blood sugar of 0.15 per cent fasting or 0.20 per cent or more after* meals in addition to glycosuria. Wilder was evidently forced to a similar conclusion, and like Fitz and ourselves has been extremely careful to exclude any but true diabetics.

The ultimate course of a diabetic hyperthyroid, however, may

furnish the key not only to his own diagnosis, but be the forerunner of real cures of diabetes. With this advanced standard if time shows the diabetes has disappeared, it will encourage the search for cures in other types of diabetes.

(*d*) **Increased Metabolism versus Abnormal Carbohydrate Metabolism.**—Exercise is an example of a state with a normal and extreme increase in metabolism. Exercise is likewise accompanied by an enormous increase in carbohydrate metabolism and indeed is carried on almost exclusively at its expense. I (E. P. J.) have never known diabetes to develop in consequence of exercise; it is proverbially rare in those who exercise freely; exercise leads to hypoglycemia instead of hyperglycemia and in the treatment of diabetes the extent of the exercise which the patient takes is a cardinal factor in his improvement.

Fever, on the other hand, is an example of a state with an abnormal increase in metabolism, which unlike that in exercise is persistent rather than temporary. During fever the potency of insulin is decreased, and in the convalescence exercise is curtailed and overfeeding present, yet the rarity of the development of diabetes is proverbial. Fever is most common in children and in children diabetes is most uncommon and this is true even of tuberculosis when fever and overfeeding exist over long stretches of time.

(*e*) **Heredity.**—The incidence of heredity in the hyperthyroid group was the same as for routine diabetics.

(*f*) **Priority in Appearance of Diabetes or Hyperthyroidism.**—If a marked priority in the appearance of symptoms of diabetes or hyperthyroidism could be demonstrated it would be of significance in the relation of the two conditions to one another. Such a demonstration, however, is not so simple as might be thought, because of the uncertain onset of each. Of the two the period of onset of diabetes is rather more easily determined. With some reservation as to their real value the statistics of the series of Fitz, Wilder, and our own can be interpreted. They are summarized in Table 327.

TABLE 327.—PRIORITY IN APPEARANCE OF HYPERTHYROIDISM OF DIABETES IN 152 THYROID DIABETES.

Condition.	Cases.	Hyperthyroidism precedes diabetes.	
		Cases.	Per cent.
Primary hyperthyroidism:			
Fitz[1]	22	21	95.5
Wilder	12	9	75.0
Joslin-Lahey	28	23	82.1
Total	62	53	85.5
Secondary hyperthyroidism:			
Wilder	19	9	47.4
Joslin-Lahey	8	5	62.5
Total	27	14	51.9

[1] Primary and secondary, not differentiated.

Fitz records but 1 instance out of 22 in which the diabetes preceded the hyperthyroidism, either primary or secondary in character. Wilder found 3 instances out of 12 cases in primary, and 10 out of 19 in secondary hyperthyroidism in which the diabetes was first. In our series also hyperthyroidism preceded the diabetes rather more commonly when it was primary (exophthalmic goiter) than when it was secondary (toxic adenoma).

(*g*) **The Incidence of Diabetes in Hyperthyroidism.**—Our 75 cases of diabetes were found in a study of 4917 true diabetics, and of 3869 patients operated upon for thyroid disease. Of these latter approximately 1751 were cases of primary hyperthyroidism and 655 were cases of secondary hyperthyroidism. Whereas nearly all hyperthyroids in the diabetic group are included, there have been a few diabetics in the hyperthyroid series which are not here tabulated. The two groups of cases by chance have been treated to a large extent in the same hospital. They indicate merely the incidence of hyperthyroidism (primary and secondary) in diabetes, which was 1.52 per cent, and, as stated, to a less accurate degree, diabetes in patients operated upon for thyroid disease which was 3.15 per cent, but by no means the incidence of either disease in the community as a whole.

TABLE 328.—INCIDENCE OF HYPERTHYROIDISM IN CASES OF TRUE DIABETES.

Type of hyperthyroidism.		
A. Primary hyperthyroidism (exophthalmic goitre)		
with operation	37	
without operation	6	
Total	43	
B. Secondary hyperthyroidism with adenomatous goiter		
with operation	26	
without operation	2	
Total	28	
C. Hyperthyroidism type unknown		
without operation	2	
with operation	2	
Total	4	
Hyperthyroidism (primary and secondary)		Total 75

The total number of cases of primary hyperthyroidism (exophthalmic goiter) was 43, of whom 37 were operated upon and 6 were not. The total number of cases with secondary hyperthyroidism with adenomatous goiter was 28, of whom 26 were operated upon and 2 were not. There were also 4 other cases of hyperthyroidism, of unknown type, because formerly treated in other clinics. Of these there were 2 with operation and 2 without operation. The total number of cases of primary and secondary hyperthyroidism

was 75 or 1.5 per cent of the total cases of true diabetes. The 43 cases of primary hyperthyroidism with diabetes constitutes 2.5 per cent of the total cases of primary hyperthyroidism seen by F. H. L. and the 28 cases of secondary hyperthyroidism with diabetes constitutes 4.3 per cent of the total cases of secondary hyperthyroidism seen by F. H. L.

The above figures are far below the incidence of frank diabetes in acromegaly which Davidoff and Cushing found to be 12 per cent in their series.

(*h*) **The Incidence of Thyroid Disease in Diabetes.**—Among 4917 cases of true diabetes there were 43 cases, 0.87 per cent, of primary hyperthyroidism, and 28 cases, 0.57 per cent, of secondary hyperthyroidism (toxic adenoma) and in addition 4 cases of one type or the other. These figures are quite the reverse of those of Wilder who among 1249 cases of diabetes found 1.1 per cent of primary hyperthyroidism and 1.8 per cent with secondary hyperthyroidism. A very approximate estimate of diabetes among our primary hyperthyroid cases would be 2.5 per cent and among the secondary hyperthyroids would be 4.3 per cent.

(*i*) **The Physiology of the Relation of the Thyroid and the Pancreas.**—Hyperthyroidism and a disturbance of sugar metabolism, and even diabetes, are distinctly related as shown by statistical evidence. Thus in 38.6 per cent in cases of primary hyperthyroidism and in 27.7 per cent in cases of secondary hyperthyroidism there was glycosuria and diabetes was present in 2.5 per cent in the former and 4.3 per cent in the latter. Let us now turn to experimental evidence obtained by physiological research. The problem is confused by an increase of the blood-sugar threshold as a result of thyroid feeding, which makes it difficult to determine the carbohydrate utilization.[1]

Feeding the thyroid gland to normal animals in certain cases has resulted in a lowering of the assimilation of glucose and according to Cramer[2] in a decrease in the quantity of glycogen stored in the liver. Conversely, thyroidectomy in normal animals increases the tolerance for carbohydrate and leads to hypoglycemia, and causes a definite increase in sensitivity to insulin for ten to twenty days after operation. In the following ten days this returns to normal and eventually there is a heightened tolerance toward insulin.[3] Yet Richardson, Levine and DuBois[4] found that the glycogen reserves of 2 patients with exophthalmic goiter were apparently as great as normal.

In depancreatized animals, experiments with the thyroid gland have been confusing and lack of space prevents discussion.

[1] Kawashima: Jour. Biochem., 1927, **7**, 361.
[2] Cramer: Jour. Phys., 1916, **50**, xxxviii.
[3] Britton: Am. Jour. Physiol., 1928, **84**, 133.
[4] Richardson, Levine and Du Bois: Jour. Biol. Chem., 1926, **67**, 737.

Following operations upon hyperthyroid patients Lund and Richardson[1] observed a rise in blood sugar similar to that in other patients. Although conditions following operation for exophthalmic goiter might cause an increased demand for glucose no instance of hypoglycemia was found, but in those cases with postoperative thyroid crises Holman found a marked hypoglycemia and the symptoms were promptly removed with intravenous glucose.

The work of Burn and Marks[2] and that of Bodansky[3] throws new light on what is taking place between the thyroid and pancreas. They have found that either by the feeding of thyroid gland or by injections of thyroid substance the liver is made hypersensitive (over-responsive) for the discharge of its sugar, as a result of some stimulation which favors the conversion of glycogen into sugar. This is illustrated by the following experiments. As a result of an intravenous injection of glucose a rabbit shows hyperglycemia which gradually disappears. If the glucose injections are continued and the same animal is fed daily with thyroid gland the fall from the (primary) hyperglycemia is broken by a secondary rise which eventually falls to a level of hypoglycemia. Ultimately if the daily injections of glucose and the thyroid feeding are continued convulsions and death ensue, because there is no more hepatic glycogen to be discharged. The secondary rise in blood sugar following glucose injections in thyroid-fed animals apparently is due to the conversion of glycogen in the liver into sugar which is discharged from that organ. Insulin will act the same as glucose in creating a lowering of the blood-sugar level and need for extra glucose from the already overworked liver.

If the discharge of glycogen is prevented by section of the splanchnics, a dose of insulin, which was without effect before the operation, now produces severe symptoms. Evidently the discharge of glycogen from the liver has been prevented.

Similarly should thyroidectomy be performed instead of severing the splanchnics, convulsions would be produced with one-third, one-fifth, or even one-sixth the dose of insulin necessary before the operation. Here too the conversion of glycogen into sugar and its discharge from the liver as sugar is prevented as a result of the thyroidectomy and in consequence less insulin is required to reduce the sugar in the blood and convulsions result.

If thyroid is fed, insulin acts less well. If, however, thyroid feeding is continued for more than ten days the reserve of glycogen in the liver becomes exhausted. Should insulin be injected at this time convulsions are produced with less than the usual dose of insulin.

[1] Lund and Richardson: Arch. of Surgery, 1925, **11**, 171.
[2] Burn and Marks: Jour. Phys., 1925, **60**, 131.
[3] Bodansky: Proc. Soc. Exp. Biol. and Med., 1923, **21**, 46; Ibid., 1923, **20**, 538.

The glycogen in the liver shows no change in the early days of feeding, but in the later is decreased and finally disappears from the liver at the end of eighteen days.

The mouse and the rabbit when fed with thyroid gland presented a considerable resistance to the action of insulin, just as the removal of the thyroid gland reduces the sensitivity of animals to insulin. In fact, there exists a definite antagonism between the thyroid and the pancreas so far as related to the metabolism of carbohydrate.

Thus from the physiological standpoint one gets an explanation of what is observed clinically. In disease of the thyroid gland glycosuria and hyperglycemia are neither casual phenomena nor dependent alone upon the increased metabolism of hyperthyroidism. There is a certain relation between the thyroid and pancreas through glycogen storage just as there is between the pituitary and pancreas. Hyperglycemia and diabetes are not as frequently associated with hyperthyroidism as they are with disease of the pars anterior of the pituitary; hypoglycemia and the non-diabetic state are not as definitely associated with hypothyroidism (myxedema) as these conditions are with the pars posterior of the pituitary, but the similarity of the relation of the two glands to the pancreas is too definite to be overlooked. One can hardly fail to reach the conclusions that if the diabetic "anlage" were present only to a slight degree in a patient, hyperthyroidism would bring a latent diabetes to the fore.

The pituitary is said to contain no insulin and it is noteworthy that the thyroid contains only relatively little of an insulin-like active substance. (Laquer).

(*j*) **The Pathology of the Pancreas in Thyroid Disease.**—Definite anatomical changes in the pancreas are said to result from the administration of thyroid, but the whole question deserves reinvestigation. Shields Warren in a study of the pancreases of 3 of our cases with hyperthyroidism reported the following:

Case No. 4289.—Pancreas is small, weighing 30 grams. The islands are normal in number and not remarkable except that there are rather more large sized islands than we commonly see. In a few of the islands there is a suggestion of lymphocytic infiltration but this might be due to naked nuclei as the preservation is not particularly good in these areas.

Case No. 5176.—In this pancreas there is moderate amount of fatty infiltration but the organ is normal in size. There are several small foci of fibrosis in the pancreatic tissue with lymphocytes, plasma cells and large mononuclear infiltration. In these foci are involved several islands which are practically destroyed. However, most of the islands appear normal and are quite numerous.

Case No. 5335.—Examination of the pancreas was not satisfactory owing to the involvement of the head and a considerable por-

tion of the body in a carcinoma with head of the pancreas which had metastasized extensively to the liver. However, in the body and in the tail and in a few places in the tumor tissue are a moderate number of normal islands.

Pancreases have also been examined for changes in 9 autopsies of cases of hyperthyroidism who have not had diabetes. No significant changes have been found.

(*k*) **The Age of Diabetic Thyroids.**—Thyroid diabetics are young diabetics, especially if we have in mind the rarity of thyroid disease in children. The average age at onset of diabetes of the 43 primary hyperthyroid diabetics was 40.5 years, and the average age at onset of the diabetes of the 28 diabetics with adenomatous goiters and hyperthyroidism was 47.8 years, in comparison with 4592 cases of true diabetes (Joslin) which was 43.8 years.

Diabetes preceded primary hyperthyroidism in only 5 of 28 cases and secondary hyperthyroidism in 3 of 8 cases. This relation of the onset of the two diseases is that usually encountered by other writers.

(*l*) **Sex.**—The female sex greatly predominated both in the cases of primary hyperthyroidism, 33 out of 43 cases, and still more in the cases of secondary hyperthyroidism, 24 out of 28 cases. No such preponderance of females is seen in uncomplicated diabetes. This is due to the fact that a much greater number of women than men have hyperthyroidism.

(*m*) **Height and Weight of Thyroid Diabetics.**—An impression of the character of the diabetes is furnished by a study of the heights and weights of the thyroid diabetics. As is well known the ordinary diabetic of forty years or above is almost universally overweight. An analysis of the height and weight in reference to sex and age has been made in 72 patients. Of these the maximum weight for the height was above normal in 60 cases or 83 per cent. This is interesting in view of the usual weight loss in thyroidism.

(*n*) **Duration of Life of Diabetic Patients With Hyperthyroidism.**—The average diabetic in a group of 600 fatal cases since the introduction of insulin has lived 7.7 years and the average age at onset of the diabetes was 46.5 years.

The durations of life of 20 fatal cases of diabetes and hyperthyroidism varied between 0.2 years and 10.3 years. The average duration for the entire group was 3.4 years. The average duration of life of the 12 primary hyperthyroids of these fatal cases was 3.2 years, but of the 31 living cases (July 1, 1926), the duration has thus far reached 3.9 years.

The adenomatous cases with secondary hyperthyroidism lived for a longer period. Thus the duration of life of 6 fatal cases is 4.1 years, and of the 21 living adenomatous cases with diabetes is already 5.5 years. It would be unfair to conclude, therefore, that the present-

day hyperthyroid diabetic would live a shorter period than the ordinary diabetic. The durations of life cited above for thyroid diabetic give but a partial picture. They are recent cases in the main and though living, the disease has not yet had an opportunity to demonstrate its benignity or seriousness. With the aid of modern surgery and insulin we would predict that the duration of life would be greater than that of the average diabetic.

(*o*) **Causes of Death.**—Since the introduction of insulin the percentage of deaths due to diabetic coma has fallen to 20 per cent and for the year ending July 1, 1927 for 1241 diabetics treated and traced there were 43 deaths with none from coma. Among the primary hyperthyroid cases there were 4 deaths from coma or 33.3 per cent of the total deaths in this group, and among the 6 fatal cases of secondary hyperthyroidism 4 cases. This relatively high percentage shows how seriously we must regard the hyperthyroid diabetic, because in general coma is characteristic of severe diabetes. The other causes of death were cardiac 2, pneumonia 2, postoperative hyperthyroidism or shock 4, and septicemia, cancer, inanition, and cerebral arteriosclerosis 1 each.

Coma is by no means always fatal in the hyperthyroid diabetic. Indeed the diagnosis of diabetes was first made in Case No. 4306, when she was found in diabetic coma. Her case is described more in detail on page 645. Cases 5346 and 5649 also survived coma.

(*p*) **The Basal Metabolic Rate.**—Before operation the patients (35) with primary hyperthyroidism showed an average basal metabolic rate of plus 61 per cent, in contrast to plus 49 per cent for 1000 cases of primary hyperthyroidism before operation in the Lahey clinic. Thus the presence of diabetes tended to elevate the basal rate. After operation the basal metabolic rate fell to plus 7.4 per cent in 33 of the thyroid diabetic patients as compared with 5 per cent for 850 cases of uncomplicated hyperthyroidism who reported for basal metabolism estimations three months after operation in the Lahey series. Partial thyroidectomy, therefore, produces identical results in the diabetic hyperthyroid as in the hyperthyroid alone.

The average basal metabolic rate before operation in 25 diabetic patients having adenomatous goiters with hyperthyroidism was plus 44 per cent as compared with a series of 245 similar non-diabetic cases in which it was plus 41 per cent. Following operation the average rate in 21 cases of the diabetic series was plus 10 per cent and of the Lahey series of 123 adenomatous goiters with secondary hyperthyroidism but without diabetes was plus 9 per cent.

(*q*) **Gain in Weight Following Operation.**—There is two-fold reason for loss of weight in the hyperthyroid diabetic, namely that caused by the increased metabolism and second that due to the loss of sugar

in the urine. But the condition is aggravated still more, because overeating, which is so generally associated with a high metabolism, makes a diabetic worse and often leads him to coma. In hyperthyroidism the overeating is continuous. Therefore, the removal of the cause of the overeating, namely the high metabolism of hyperthyroidism, by surgical procedures ought to yield striking results in diabetes. Such in fact is the case because in 22 of the primary hyperthyroid cases the gain in weight was 21 pounds and in 19 of the hyperthyroid adenomatous cases it was 13 pounds after operation. In certain of these cases the period which had elapsed since operation was only a little over three months.

(*r*) **Race.**—The Jewish race is proverbially emotional and their tendency to diabetes is also well known in Boston amounting to two and a half times that of the general population. Among the 75 hyperthyroid diabetics there were but 13 Hebrews, 17 per cent; among the 43 cases of primary hyperthyroidism there were 6 Hebrews, and 5 among the 28 secondary hyperthyroid cases. In the series of 5086 true diabetics (Joslin) the Jewish incidence is 13 per cent; in the Lahey series of 1000 recent primary hyperthyroids it is 15 per cent and in 245 secondary hyperthyroids it is 16 per cent.

(*s*) **Relief of the Hyperthyroidism.**—The favorable influence of iodine in hyperthyroidism with diabetes was observed by Labbé.[1] It has been difficult to estimate it in our cases, because insulin, diet and iodine (usually as Lugol's solution) have been begun simultaneously in our zeal to ameliorate the condition of the patient. About all we can say is that the three as thus combined work well.

(*t*) **Treatment Before and After Operation.**—No serious attempt has been carried out before operation to make the urine completely sugar-free with diet or insulin. The carbohydrate has been maintained at about 100 grams, the protein at approximately 1 gram and the total calories at not far from 30 per kilogram body weight. Insulin has been given in small doses, usually 5 units, three or more times a day. If prompt response to diet and insulin did not occur the insulin was increased to 10 units at a dose and the frequency increased. Great pains were always taken to give food within three hours before the operation, but usually this did not exceed 20 grams of carbohydrate in the form of oatmeal gruel, orange juice or ginger ale. Simultaneously the dose of insulin before operation always erred in being too small rather than too large.

Following operation great effort was made to give as much as possible of the carbohydrate of the original diet. The frequency and the dose of insulin were seldom increased save in the exceptionally severe cases for we have found the sudden increase in glycosuria after operation was temporary and unattended with obvious harm.

[1] Labbé: Annales de Med., 1920, **7**, 95.

The quantity of iodine given daily before operation was 10 minims three times a day for eight to ten days. The dose then increased to 20 minims three times a day the day before operation. After operation Lugol's solution, 10 minims three times a day was given during the stay in the hospital, usually eight days and then 10 minims weekly for three months.

Intravenous Injections of Glucose.—In patients with postoperative reactions of any severity or whose preoperative course was such that a postoperative thyroid reaction was anticipated, intravenous infusions of 50 grams of glucose with 750 cc. of normal saline solution were given once or more during the immediate postoperative period.

Surgery.—Primary Hyperthyroidism.—Thirty-seven of the 43 cases were operated upon with 1 fatality. Most of these patients were operated upon in two or more stages, but the number of operations per patient has been steadily decreasing. In all there have been 64 operations. This makes a mortality per operation of 1.56 per cent and per patient of 2.7 per cent.

Secondary Hyperthyroidism.—There were 28 cases and 26 of these underwent operations. Here the number of operations was distinctly less, because the total was but 39. There were 2 deaths, making the mortality per operation 5.1 per cent, and per patient 7.7 per cent.

Among the 8 cases of non-toxic adenomatous goiter associated with diabetes there have been no deaths.

Results of Operation.—The basal metabolism of the hyperthyroid diabetics has been already discussed on p. 887, as well as the changes in weight on p. 887, and the duration of life since onset of diabetes on p. 886.

No instance of a cure of the diabetes has been observed among patients with primary or secondary hyperthyroidism following operation. In general, a gain in tolerance for carbohydrate has been greater with the secondary than with the primary hyperthyroid. Each group of cases appears to do rather better than the ordinary diabetic, but it is clearly evident that end-results must be awaited until a longer period of time has elapsed.

The increase in tolerance for carbohydrate has been not far from 30 grams.

Gain in tolerance is difficult to measure because so often the hyperthyroid whether primary or secondary enters the hospital with between 2 per cent and 8 per cent of sugar in the urine which quickly clears up with diet and insulin. In other words it is hard to decide what the actual base line of carbohydrate tolerance was before operation.

Many of these hyperthyroid patients have been operated upon

for many other conditions as well. Thus, Mrs. T., Case No. 3483, a year before the goiter was removed had a nephrectomy for an abscessed kidney and she still has a gall-bladder filled with stones.

Eleven other cases of hyperthyroidism originally classified as diabetes, but on account of the standards set in this discussion for diabetes not included in the present group, will also be kept under observation in order to determine whether they later become positive diabetic cases. So too will 9 cases of hyperthyroidism showing glycosuria who thus far have only been classed as "potential diabetics." Diabetes developed subsequently to an operation for hyperthyroidism in 8 of our 75 hyperthyroid diabetics. Such cases are mentioned by Wilder,[1] Holst,[2] and Labbé.[3] In 2 of Holst's cases diabetes occurred after a partial thyroidectomy, but in both of these cases the symptoms of hyperthyroidism had persisted. Wilder reports 2 cases of diabetes developing in thyroidectomized patients. The hyperthyroid who has been operated upon therefore should be warned of the possibility of developing diabetes later even though the disease may not be so likely to appear as if he had not been operated upon at all. Progressing longevity increases the incidence of diabetes in the community and this progressing longevity of the hyperthyroid, brought about by operation, may also be a factor in that it brings him into the diabetic age zone, the most frequent year for onset of the disease in females being fifty years and for males fifty-one years.

2. **Myxedema and Diabetes.**—Myxedema is rare in diabetes. I have had one undoubted case, Wilder[4] has reported another, and still others have appeared in the literature.[5]

Case No. 2899 had an operation for uterine fibroids at the age of twenty-eight years in 1897, noticed an enlarged thyroid in 1920, hoarseness in October, 1921, and at her first visit to me in February, 1922, when her weight was 213 pounds dressed, my associate, Horace Gray noted the symptoms of myxedema with a large multiple adenomatous goiter. The urine was sugar-free and the blood sugar 0.1 per cent. The metabolism was −32 per cent. With thyroid extract she promptly improved.

The urine remained sugar-free in February, March, April, June and September, 1922. The blood-pressure which was 170/110 in February, 1922, gradually fell by June 5, 1922 to 110/90, rising in September, 1922 to 145/90. Upon November 16, 1922, she reported that her eyesight failed a month before and that polyuria and pruritus vulvæ developed. The urine contained 8.4 per cent sugar.

[1] Wilder: Arch. Int. Med., 1926, **38**, 736.
[2] Holst: Schweiz Med. Wchnschr., 1923, **53**, 725.
[3] Labbé: Annales de méd., 1920, **7**, 95.
[4] Wilder: Arch. Int. Med., 1926, **38**, 736.
[5] Holst: Schweiz Med. Wchnschr., 1923, **53**, 725.

With dietetic treatment she promptly became sugar-free and could easily keep so upon about 100 grams carbohydrate. Thyroid medication has been continued by herself according to her symptoms and she has been comfortable save when the coal strike "hit her hard" in 1925–1926. In November, 1927 the metabolism was −14 per cent. At her last visit on March 28, 1928 the urine contained 3.1 per cent sugar, the blood sugar was 0.31 per cent fasting, metabolism −9 per cent and weight 178 pounds dressed. The blood-pressure was 130/80. This patient has refused hospitalization and insulin, and indeed with moderate dieting can keep sugar-free. A child with tuberculosis and a husband with epilepsy in addition to lesions in the uterus, thyroid and pancreas are handicaps, yet she maintains a cheerful demeanor. She takes 5 grains thyroid gland daily.

Wilder describes his case as follows: "A male child, aged seven years, had been a full term infant with normal health and normal growth up to the age of fifteen months. He then manifested polydipsia and polyuria, and sugar was found in the urine. He was placed on a strict diet which, after six months, could be somewhat relaxed without causing a return of glycosuria. Delayed growth and increasing coarseness of the hair led to the diagnosis of hypothyroidism, when he was aged three years. Thyroid treatment was begun but was discontinued because of the return of intense glycosuria and the occurrence of acidosis. During the period of thyroid treatment growth had been resumed. After its discontinuance growth again stopped and the tolerance improved so much that the child 'could eat anything without excreting sugar.'

"On examination at the clinic this patient presented a fully developed picture of juvenile myxedema, the face dull and expressionless, the skin dry and thick, the hair coarse and scanty. Mentality and physical development were much retarded; the height was 38.5 inches, the weight 34 pounds (15.4 kg.). The basal metabolic rate was −45 per cent. The urine was sugar-free; the blood sugar 0.12 per cent.

"There was some difference of opinion among the examining physicians as to whether this child could have had diabetes. My prediction was that when the metabolic rate was raised to normal, diabetes would be evident and insulin would be needed in order to make possible the feeding of a satisfactory diet. Thyroid was administered in small doses and the metabolism raised very gradually. At the same time the diet was rigidly restricted in carbohydrate and protein. August 2, the basal metabolic rate reached −10 and sugar appeared in the urine. Later under the reëstablished metabolic rates sugar continued to be excreted in amounts as high as 20 grams a day, and the fasting blood-sugar level reached

0.145 per cent. At the last report, December 29, 1925, the child was gaining in weight and strength but showing sugar despite a rigid diet (glucose equivalent 76 grams) and 10 units of insulin daily."

Another patient, Case No. 3565, is remarkable for the duration of the diabetes, although data are less complete. She developed the symptoms of diabetes in 1912 at the age of thirty-five years and 2. per cent sugar was found the following year. In 1920, the blood sugar at the Massachusetts General Hospital was 0.328 per cent. The Wassermann reaction was negative. At her first visit to me in 1923 the urine contained 0.7 per cent sugar and when the diet was raised to carbohydrate 136 grams the blood sugar after a meal was 0.17 per cent. The basal metabolism averaged on two occasions −20 per cent. Her dry hair, hard and brittle nails, yellow pallor and dry skin, together with the low metabolism made the diagnosis of myxedema probable, and with thyroid extract she promptly improved, and was alive in June, 1926.

Wright[1] reports 2 cases of myxedema and diabetes. The administration of thyroid extract had no untoward effect on the action of the insulin.

Case No. 5143 has shown a low metabolism since 1923 when she was started upon thyroid extract in another clinic and has been obliged to continue it. Though she does not show many of the characteristic symptoms of myxedema she still has a metabolism of −17 per cent and the therapeutic test makes that diagnosis probable. Her diabetes began in May, 1919, at the age of 38.3 and she requires about 30 units of insulin to keep sugar-free on a diet containing 130 grams carbohydrate.

No case of myxedema and only 1 of a notable hypothyroidism have followed operation in the 75 cases of hyperthyroidism and diabetes reported by me in conjunction with F. H. Lahey. Holst[2] has reported 1 such case.

Geyelin found the fasting blood-sugar level low in 4 cases of hypothyroidism and that the administration of thyroid extract to these cases produced a definite hyperglycemia. Janny and Isaacson showed the presence of hypoglycemia in cases of myxedema. Gray, however, in 8 cases from the literature found the blood sugar only slightly lower in hypothyroidism than in hyperthyroidism, and even higher than in normal. Gardiner-Hill in 15 well-marked myxedema cases showed the fasting level of blood sugar in the majority of cases to be within normal limits. According to Brett, Smith and Hill,[3] the limit of assimilation for carbohydrate is increased in myxedema,

[1] Wright: Clifton Med. Bull., 1926, **12**, 88.
[2] Holst: Schweiz Med. Wchnschr., 1923, **53**, 725.
[3] Brett, Smith and Gardiner-Hill: Quart. Jour. Med., 1925, **18**, 327.

and the blood sugar may be low, but the blood-sugar curve is higher and more prolonged than in normals. Glycosuria is rare and they suggest that the renal threshold is raised.

C. THE SUPRARENAL AND DIABETES.

No attempt will be made here to present the complicated problems of the relation of the suprarenal gland to the pancreas. As yet in the actual treatment of diabetic patients one is seldom confronted with these save advantageously in the utilization of the known antagonistic effect of insulin and epinephrine in the presence of insulin shock. I regret space does not permit the inclusion of the work performed by W. B. Cannon and his associates. Its importance is recognized.

Hypoglycemia was first noted in Addison's disease by Porges in 1910. Other references to the literature of hypoglycemia in this disease are given by Longcope.[1] Stenström[2] records a case of spontaneous hypoglycemic coma, relieved by adrenalin, and of pleuriglandular origin. Jacot[3] has published a monograph, *Glycogène, Adrénalin et Insuline.*

No case of disease of the adrenals has been recognized in this series and indeed in the entire literature Arnett[4] says but 5 cases of Addison's disease are recorded and the diagnosis is to be questioned in each. He himself reports one case in detail and summarizes the literature. I cannot do better than to quote his conclusions.

"The combination of Addison's disease and diabetes mellitus is extremely rare. It is moreover of great interest, because the two ductless glands involved, namely, the suprarenals and the islands of Langerhans, secrete hormones producing opposite glycemic effects. The case herewith reported presented both the clinical and chemical evidences of diabetes mellitus, together with the pigmentation, asthenia, low blood-pressure and vomiting which are characteristic of Addison's disease. Autopsy bore out this diagnosis. Unusual therapeutic difficulties were encountered owing to the existence of a hypersensitivity to insulin and a marked tendency to ketosis, the former no doubt being due to suprarenal insufficiency."

Marañon[5] noted increased susceptibility to insulin in 2 patients with Addison's disease and it was more marked than in certain other patients similarly cachectic. He emphasizes the importance of examination of the suprarenals in death from coma, particularly in those cases in which death ensues when the acidosis is overcome.

[1] Longcope: Jour. Am. Med. Assn., 1928, **90**, 1.
[2] Stenström: Deutsch. Arch. f. klin. Med., 1926, **152**, 173.
[3] Jacot, M.: Glycogène, Adrénaline et Insuline, Paris, Masson et Cie, 1926.
[4] Arnett: Arch. Int. Med., 1927, **39**, 698.
[5] Marañon: Press Medicale, 1925, **33**, 1665.

D. THE THYMUS AND DIABETES.

In Major's[1] case a child, aged eleven years, with diabetes of two years' duration, and occasional attacks of asthma becoming increasingly infrequent, was brought into the hospital in deep coma, sterterous respiration, blood sugar 0.645 per cent and carbon dioxide tension about 4.5 per cent. She survived but four hours.

The necropsy showed edema of the lungs, an unusually large thymus covering the entire surface of the pericardium anteriorly and weighing about 50 grams. The abdominal lymph glands were enlarged. In the pancreas the islands were strikingly reduced in number but without evidence of degeneration.

[1] Major and Helwig: Jour. Am. Med. Assn., 1926, **86**, 1766.

SECTION XVI.

DIABETES IN THE OLD AND OF PROLONGED DURATION.

A. DIABETES IN OLD AGE.

My oldest diabetic, Case No. 1513, reached the age of ninety-four years and ten months. Two of the 51 cases who had the disease over twenty-five years reached the ninth decade and 5 of the 161 cases with a duration above twenty years did the same. Among 5086 patients there were 653 with onset in the seventh decade and 131 with onset in the eighth decade. Among the cases of twenty years' duration there was 1 instance with onset in the eighth decade. Already it has been mentioned that the average age at death of the 43 cases among the 1241 treated and traced in the year ending July 1, 1927, was 60.9 years. In 1917 the percentage of cases with a duration of twenty or more years was 1.9 for 1187 cases, in 1923 was 2.2 for 3000 cases and is now 3.2 for 5086 cases. But this does not portray the incidence aright. If statistics are limited to all my cases numbering 171, who were seen twenty years ago, *i. e.*, prior to 1908, the number of twenty-year cases rises to 9.9 per cent. It is therefore justifiable to make the statement that at least 1 diabetic in 10 will live twenty years or more and in consequence is a candidate for old age, because the onset of the average diabetic is about fifty years. It is worthy of record that of 5 of those 17 cases seen prior to 1908 who ultimately lived over twenty years two were doctors, two were doctor's relatives, one was a druggist.

The percentages of cases originating in the seventh and eighth decades, as recorded in successive editions of this book, have been remarkably constant. See Table 329.

TABLE 329.—PERCENTAGE OF AUTHOR'S DIABETICS WITH ONSET IN SEVENTH AND EIGHTH DECADES.

Edition of this book.	Year.	Seventh decade, per cent.	Eighth decade, per cent.
First	1916	11.9	2.8
Second	1917	11.9	2.8
Third	1923	8.7	1.6
Fourth	1928	12.8	2.6

Diabetes burns out in the old and the tendency of the diabetic is to outgrow the symptoms of his disease. In the care of the elderly patient the physician therefore must not be meddlesome. He must realize that the old man's diabetes is inherently mild. "No really severe diabetes could have continued so long as this. . . ." Woodyatt.[1] Many of these cases eventually become sugar-free, if placed upon a constant diet, with a liberal quantity of carbohydrate, but just sufficient calories to maintain body weight. This may not occur in four days or even four weeks, but ultimately the glycosuria disappears. It is often claimed that such patients need no treatment, and are, in fact, better off without it. With this statement I disagree. Often they are very uncomfortable without medical advice and very grateful to receive it. They are furthermore satisfactory cases to treat, because it is easy to help them acquire a high tolerance. Indeed insulin proves to be a great comfort and, though at first its benefits are not realized and its subcutaneous use disliked, in the course of time patients fully appreciate the benefits it confers and what is more, they may discover in the course of a few weeks that they are able to omit it and yet retain their increased diet.

Elderly patients are often easily depressed, easily lose their appetite, easily acquire indigestion, and the danger of acidosis is by no means slight. The patient should be considered from a broad standpoint, and the diabetes viewed with a proper perspective.

So many of the cases of twenty years' duration fall into the old age group that certain facts relating to the same are inserted here. Of the 161 cases the onset of but 1 was in the first decade, 2 in the second, 18 in the third, 52 in the fourth, 60 in the fifth, 24 in the sixth, 3 in the seventh and 1 in the eighth. The males numbered 98, the females 63 which as in the case of the twenty-five-year cases may be explained by the diabetes having been originally discovered by insurance in 39 men, but in only 1 woman. One hundred and twenty-six of 160 cases with known data were obese before onset. A positive diabetic heredity was present in 31 per cent of 160 cases. There was a history of syphilis in 3 of 160 cases, but only 1 positive Wassermann among the 69 patients thus tested.

The causes of death of the 56 known fatal cases were as follows: coma, 7; cardiac disease, 19; nephritis, 2; apoplexy, 6; arteriosclerosis, 1; pneumonia, 4; gangrene and sepsis, 5; tuberculosis, 1; cancer, 3; old age, 1; diabetes, 6 and unknown, 1. It is not an accident that so few of these cases succumbed to gangrene. They were unusually intelligent and cared for their feet.

Illustrative cases of the success of treatment of diabetic patients of advanced years are numerous. Case No. 629, cited in detail under Tuberculosis, p. 745, led an active life until the age of seventy-

[1] Woodyatt: Southern Med. Jour., 1924, **17**, 145.

eight years, took up politics, and died at the age of eighty-four. Case No. 559, was in good health five years after onset of diabetes at the age of seventy-two, remained so following the removal of the prostate gland four years later, but succumbed at the age of seventy-eight years to tuberculosis. Case No. 687, from being a semi-invalid, recuperated sufficiently to enjoy life for several years, retained a carbohydrate tolerance of 100 grams, but unfortunately became blind and died at 85.7 years. When I first saw her at the age of seventy-five years, the urine contained 7 per cent sugar. Case No. 90, who developed diabetes at the age of seventy-nine years, lived ten years, during which time she made frequent trips to the tropics, and finally died in England. Case No. 899 in whom diabetes was known not to have been present at the age of eighty-three years, was according to a letter from her daughter "wonderfully improved by treatment and remains sugar-free." She was one of the few patients whose tolerance came back to such an extent that she could eat rich pastry without the return of glycosuria. At the age of eighty-six years she died of hemiplegia. Case No. 2771 developed diabetes at the age of 80.6 years, and at eighty-eight years is, I believe, my oldest living diabetic.

Old age is no excuse for neglect of diabetic treatment.

B. CASES OF DIABETES OF TWENTY-FIVE OR MORE YEARS' DURATION.[1]

One in 100 of the diabetics, 51 among 5086, had the disease twenty-five or more years. The males predominated comprising 65 per cent of the group in contrast to 50 per cent for the entire series. This is probably explained by the fact that 12 cases were discovered through examination of urine for life insurance, and all of these were males.

The importance of obesity, both as a predisposing and as a favorable prognostic condition, is borne out by the fact that it was present in 40 out of 50 of these patients.

Heredity was present in 21 of the 50 cases, a proportion much greater than the incidence for the entire series. This is confirmatory of the impression that hereditary diabetics are mild diabetics.

Syphilis was unimportant in this group of diabetics as in the entire series. Wassermann reactions were done on 31 of the patients. In only 1 to whom the test was applied was a Wassermann reaction positive. This case had other clinical evidence of old syphilis. One other had a history of syphilis.

[1] I am greatly indebted to Dr. Albert A. Hornor for his aid in the preparation of this section. For a former study of my cases of fifteen or more years' duration, see Hornor and Joslin: Am. Jour. Med. Sci., 1918, **155**, 147.

A severe type of diabetes is rare in this group. Actually only 3 were classified as such. Ten were classified as moderately severe, and the remaining 38 mild. Treatment was occasionally neglected by many of these patients but most of them usually took moderate care with their diet. Occasionally cerebral arteriosclerosis had developed to such an extent that a patient could not be reasoned with about his treatment. One such case refused to take insulin although he was repeatedly told, what his family fully recognized, that at that time his condition was such that without insulin little hope could be held out for prolongation of life.

Coma was the cause of death of only 8 per cent (2) of the 25 fatal cases, 15 died of cardio-vascular disease, only 2 of these, however, being due to gangrene. One died of pneumonia and the cause of death of 1 was unknown. In 2 cases the cause of death is given as diabetes. One of these died in 1920, before the discovery of insulin, the other was the one referred to above as refusing insulin.

The natural expectation of life, based upon age at onset of the diabetes, was exceeded by 35 per cent (7) of the 20 fatal cases and 19 per cent (6) of the living cases. If this expectation of life be corrected for the number of pounds overweight at time of maximum weight for the 13 fatal cases for whom complete data exist, it may be stated that 77 per cent (10) lived longer than the average duration at that weight, and 1 equalled the duration. Similarly sufficient data are available for 29 of the living cases to show that already 34 per cent (10) have outlived their corrected expectation of life and another has equalled such an expectation.

Arteriosclerosis existed in at least 35 of the 45 cases on whom we have sufficient data. The arteriosclerosis in many of these 35 cases was well marked. This incidence of arteriosclerosis among the cases of diabetes of twenty-five years' duration may be taken as evidence that arteriosclerosis itself does not increase the severity of diabetes.

The diabetes was considered to be controlled in 19 of the 48 cases on whom the data were sufficient. Of these 19 cases, 4 are dead, 15 are living. In 1 of these 15 cases, however, the diabetes was under control for twenty-five years but not for thirty years. In this study it was considered that a controlled case is one which maintains a satisfactory weight on a diet containing 150 to 300 grams of carbohydrate without insulin, the urine sugar-free or a fasting blood sugar less than 0.14 per cent or a blood sugar at one hour after a meal less than 0.17 per cent.

SECTION XVII.

RENAL GLYCOSURIA.

A DIAGNOSIS of renal glycosuria is uncertain unless the element of time is added to the four other cardinal requirements namely: a persistent glycosuria, relative independence of the diet, absence of hyperglycemia and freedom from the symptoms of diabetes. Serious results may ensue if the diagnosis is carelessly made or overlooked.

Diabetes is hereditary and familial, and so is renal glycosuria. Many writers report hereditary cases. Hatlehol[1] described 5 cases of renal glycosuria among 12 families with diabetic relatives. I[2] described the instance of a mother with two children, Cases Nos. 1266 and 1612; the former was killed in a coasting accident and did not develop symptoms of diabetes within 6.5 years of onset; the latter and the mother have had a renal glycosuria for 10.3 and 9.3 years respectively. A father and a son, Cases Nos. 2636 and 3158 with histories extending over periods of thirteen years and six years respectively, were originally diagnosed as renal glycosuria, but in the latter the diagnosis has been changed to diabetes mellitus.

The more carefully these cases are studied certain resemblances to true diabetes are found, but I do not wish to go on record that the one is apt to change into the other. Case No. 3607 was transferred from the renal glycosuric to the unclassified group of glycosurias. I was told of an interesting case at the Children's Hospital, their number 24069, in whose family there were several true diabetics and yet when first seen the child appeared to have renal glycosuria. Such a case should be watched for life. I believe that the original diagnosis in each instance should be strongly fortified. I am inclined to agree with Frank[3] that once a renal glycosuric always a renal glycosuric, despite the two changes thus far made in my own group. Renal glycosuria is a mild condition and it is easy for confusion to arise with diabetes of hereditary origin which is also apt to be mild or with the unclassified glycosurias which are so

[1] Hatlehol: Acta Med. Scan., Suppl., 1924, **8**, 140.

[2] Joslin: Oxford Medicine, London, 1st ed., 1921, **4**, 140.

[3] Frank, E.: In Verhand. d. Kongres. f. inn. Med., 1921, p. 240, gives a summary of the early literature.

commonly encountered upon routine examination of the urine. Mosenthal,[1] has studied such cases with unusual care and Castex and Beretervide[2] give an extensive literature.

"Renal glycosuria is by no means uncommon," according to Folin and Berglund[3] "and most observations on alimentary glycosuria represent nothing else. From a class of 100 students one can usually find at least 1, and often 2 or more, who find sugar in their own urine when learning to make the test for sugar." These are important cases to watch, because the diagnosis rests primarily on time as was said in the opening sentence. Among 40 cases coming for treatment of diabetes at the U. S. Army General Hospital (No. 9), Allen[4] found renal glycosuria 3 times. Rabinowitch[5] in 275 consecutive cases found it 6 times. It has occurred infrequently in my own series, 49 times among 6000 cases of glycosuria, although the incidence of glycosuria not classified as diabetes was great. See p. 548.

Like diabetes, renal glycosuria occurs in all decades, but unlike diabetes, in the majority of the cases the diagnosis is made before the patient is forty years of age. Its frequent occurrence among children suggests the possibility that it is a congenital anomaly, but it may be an acquired lesion as in Mosenthal's case[6] A. W. G., who for twenty years had examined the urine every two weeks and at the age of sixty-six years developed a symptomless glycosuria with normal blood sugar. At the age of seventy-seven he was still in perfect health. Twenty-eight of my cases were males and 19 females. It is evident that I have excluded 2 (Case Nos. 2513, 2722) of my original 49 cases.

TABLE 330.—RENAL GLYCOSURIA, AGE AT ONSET BY DECADES.

Total glycosurics.	Decades.					
	1.	2.	3.	4.	5.	6.
1 to 1000	0	0	0	0	0	0
1000 to 2000	1	2	1	1	0	0
2000 to 3000	0	5	3	6	0	0
3000 to 4000	1	0	4	0	1	1
4000 to 5000	1	2	3	4	2	2
5000 to 6000	0	1	3	1	1	1
Total glycosurics	3	10	14	12	4	4

[1] Mosenthal: Med. Clin. North Am., 1925, **9**, 549.
[2] Castex and Beretervide: La Prensa méd. argen., 1925, **11**, 769.
[3] Folin and Berglund: Jour. Biol. Chem., 1922, **51**, 213.
[4] Allen: Arch. Int. Med., 1919, **24**, 523.
[5] Rabinowitch and Finley: Quar. Jour. Med., 1924, **17**, 260.
[6] Mosenthal: Med. Clin. North Am., 1925, **9**, 549.

The functions of oxidation and storage of sugar in renal glycosuria both Rabinowitch,[1] Paullin[2] and Govaerts[3] have shown to be normal. After the ingestion of 100 grams of glucose in 5 cases Rabinowitch demonstrated an average increment in the respiratory quotient of 0.11. The blood-sugar curves simultaneously taken were of the generally accepted normal type. Ladd and Richardson[4] also found their renal glycosuric was able to utilize carbohydrates to the same extent as a normal individual, thus taking away the ground from the theory that renal glycosuria is similar to diabetes or likely to pass into it. The opposite view is held by Geyelin.[5]

The fat metabolism is not abnormal. Ketosis occurs in these patients under starvation or low carbohydrate diets, as it does with normal individuals. Such a case is reported by Taussig.[6] Ketonuria occurred after an accident, when the patient was eating little, and disappeared when the carbohydrate was raised to 110 grams. Such a condition is confusing without a knowledge of the percentage of sugar in the blood. It also occurred in Case No. 2165.

In a single observation Allen found the blood cholesterol value to be normal, but in studying the fat partition the lecithin value was found to be high.

Permeability of the kidneys has long been considered the pathological lesion. In experimental phlorizin diabetes, which this condition so closely resembles, the role of the kidney was first recognized by von Mering. Later Zuntz established the fact that this type of glycosuria was of a certainty of renal nature. Phlorizin injected into the renal artery was followed by prompt excretion of sugar on the side injected and excretion was delayed on the opposite side. Hamburger and Brinkmann[7] have shown that alteration of sodium, potassium and calcium ions in the liquid contents of the glomeruli allows the glomerular epithelium to excrete glucose at a level above 0.07 per cent.

A lowered renal threshold associated with disorders of the endocrine glands is a common occurrence. In hyperthyroidism and dyspituitarism there are cases excreting small amounts of sugar with a low blood-sugar level and large amounts of sugar with a slight elevation of blood sugar above normal. Similarly pregnancy is frequently accompanied by glycosuria, especially in its latter half, without hyperglycemia and this state is usually, but not always

[1] Rabinowitch: Jour. Clin. Inves., 1926, **2**, 143.
[2] Paullin: Arch. Int. Med., 1926, **37**, 88.
[3] Govaerts: La Presse méd., 1927, **35**, 771.
[4] Ladd and Richardson: Jour. Biol. Chem., 1925, **63**, 681.
[5] Geyelin: In Cecil, Text Book of Medicine, W. B. Saunders Company, 1927, p. 578.
[6] Taussig: Med. Clin. North Am., 1927, **11**, 355.
[7] Hamburger and Brinkmann: Bioch. Ztsch., 1918, **88**, 97.

benign. The glycosuria is occasionally repeated in successive pregnancies and sometimes this apparently innocent glycosuria changes over after a term of years into true diabetes. The more closely, therefore, the glycosuria of pregnancy is shown to resemble renal glycosuria, the more apprehension is awakened for cases of idiopathic renal glycosuria.

Bowcock and Greene[1] report an interesting case of renal glycosuria of 4.7 years duration in which there had been two successful pregnancies and an attack of typhoid. The urine was sugar-free on only two occasions: during typhoid and on the sixth day of the puerperium of the second pregnancy.

The older conception of a renal pathology in renal glycosuria has not been borne out by my cases, because albumin and casts have been infrequent: two-hour renal tests and phenolphthalein tests were essentially normal.[2] The blood-pressure is not raised. The benignity of renal glycosuria, however, has prevented the study of the kidneys themselves.

Case No. 2165 had a blood-pressure of 130/80, pulse of 80, no arteriosclerosis, heart normal after twenty-seven years. There was but a slight trace of albumin in the urine, no casts, blood or pus. The phenolsulphonephthalein excretion was 62 per cent in two hours and ten minutes. Despite his heavy intake of protein, as shown by an excretion of 21.3 grams urinary nitrogen in twenty-four hours, the non-protein nitrogen in the blood was 33.6 mg. per 100 cc. Even after a duration of the condition for 32.1 years the urinary sediment still contains no casts, no blood and only an occasional leukocyte.

Different types of severity exist among renal glycosurics just as among true diabetics. It is also probable that there are different thresholds at which a renal glycosuria becomes manifest and Vogelenzang[3] goes so far as to report the combination of diabetes and renal glycosuria in the same patient. In the majority of the cases the quantities of sugar voided are small. Case No. 2165 with a renal glycosuria for 32.1 years excreted 58 grams of glucose in twenty-four hours, yet after a meal of about 75 grams carbohydrate the highest percentage of sugar in the blood was 0.1 per cent. Case No. 2279 excreted 87 grams glucose, and his highest blood sugar during nineteen months either after or before a meal has been 0.14 per cent.

The prognosis of a case of renal glycosuria is evidently good, because my patient has lived 32.1 years and of my 47 cases there have been but 3 deaths. The prognosis must be guarded because of the possibility of the change of a supposed renal glycosuria into true

[1] Bowcock and Greene: Jour. Am. Med. Assn., 1928, **90**, 502.
[2] Joslin: Med. Clin. North Am., 1921, **4**, 1723.
[3] Vogelenzang: Cit. Jour. Am. Med. Assn., 1925, **85**, 1173.

diabetes. Hatlehol has never seen a case of renal glycosuria become a true diabetic. Gulland[1] says he has seen cases of renal glycosuria go over into true diabetes. But the difficulty of differentiating those cases of diabetes mellitus with a lowered threshold from true renal glycosuria is great. Dr. Priscilla White, who has taken an active part in the preparation of this section, plans to restudy all my cases of renal glycosuria and report upon them.

Essential pentosuria presents a problem for differential diagnosis, when the diagnosis of renal glycosuria is raised. The clinical picture is as innocuous as that of renal glycosuria and both conditions may occur in several members of one family. Jones and Sussman[2] stress the fact that in the majority of so-called renal glycosurics pentosuria has not been excluded. They advocate for this purpose the use of the Bial test, the special fermentation method of Castellani and Taylor, the determination of the melting-point of the crystals of phenylhydrazin, the nitrogen content of the crystals and the spectrum test of Neuman.

[1] Gulland: Brit. Med. Jour., 1927, i, 363.
[2] Jones and Sussman: Am. Jour. Med. Sci., 1927, **173**, 513.

SECTION XVIII.

THE MANAGEMENT OF THE DIABETIC IN OFFICE AND HOSPITAL.

A. THE EDUCATION OF THE DIABETIC.

The education of the diabetic is considered so essential a part of the treatment of the diabetics committed to their care that the Trustees of the New England Deaconess Hospital have provided them with a school-room. This accommodates the scholars and affords a favorable opportunity for the instruction of patients, relatives, and friends. The prevention of gangrene is so important that a Beauty Parlor for Diabetic Feet has been established with space for a chiropodist. Next to it is a room in which three treatments with ultra-violet rays can be carried on simultaneously. Dental needs led to another room for the dental hygienist and dentist and now we are about to have a gymnasium which will make exercise, so essential for diabetics, possible in inclement weather.

The amount of information a class of diabetics will imbibe is astounding. The teacher benefits quite as much as the scholars in such a school. I know I learn advantageous points of treatment by this intimate contact and I do not regret the time spent, even though it is a routine. The scholars want concrete facts. They want to see displayed in lump sugar the amount Janette voided the day before she came in and to see her Benedict test now. They want to see the baby of the class perform a Benedict test. They like to look at the diet of one of their number for the day before he is discharged and vote whether he knows enough to leave. And if a dignified but, in this particular, ignorant doctor or relative is present who does not know the simple weight which represents 5 grams, the entire class rejoices in seeing its youngest member impressively teach the ignoramus by removing from his supply of change a buffalo nickel, which chances to represent that weight exactly. These kindergarten methods are not foolish. It is worth while to tell the patients about coma and gangrene and to encourage them to answer questions: What are the worst enemies of the diabetic, and what are the standard rules for their prevention? I never teach the

premonitory symptoms, but say: "If you are sick, call it coma, and (1) go to bed," etc. (See p. 649.) The premonitory symptoms of coma are too indefinite. It is safer to call anything coma. The treatment will do no harm and it may save me the disgrace of having a patient die needlessly of coma years after in his own home, and the same principle applies to gangrene. Occasionally I have the temerity to ask a patient to exhibit his feet and hint that the request may be general at another time.

Then, the patients like to talk, to tell their troubles, to display their knowledge, to help one another, and to be a happy, cheerful family. There is not one-half the fun in treating a patient alone, and it is so costly in time.

Questions from a diabetic are as encouraging as from children. Do not stifle them. Foster the habit, but have the questions written down by the patient and then write the answers. That is the secret. When written, a large percentage are duplicates, but, when asked and *not* answered, are "the doctor was too busy to answer my question."

The patients must "see all nor be afraid." Tell them the best and the worst. Let them see a case of coma and gangrene and learn the reasons therefor. Urge them to study their charts and to note the orders recorded. Have no secrets. Always make them realize that they have the diabetes, not you, and it is up to them to master it. They should understand that faithful treatment usually lasts for life. Prof. Naunyn wrote: "From my experience I consider it highly probable that among the early strictly treated cases, which originally were considered severe, but later ran a favorable course, there is many a one for which one must thank this early strict treatment, while, on the other hand, there can be no doubt that the cases which ran ultimately a severe course underwent little or no care." Not infrequently those who have diabetes outlive their normal expectation of life. Diabetes is a disease which depends upon the honesty and intelligence of the patient for successful treatment. It develops character, for to follow the rules of diet involves constant self-control.

A diabetic patient upon entrance to a hospital should be made to understand that he is taking a course in diabetes. It is ideal if entrance can be at the beginning of the week and discharge at the end. A simple diabetic textbook should be distributed and upon this he should be questioned in recitations and at other times as well. He should attend the diabetic classes on diet, treatment, and insulin administration. He should be drilled in weighing food or estimating food values, and easy opportunities for this should be afforded. For successful graduation in the course he should be able:

1. To demonstrate how to test a urine for sugar.

2. To record a summary of his diet for the previous day.
3. To explain the quantity of carbohydrate which it contains.
4. To describe what he is to do if sugar returns in the urine.
5. To demonstrate how to give insulin.
6. To give the symptoms and treatment of an insulin reaction.
7. To tell how to avoid coma.

Several years ago the hospital class system for diabetic patients was introduced by Dr. Mosenthal into the Vanderbilt Clinic in New York City; shortly afterward it was adopted by my former assistants, H. W. Goodall at the Boston Dispensary and F. G. Brigham at the Massachusetts General Hospital, and it is now universally employed. It is adaptable to an office practice and in this way will release hospital beds for the more serious diabetics and other diseases. So employed it can greatly lessen the expense of treatment.

B. HOSPITAL TREATMENT.

More than once I have cleared up the mysterious downward course of a case of diabetes by sending the patient to the hospital. It is surprising how benign severe cases of diabetes become when under the physician's eye. On the other hand, great caution is necessary in the treatment of severe cases of diabetes in the first few days following their entrance to an institution. Habits of life and of diet are broken, and the patient is under some excitement. Formerly coma was by no means an uncommon occurrence, because of the radical elimination of carbohydrate and the change to an excessive protein-fat diet. Now all this is altered. Nevertheless, watchful care over each patient should be exercised, and no matter how mild the case, the patient should be seen daily by the physician until his exact condition is understood. If acidosis is present, remember that what is done the first hour counts toward its cure more than what is attempted the next twenty-four. By this means threatening coma is often averted. The patient's routine should be disturbed as little as possible. Entrance to a hospital by no means eliminates his going outdoors. It is quite as harmful to rest too much as too little. The utmost simplicity of diet should be maintained. A complete physical examination of the patient should be made just prior to his discharge. This is more important than ever now, because so many patients live to the arteriosclerotic stage. Case No. 6246 had a little "indigestion,' but left without complete examination and died before rising while chatting with a friend the next day. He told another friend he had concealed his feelings from doctor and nurse. He was sixty years old, a locomotive engineer. The heart was of normal size; arteries much sclerosed; Wassermann positive, for which he was to receive

TABLE 331.—HISTORY SHEET.

NAME — AGE Yrs. Mos. — M F W S M — REFERRED BY DR. — No. — DATE

ADDRESS — ADDRESS

OCCUPATION — RACE — Born: Yr. Mo.

FAMILY HISTORY — F. — M. — Children / Spouse / Other relatives

Bro. — Sist.

HABITS — C_2H_5OH — Tobac. — C't'a or Ven. — Activity

PAST HISTORY — S. F. — Typh. — Pneu. — R. F. — Chor. — Jaun. — Tonsil. — Diph. — Malaria — Meas. — Mumps — Pert.

ONSET — Date — Sudden / Rapid — Gradual / Indefinite — SYMPTOMS

SUGAR FIRST DISCOVERED — CAUSE OF EXAMINATION — Insurance / Routine

LAST PRIOR EXAMINATION

ETIOLOGY: Give date of infection or injury if within six months preceding onset

(*a*) Obesity (*b*) Heredity (1) Hereditary (2) Familial (*c*) Dietary excess (*d*) Strenuous life (*e*) Nervous
(*f*) Infections (*g*) Arteriosclerosis (*h*) Syphilis (*i*) Traumatic (*j*) Pancreas, abd. pain fatty stools
(*k*) Thyroid, size exophth. tremor nervousness palp. vom. diarrhea perspiration
(*l*) Hypophysis, acromegaly adolescence gigantism diab. incip.
(*m*) Gall stones (*n*) Gout (*o*) Kidney

SYMPTOMS SINCE ONSET:

(*a*) Maximum: Weight Height Date
At onset
First visit
Substandard

(*b*) Loss of strength
(*c*) Polyuria
(*d*) Polydipsia
(*e*) Polyphagia
(*f*) Pruritus

(*g*) Pains
(*h*) Extremities
(*i*) Cramps
(*j*) Mouth
(*k*) Bowels

OTHER SYMPTOMS:

(*a*) Digestive N. V. P. (*b*) Circ. D. P. Vertigo Pain (*c*) Nervous
(*c*) Renal D. N. (*d*) Resp. C. S. (*f*) Vision

PRESENT COMPLAINT:

PHYSICAL EXAMINATION General appearance Hair Skin and mucous membranes Thyroid
Pupils and muscles Eye grounds Glands: C. A. I. E. Tonsils
Hearing Breath: Acetone Al. air: CO_2 Teeth
Pulse A. S.: 0 1 2 3 4 Bl. Pr. (recumbent) Syst. Dias. Apparatus Breasts
Heart Apex size Sounds Rickets
Lungs
Abdomen Liver Spleen Kidneys

Dorsalis pedis, right Left Hernia Edema Knee-jerks

BLOOD Wassermann Sugar: Per cent Fasting After food Hours CO_2 tension N. P. N. Fat

URINE Date Vol. Reac. Sp. gr. Alb. Acetone Diacetic Sugar: Reduction Total gms.
Sed.
W. B. C.
R. B. C.
Casts

DINSTINCTIVE FEATURES AND COMPLICATIONS:

TABLE 332.—HOSPITAL CHART WITH THE HEADINGS OF ITS TWO SIDES.

No. Name Hospital

Standard weight in kilograms:
Onset:
Net height in centimeters:
Net weight in kilograms:

Date.	Vol. cc.	Sp. gr.	Reac.	Alb.	Sodium chloride, gm.	Nitrogen, gm.	Diacetic acid.	Sugar in urine.		Diet in grams.				Glucose balance, gm.	Naked weight, lbs.	Non-protein nitrogen.	Bloor's blood fat, %.	Blood sugar, %.	Blood CO_2 vol., %.	Alveolar air CO_2, mm. hg.	Insulin.				Remarks.
								Reduction, %.	Total gm.	Carbohydrate.	Protein.	Fat.	Calories.								Units. Order.	Units. Given.	Time given.	Sugar in single spec.	

Name of Patient

Date.	Orders.	Meal.	Meat.	Dietary Prescriptions in Grams.																	
				Egg.	Chicken.	Vegetables. 5%.	Vegetables. 10%.	Bacon.	Uneeda.	Butter.	Cream. 20%.	Cream. 40%.	Potato.	Oatmeal.	Shredded wheat.	Grapefruit.	Orange.	Cheese.	Fish.	Oil.
		Breakfast Dinner Supper																		
		Breakfast Dinner Supper																		
		Breakfast Dinner Supper																		
		Breakfast Dinner Supper																		
		Breakfast Dinner Supper																		

treatment at home. At the hospital he became sugar-free without insulin and was discharged with carbohydrate 88 grams, protein 81 grams, fat 138 grams.

The first specimen of urine voided by the patient on entrance to the hospital gives little indication of his true condition. It is the rule to find that diabetic patients have made violent alterations in their diet in the few days preceding entrance. They have either broken all dietetic rules which they may have previously followed with considerable care, fearing that their diet is to be curtailed, or, in order to make a favorable impression upon the physician, may have lived upon a far more rigid diet than that to which they have been accustomed. This was well illustrated by Case No. 759. This patient had been free from acidosis for a considerable length of time, but, prior to her first visit to me, a diabetic relative had suggested restriction of diet, and this resulted in the appearance of a four plus diacetic acid reaction.

The trained diabetic is critical. If a nurse or doctor is not conversant with the diet and makes a plain blunder, confidence goes. These diabetics tolerate no mistakes in others.

Hospital treatment fails of its purpose unless the patient is discharged to the care of his physician at home with a report of his condition while at the hospital and with recommendations for future care. This entails much labor, which at times may not be appreciated by either patient or physician, but it is a duty which the hospital doctor should never neglect. Three talks by the doctors and three by the nurses are given weekly for the benefit of the patients, their physicians, nurses, and relatives. Every effort should be made to interest the family physician in the care of the case, and the directions given the patient should be in such form that a busy practitioner can readily acquaint himself not only with what has been done, but how he should proceed.

The surgical diabetics in a hospital need supervision even more than the diabetics who enter medical wards. Hospital diabetic mortality is largely surgical and undoubtedly is as high as it is because of lack of intimate coöperation between physician and surgeon. The surgical diabetic is always the case to be seen first by the physician.

The annoyances from diabetic patients breaking the diet in open wards are now practically abolished. All patients are expected to have the urine free from sugar. It does not take long for the patient to learn that although he may "cheat the doctor, he cannot cheat the disease." Charity patients must be told that charity ceases when the diet is knowingly broken. When a child or an adult for that matter breaks the diet, he should go to bed and remain in bed until sugar-free.

The weight of the patient recorded in terms of the naked weight should be taken daily at the same morning hour.

The diabetic diet in a hospital should be very simple. Emphasis should be placed upon the point that the patient shall be taught the value of each portion of food he receives. It may be easier for the hospital dietitian to have the physician specify the grams of carbohydrate, protein and fat which the patient is to have, but in so doing the doctor fails to treat his patients unless the nurses explain the quantity of carbohydrate, protein, and fat in each different article. From the first day of entrance to the hospital the patient should begin to learn his diet, and unless his food is given to him in forms which he can easily duplicate upon leaving the institution, his hospital stay is a failure. Amost anybody can get a diabetic patient sugar-free, but the education of the patient to care for himself upon leaving the hospital constitutes more than 90 per cent of the treatment.

Simplification in weighing food is accomplished by the use of scales[1] of 500 grams capacity with a movable dial which can be set at zero when an empty dish is placed upon them. Food can then be placed in the dish and the weight instantly read off. Such scales reduce greatly the labor of weighing food as compared with scales where weights must be added to a pan or lever.

C. AMBULATORY TREATMENT.

Most diabetic patients in the past have been treated in physicians' offices, and most diabetic patients in the future will continue to be treated in the same manner. I intend to adopt this plan more and more. It is perfectly possible to carry out good treatment under these circumstances, but it involves great patience, much time in the education of the patients, and thus expense. It is advantageous in that the habits of the patient are little changed, the whole responsibility is placed upon him and from the start the diabetic treatment is made to fit into the routine of life. The danger of this method is chiefly that the patient is not seen frequently enough, both at the very beginning of treatment and later when he ceases visits, because of his improvement although his knowledge is inadequate. The diabetic diet and insulin are two-edged tools. With the alteration of diet there is a possibility of acidosis on the one hand or an insulin reaction on the other. With the limitation of fat in the diet and thus the reduction of calories for the first days and with minimal doses of insulin these dangers are greatly lessened.

The same routine as that carried out at the hospital should be taught the patient. In general, he should be made conversant with

[1] John Chatillon & Sons, New York.

the rules embodied in A of this section. Much time will be saved if the patient is accurately taught at the start how to save the urine, to measure the food, and to record it neatly and in a systematic manner so that the physician can quickly detect mistakes in the diet. Under no condition allow the patient to tell what he has eaten, but insist on his presenting a written record of what he has eaten. The urine, and if possible the blood, should be examined and reported upon while the patient is in the office. The extra expense and trouble entailed are offset by the prompt application of treatment, the satisfaction of the patient, and the lessening of secretarial expense. A patient with acidosis should go to a hospital or be seen twice a day. A glycosuria of 5 per cent demands daily reports if one desires to advance in diabetic treatment.

Most of my cases up to 1915 were treated as ambulatory patients. This was far more difficult under the older methods of treatment than today. With a fairly intelligent patient in a single visit the history can be taken, physical examination made, the principles of treatment explained and instruction given in the use of the Benedict test and insulin. Under favorable conditions it is then possible for a patient to attend to some of his routine work, become sugar-free and present himself for a second visit after a few days. Whereas it is seldom feasible to accomplish as much at a single visit, it does show the contrast in the expense of treatment for a patient under the old and new regimen. See Case No. 1796, p. 536 as an illustration of the value of a single visit to a doctor's office

D. DIETETIC SUGGESTIONS AND RECIPES.

Many books have been written containing recipes for diabetic patients. Modern methods of treatment make most of these needless. For severe diabetic patients such rules are often dangerous because of the high content in fat in the foods produced. In general patients prefer and should be encouraged to take simple natural foods rather than artificial ones. The mild cases of diabetes need no special recipes.

1. **Substitutes for Bread.**—Many of the preparations upon the market as shown by Table 334, contain as great, or even a greater, quantity of carbohydrates than ordinary bread; a few contain less; but the percentage of carbohydrate may vary from time to time. Patients, and sometimes physicians, forget that substitutes for bread must be prescribed only in definite amounts. A diabetic bread should never be prescribed without a knowledge of its content of carbohydrate, protein and fat.

The bread of one of the largest bakeries in Boston, upon analysis, showed 55 per cent carbohydrate. Bread made without milk or

sugar, but with water and butter, contains 45 to 50 per cent carbohydrates. Such a bread is undoubtedly superior to many different bread substitutes upon the market. The percentage of carbohydrate in toast is greater than in plain bread, such as rye bread, Graham bread. Black bread and pumpernickel, contain somewhat less carbohydrate. Never give bread substitutes early in treatment. Teach patients to live without them. Potatoes are safer than bread and a banana safer than a potato, though both contain equal percentages of carbohydrate, because the former is limited in size, usually containing about 20 grams carbohydrate, and the latter almost unlimited.

There are four types of bread substitutes:

(*a*) **Bran Bread.**—Bran is employed in the diet of diabetic patients, but it is usually bran washed nearly free of carbohydrate. (See below.) This is neither more nor less than the use of cellulose, and this is supposed to have no effect upon the metabolism. Unfortunately, the availability of the protein, fat, and carbohydrate of unwashed bran to the diabetic patient has not been determined, although there are plenty of data upon its digestibility by ruminant animals. Bread made of bran alone is not very palatable, though with the fat of bacon or butter it is liked better. It furnishes bulk and acts favorably upon constipation. It should be remembered that untreated bran contains about 56 per cent of carbohydrate of which approximately one-half is assimilable. For this reason bran biscuits bought at a restaurant often prove to be a delusion and a snare. In purchasing bran to use for washed bran go to a feed store and ask for coarse bran for cattle and not for bran for the table or secure packages of washed bran which are now on the market. The various preparations of bran, bran breads, and cookies sold under trade names often contain carbohydrate other than bran, hence the reason for their palatable taste; beware of them. They may contain over 60 per cent carbohydrate, of which less than 10 per cent is real bran. Mild diabetics get into little trouble with bran, but the serious ones often suffer.

To free bran from starch first sift in an ordinary flour-sifter. This eliminates a great deal of the finer starch, then tie the bran in cheesecloth and fasten the same on a faucet. It should be thoroughly mixed and kneaded from time to time to be sure the water reaches all portions and should be washed until the water comes away *clear*. This may require an hour.[1]

[1] Four preliminary analyses of washed bran showed the following percentages of starch: 0.6, 1.8, 2.7, 5.2 per cent. Two preliminary analyses made under the direction of Dr. K. L. Mark, of Simmons College, showed pentosan 29.8 and 33.5. The wide variations in the percentages of starch will account for the occasional occurrence of sugar in the urine following the use of bran cakes.

BRAN WAFERS.

Washed bran	2 cups	Salt and saccharine to taste.	
India gum	1 tablespoonful	Ginger, cloves, anise or caraway seed,	
Mineral oil	1 tablespoonful	½ teaspoonful, if desired.	

Mix dry ingredients and then add bran and mineral oil with enough water to make a stiff dough. Knead with finger tips. Pat out and cut into thin cookies. Bake about forty-five minutes in a moderate oven until crisp.

BRAN CAKES FOR DIABETICS.

Food.	Amount.	Protein, gm.	Fat, gm.	Carbohydrate, gm.	Calories.
Bran	2 cups				
Melted butter	30 gm.	..	25	...	225
Eggs (whole)	2	12	12	...	156
Egg-white (1)	25 gm.	3	..	...	12
Salt	1 teaspoonful				
Water,					
		15	37	0	393

Mix the thoroughly washed and dry bran, well beaten whole eggs, butter and salt. Beat the egg white very stiff and fold in at the last. Shape with knife and tablespoon into three dozen small cakes. If desired, ½ gram of cinnamon or other flavoring may be added. Each cake contains: protein 0.5 gram, fat 1 gram, calories 11.

(*b*) **Gluten Breads.**—These breads are made by removing the sugar-forming material from the flour. It is surprising how thoroughly this can be done. I have often found the percentage of carbohydrate in one such flour to be negligible. The large quantity of protein which they contain in small bulk is objectionable.

(*c*) **Light Breads.**—French bread cut in thin slices is a possible substitute for bread, because it is bulky, gives the appearance of a large quantity, and carries much butter. Manufacturers have taken advantage of this idea, and many light breads are on the market. These breads often contain about the same quantity of carbohydrate as ordinary bread, though a few contain considerably less. Their virtue consists solely in their bulk, which allows a surface on which to spread butter. It is better for the patient to forget the taste, and to follow the advice of Case No. 2962, who replied at a clinic before the Tri-State Medical Society at the Harvard Medical School when I asked what diabetics were to do with apples—"throw them away." Apples are very large when selected by a diabetic and might easily contain 30 to 45 grams, one to three tablespoonfuls, of sugar. One eats a *whole* apple, but never a whole orange or banana. Hence, my aversion for apples for diabetics.

(*d*) **Various Other Substances** have been used for flour in the manufacture of bread. Thus, aleuronat meal, corn cob meal, casein under various trade names, and soy bean have been employed, and the manufacturers have been most ingenious in their preparation.

Soy bean is extensively used, and probably deserves a still wider introduction into the diabetic diet. The carbohydrate in it is unassimilable. Agar-agar may be used to dilute the flour or to add to bran and also to relieve the constipation of the diabetic, which is frequently troublesome. For the last few years India gum, suggested to me by Dr. Allen, has been substituted. It is much cheaper, and is as satisfactory. India gum will thicken broth or any fluid. In the right proportions it is the fundamental for a good many palatable recipes.

2. **Substitutes for Milk.**—A few tablespoonfuls of cream are a great comfort to a diabetic patient. The average patient usually receives 120 cc. to 240 cc. of 20 per cent cream daily. If it is desirable to give more fat without increasing carbohydrate and protein, 40 per cent cream may be substituted.

It is economical and convenient to give either $\frac{1}{4}$ of a pint or $\frac{1}{2}$ of a pint of cream a day. This makes the quantity definite, corresponds to the customary quantity which is sold and will last either one day or two days. Twenty per cent cream is also the upper 4 ounces on a quart of milk which has stood twenty-four hours.

The fat having been removed the chief value of milk to the diabetic patient is lost. The percentage of sugar in sour milk is not much less than in fresh milk. Sugar-free milks[1] have been put upon the market on a large scale, and many of my patients, particularly children, have found them of distinct advantage, but today the higher carbohydrate diets allowed with the help of insulin make them unnecessary.

Rennet may be made from milk, but unless the curd is carefully washed it will contain 2 to 2.5 per cent lactose. When the rennet is made from cream, the lactose is materially diminished. Kefir contains approximately 2.4 per cent milk sugar. Von Noorden says this milk has been of great help in the treatment of diabetes in children.

BAVARIAN CREAM (DIABETIC).

Food.	Amount.	Protein, grams.	Fat, grams.	Carbohydrate, grams.	Calories
Cream, 40 per cent	90 cc	3	36	3	348
Water	10 cc				
Egg (1)	50 gm.	6	6	..	78
Gelatin	2 gm.	2	..	..	8
Saccharin (to sweeten), Flavoring(to taste)					
		11	42	3	434

[1] See page 956.

Soften the gelatin in cold water, then add to the cream, which has been heated. Stir until dissolved, pour on the beaten egg, cook like soft custard, turn into mold and chill.

ICE CREAM (DIABETIC).

Food.	Amount.	Protein, grams.	Fat, grams.	Carbohydrate, grams.	Calories.
Cream, 40 per cent	90 cc	3	36	3	348
Water	10 cc				
Egg (1)	50 gm.	6	6	..	78
Saccharin (to sweeten)					
Flavoring (to taste)					
		9	42	3	426

Make a soft custard of the egg, 50 cc. of the cream, and the water. Whip the remaining 40 cc. of cream and fold into custard. The saccharin may be added to the egg. The flavoring should be added last.

Cracked Cocoa.—Cracked cocoa (cocoa nibs) makes a most useful drink for diabetic patients. This is not generally appreciated by the profession.

The sample of cracked cocoa (cocoa nibs) used has been purchased of the S. S. Pierce Co., Boston. It was analyzed by Prof. Street, with the following result:

Moisture	2.83
Protein	14.69
Fat	51.42
Fiber	4.32
Ash	3.88
Starch	7.48
Reducing sugar, as dextrose direct	None
Reducing sugar, as dextrose after inversion	0.94

The cocoa is prepared for the table by adding a cupful of the cracked cocoa to a quart of water and letting it simmer on the back of the stove all day, adding water from time to time. The strained infusion alone should be taken and not the nutritious grounds or nibs. Prof. Street was good enough to analyze the infusion, and wrote me: "The cocoa prepared according to directions contained 0.032 per cent of reducing sugar as dextrose direct and 0.138 per cent of total reducing sugars."

Cocoa shells are extensively used as a beverage. One cup of cocoa shells to a quart of water should be used, allow to simmer at least one-half hour. Drink the strained infusion. Cocoa shells are far cheaper than cocoa nibs.

Desserts can often be made with gelatin and this may be flavored with coffee, lemon, rhubarb, or cracked cocoa. In preparing such desserts if saccharin is used it should be added as late as possible

during the cooking for it is apt to become bitter with heat. It is always a safe rule to add too little rather than too much saccharin.

Extracts.—In making agar jelly, gelatin and other desserts flavoring extracts can be used. The general rule is one teaspoonful of extract to a pint of liquid. The standard extracts and vegetable colorings can be employed. Some patients over-indulge in the use of extracts by putting a teaspoonful in every cup of cocoa shells or coffee that they drink as well as by increasing the amount allowed in receipes. This should be avoided.

Sea moss farina and Irish moss are usually allowable for diabetic patients. Most of the carbohydrate in these materials is in the form of pentosans and galactans, which Swartz[1] has shown to be quite inert in the body. Unfortunately these products are sometimes adulterated with other carbohydrates. This emphasizes the fact that no matter how useful a food may be in itself, one must always be on the lookout for adulteration.

Agar-agar Jelly.

Agar-agar (powdered) 1 teaspoonful.
Water, strained cocoa shells, or coffee, 1½ pints.
Flavoring extract 1 teaspoonful.

Mix agar with a little of the water until it forms a smooth paste. Add rest of water and boil ten minutes. Strain, flavor, color, and sweeten with saccharin as desired. Pour into molds and cool at room temperature.

LEMON JELLY (DIABETIC).

Food.	Amount.	Protein, grams.	Fat, grams.	Carbohydrate, grams.	Calories.
Lemon juice	30 cc	..	..	3	12
Water	50 cc				
Gelatin	4 gm.	4	..	..	16
Saccharin (to sweeten)					
Cream	30 cc	1	12	1	116
		5	12	4	144

Soften gelatin in a part of the cold water. Heat the remaining water and lemon juice and pour over the gelatin. Stir until dissolved. Add saccharin, strain into cups. Serve with cream.

Lime juice is used in flavoring. One teaspoonful in a glass of water makes a good beverage in hot weather. One must be very sure that the lime juice is free from sugar or contains but a trace.

The proper seasoning of the food is a great help to the diabetic patient. So many articles are excluded from the diet that the great variety which is possible in the preparation of the food by the help of seasoning is overlooked. Horseradish, to be sure, contains 10 per cent of carbohydrate, but it would take at least

[1] Swartz; Trans. Conn. Acad. Arts and Sci., 1911, **16**, 247.

2 teaspoonfuls to contain a gram, and probably far more. Sour pickles are allowable, and other pickles made from the group of 5 per cent vegetables, provided one is assured that they have been prepared without sweetening. Mint, capers, curry, tarragon vinegar, distilled vinegar, bay leaf, cloves, ginger, mustard, paprika, anise seed, caraway seed, celery salt and onion extract may all be used as seasoning.

Five per cent vegetables furnish the bulk of a diabetic patient's diet and their variety leaves little chance for monotony. Lettuce, endive, chickory and water cress combined with other fresh vegetables furnish salad all the year round. Cabbage is inexpensive and very good. White, green, red, or Chinese cabbage chopped finely, served cooked or raw as cold slaw, may be used. Greens, chopped, can be blended in cooking as, for example, Abyssinian senel and chard, Chinese mustard and spinach. For the last few years we have used lettuce instead of washed vegetables. It has but 2 per cent carbohydrate and is more palatable in the end. One patient for over a year before insulin days took 600 grams daily.

Miss McCullough suggests that large outer stalks of cauliflower, slightly green covering, be carefully cleaned, cut in half-inch pieces and boiled until tender. Similarly, green leaves and any small pieces of lettuce may be shredded and served as spinach. The flat, large, celery stalks with any or all leaves chopped finely answer well. Rhubarb retains its acid flavor and has proven so acceptable an addition to the diet that canning it by cold water method for future use should be encouraged.

Diabetic patients should be urged whenever possible to have a garden. This, too, enables a patient to can his own winter's supply of vegetables and the chance to enjoy a variety of vegetables during the winter which otherwise could not be obtained.

At the New England Deaconess Hospital we have seldom found trouble with canned vegetables but it is quite advantageous to use those put up especially for diabetics without the addition of sugar or salt. (See p. 956.) The small stringless beans with practically no bean in them at all are perfectly safe for general use as a 5 per cent vegetable. One must always be careful in using canned vegetables because of sugar which may have been added.

SECTION XIX.

FOODS AND THEIR COMPOSITION.

A. DIABETIC FOODS.

The improvement in the treatment of diabetes owes much to the recent dissemination of knowledge regarding the composition of foods. To the United States Government we are indebted for an excellent monograph by Atwater and Bryant entitled "The Chemical Composition of American Food Materials, Bulletin No. 28, Revised Edition," which was first issued in 1906. This can be purchased by sending ten cents in coin to the Superintendent of Documents, Washington, D. C.

Diabetics everywhere throughout the world owe a debt of gratitude to Dr. W. A. Orton of the U. S. Department of Agriculture for his earnest endeavor to increase the number of agreeable vegetables. For this purpose he has brought to Washington specimens from all over the world. It is to be hoped that he will shortly publish a monograph giving the results of his work. Already there has appeared an article on the subject.[1] In England, also, the subject of gardening and vegetables for diabetics has been seriously considered by Spriggs.[2]

The State of Connecticut, from its Agricultural Experiment Station in New Haven, has also published excellent special reports on diabetic foods, and from year to year adds analyses of new preparations. So far these have been distributed upon request. Prof. Street formerly and Prof. E. M. Bailey recently who have been intimately concerned in these investigations have been kindness itself not alone to me, but to my inquisitive patients. A large number of analyses of Mexican foods has been complied by Quiñones.[3]

No Particular "Diabetic" Food is Recommended.—Whereas the analyses of many so-called diabetic foods are recorded in Table 334, no particular food is recommended. The purpose of this compila-

[1] Orton, W. A.: Am. Jour. Med. Sci., 1921, **162**, 498.
[2] Spriggs, E. I.: Duff House Papers, Henry Frowde, London, 1920, 1.
[3] Quiñones: La Diabetes, su Tratamiento, Mexico, 1925, p. 109.

tion of analyses is merely to show the composition of the various types and brands of materials offered for the special purpose of diabetic feeding, but the inclusion of any particular food in this list is not to be regarded as in any sense an official approval or recommendation of that food. As a matter of fact no special diabetic food is used at the hospital. This is not meant to disparage such foods but to show that they are accessories without which the diabetic can get along very well.

What is a "Diabetic" Food?—A suitable diet for a diabetic patient depends upon so many variable factors, particularly the tolerance of the individual, that no general definition[1] of a "diabetic" food can be satisfactorily fixed. The discovery of insulin, for example, has materially modified both the theory and practice of diabetic dietetics.

The narrow confines of the diabetic diet have greatly stimulated the manufacture of so-called diabetic foods. These are often serviceable, but are to be employed with discretion. Their use should be discouraged at the beginning of treatment. The patient should never become dependent upon special diabetic foods, for they are often unobtainable, always make him conspicuous, and when he acquires a disgust for foods of this class it is all the harder to abide by the original diet. When the patient buys one of these foods, unfortunately he is often given a list of other diabetic foods and a new diabetic diet list, and confusion in the diet frequently results. The patients under my care who have done best either never use special diabetic foods or use only a few varieties. Such foods to be of service to the physician or to the dietitian should bear correct statements of the percentages of protein, fat and carbohydrate which they contain; and under no circumstance should the label bear any statements which convey the impression that such foods may be eaten without restriction.

The high content of protein is one of the most serious drawbacks to diabetic foods. Formerly when it was not realized that from 100 grams protein 50 grams or more of carbohydrate might be formed, these special foods with low actual carbohydrate content were considered a great boon. Today we look at the matter differently.

B. COMPOSITION OF COMMON FOODS.

The following food tables were prepared for me under the supervision of Prof. E. M. Bailey of the Connecticut Agricultural Experiment Station situated in New Haven, Connecticut. Prof. Bailey makes the following comments upon Tables 333 and 334.

[1] The official definition of "diabetic" food as given in Circular No. 136, U. S. Department of Agriculture, Office of the Secretary, has been revoked.

"In the table 'Composition of Common Foods' many of the analyses are based largely on the authority of Atwater and Bryant's compilation. In substituting or adding other analyses frequent reference has been made to Prof. Sherman's 'Food Products'[1] which is also largely quoted from the authority just named. Leach, 'Food Inspection and Analysis'[2] and various reports and bulletins of the Connecticut Experiment Station have also been freely consulted.

"The general plan of arrangement of items in the table has been to present those foods which are essentially protein, fat and carbohydrate in the order named. In choosing analyses many discrepancies are found between the various authors. These are due partly to different methods of analysis and different forms of expression but more frequently, no doubt, to variations in the composition of the material examined. In such cases the analysis which represents the average of the greatest number of individual analyses or the one which, for one reason or another, seems preferable, has been used.

"The significance of the term *protein* in this table is *nitrogen* × *6.25* except in the case of milk and milk products where the factor 6.38 is more correct and has been used. *Fat* means substances soluble in ether or 'ether extract.' It is probable that many of the figures for fat in baked products are too low. Where new analyses have been inserted fat has been determined by an improved method,[3] which gives results considerably higher. *The term 'carbohydrate' is to be accepted generally in the sense of 'nitrogen-free extract' which is the percentage obtained by deducting the sum of the percentages of water, ash, protein, fat and fiber from 100 per cent.* This proximate group includes the more readily assimilable carbohydrates, such as starch, dextrins, maltose, glucose, sucrose, invert sugar, raffinose, lactose and some other less common sugars, and also carbohydrates of doubtful or undetermined availability in human metabolism such as hemicellulose complexes, vegetable gums, mucilages, etc. A critical study of some of these less familiar carbohydrates has been made by Swartz.[4] Whenever the sense of 'carbohydrate' in the table is known to be other than that just stated the explanation is given in a footnote.

"In Table 334, analyses of special foods are given. These are taken largely from our Bulletin 286 with the deletion of most of the analyses made before 1913. In many cases there are no new analyses to substitute for those thus omitted but very old analyses

[1] The Macmillan Company, New York, 1918.
[2] Wiley & Son, New York.
[3] Connecticut Exp. Station Bull., 1917, **200**, 133.
[4] Swartz: Trans. Connecticut Acad. Arts and Sci., 1911, **16**, 247.

of commercial products of this kind serve no practical purpose. There is not the same objection to old analyses of staple articles of food.

"The general significance of the terms protein, fat and carbohydrate in this table is the same as already explained for common foods. *Protein*, however, in those products known or declared to be made from gluten, has been estimated on the basis of the factor 5.7 and under 'Protein Preparations' protein in casein products has been estimated using the factor 6.38. The *carbohydrate* group is subdivided into two parts but it should be understood that total carbohydrate is the sum of the two. The idea of the separation is to show how much of the total carbohydrate is available, the figure in the column headed 'starch' representing this available portion so far as it has been determined or can be stated. Thus Barker's gluten Food A contains 12.4 per cent of total carbohydrate; 2.6 per cent is certainly available but the availability of the 9.8 per cent has not been determined. Wherever the figure in the starch column includes water-soluble carbohydrate, as for example, Cheltine Diabetic Food, the figure given probably represents all of the carbohydrate that is utilized in human digestion.

"Calories have been calculated generally on the basis of total carbohydrate in the conventional way. In some instances, where much of the carbohydrate is regarded as unavailable or where the 'fat' is largely mineral oil and indigestible, calorie yields have not been estimated."

TABLE 333.—COMPOSITION OF COMMON FOODS.

MEAT PRODUCTS.

Name and description of food.	Protein, per cent.	Fat, per cent.	Carbohydrate, per cent.	Calories, per 100 gms.
Beef, fresh:				
Brisket, medium fat, edible portion	15.8	28.5	..	319
Chuck rib, edible portion, all analyses	19.0	13.4	..	197
Flank, edible portion, all analyses	19.6	21.1	..	268
Loin, edible portion, all analyses	19.0	19.1	..	247
Neck	20.7	12.7	..	197
Plate	16.8	26.9	..	309
Ribs, edible portion, all analyses	17.8	24.6	..	293
Round	20.9	10.6	..	179
Rump, lean	20.9	13.7	..	207
Shank, fore	21.4	8.1	..	158
hind	21.7	8.7	..	165
Shoulder and clod, edible portion, all analyses	20.0	10.3	..	173
Soup stock	5.8	1.5	..	36
Miscellaneous cuts, free from visible fat	22.4	2.9	..	116
Brain, edible portion	8.8	9.3	..	119
Heart, edible portion	16.0	20.4	..	248
Kidney, as purchased	13.7	1.9	Trace	72
Liver, as purchased	20.2	3.1	2.5[1]	119

[1] Largely, or in part, glycogen.

TABLE 333.—COMPOSITION OF COMMON FOODS.—(*Continued.*)

MEAT PRODUCTS—*Continued.*

Name and description of food.	Protein, per cent.	Fat, per cent.	Carbohydrate, per cent.	Calories, per 100 gms.
Lungs, as purchased	16.4	3.2	..	94
Marrow, as purchased	2.2	92.8	..	844
Sweetbreads, as purchased	16.8	12.1	..	176
Suet, as purchased	4.7	81.8	..	755
Tongue, edible portion	18.9	9.2	..	158
Beef, cooked:				
Roast	22.3	28.6	..	347
Steak, round	27.6	7.7	..	180
sirloin	23.9	10.2	..	187
tenderloin	23.5	20.4	..	278
Beef, canned:				
Corned[1]	26.6	11.4	..	209
Dried and smoked[2]	32.6	7.5	..	198
Kidneys, stewed	18.4	5.1	2.1	128
Luncheon beef	27.6	15.9	..	254
Roast	25.9	14.8	..	237
Sweetbreads	20.2	9.5	..	166
Tongue, ground	21.4	25.1	..	312
whole	19.5	23.2	..	287
Tripe	16.8	8.5	..	144
Beef, corned and pickled:				
Corned beef, all analyses, edible portion	15.6	26.2	..	298
Spiced beef, rolled	12.0	51.4	..	511
Tongue, edible portion	12.8	20.5	..	236
Tripe	11.7	1.2	Trace	58
Beef, dried, salted, smoked, edible portion	30.0	6.5	..	179
Veal, fresh:				
Breast, edible portion, all analyses	20.3	11.0	..	180
Chuck, edible portion, all analyses	19.7	5.8	..	131
Flank, edible portion, all analyses	20.1	12.7	..	195
Leg, edible portion, all analyses	20.7	6.7	..	143
cutlets, edible portion	20.3	7.7	..	151
Loin, edible portion, all analyses	19.9	10.0	..	170
Rib	20.2	9.4	..	165
Rump	19.8	16.2	..	225
Shoulder	20.7	4.6	..	124
Heart, as purchased	16.8	9.6	..	154
Kidney, as purchased	16.9	6.4	..	125
Liver, as purchased	19.0	5.3	..	124
Lungs, as purchased	17.1	5.0	..	113
Lamb, fresh:				
Breast, edible portion	19.1	23.6	..	289
Leg, hind, medium fat, edible portion	19.2	16.5	..	225
Loin, without kidney and tallow, edible portion	18.7	28.3	..	330
Shoulder, edible portion	18.1	29.7	..	340
Lamb, cooked:				
Chops, broiled, edible portion	21.7	29.9	..	356
Leg, roast	19.7	12.7	..	193
Lamb, canned:				
Tongue, spiced, cooked, edible portion	13.9	17.8	..	216

[1] Average, 3.4 per cent salt (sodium chloride).
[2] Average, 9.7 per cent salt (sodium chloride).

TABLE 333.—COMPOSITION OF COMMON FOODS.—(*Continued.*)
MEAT PRODUCTS—*Concluded.*

Name and description of food.	Protein, per cent.	Fat, per cent.	Carbohydrate, per cent.	Calories, per 100 gms.
Mutton, fresh:				
Chuck, edible portion, all analyses	14.6	36.8	..	390
Leg, hind, medium fat, edible portion	18.5	18.0	..	236
Loin, without kidney and tallow, edible portion	16.0	33.1	..	362
Shoulder, medium fat, edible portion	17.7	19.9	..	250
Heart, as purchased	16.9	12.6	..	181
Kidney, as purchased	16.5	3.2	..	95
Liver, as purchased	23.1	9.0	5.0[1]	193
Lungs, as purchased	20.2	2.8	..	106
Mutton, cooked:				
Leg roast, edible portion	25.0	22.6	..	303
Mutton, canned:				
Corned	28.8	22.8	..	320
Tongue	24.4	24.0	..	314
Pork, fresh:				
Ham, lean	25.0	14.4	..	230
Ham, medium fat, edible portion	15.3	28.9	..	321
Head cheese, edible portion	19.5	33.8	..	382
Loin (chops), lean, edible portion	20.3	19.0	..	252
Loin (chops), medium fat, edible portion	16.6	30.1	..	337
Shoulder, edible portion	13.3	34.2	..	361
Side, lard and other fat included, edible portion	9.4	61.7	..	593
Side, lard and kidneys not included, edible portion	9.1	55.3	..	534
Brains, as purchased	11.7	10.3	..	140
Heart, as purchased	17.1	6.3	..	125
Kidney, as purchased	15.5	4.8	0.7	108
Liver, as purchased	21.3	4.5	1.4[1]	131
Lungs, as purchased	11.9	4.0	..	84
Pork, pickled, salted or smoked:[2]				
Ham, lean, smoked, edible portion	19.8	20.8	..	266
Ham, medium fat, smoked, edible portion	16.3	38.8	..	414
Ham, luncheon, cooked	22.5	21.0	..	279
Shoulder, medium fat, smoked, edible portion	15.9	32.5	..	356
Pig's tongue, pickled, edible portion	17.7	19.8	..	249
Pig's feet, pickled, edible portion	16.3	14.8	..	198
Salt pork, clear fat	1.9	86.2	..	783
Bacon, smoked, all analyses, edible portion	10.5	64.8	..	625
Ham, deviled	19.0	34.1	..	383
Sausage:				
Arles, edible portion	26.8	50.6	..	563
Bologna, edible portion	18.7	17.6	0.3[3]	234
Frankfort	19.6	18.6	1.1[4]	250
Pork, as purchased	13.0	44.2	1.1[5]	454
Deerfoot Farm, cooked (analysis furnished by manufacturer)	19.9	54.2	0.3	569
Pork and beef, as purchased	19.4	24.1	..	295

[1] Largely, or in part, glycogen.
[2] The range of salt content for cured pork products may be taken as 3 to 5 per cent.
[3] Carbohydrate range, 0.2 to 3.1 per cent.
[4] Carbohydrate range, 0.0 to 6.6 per cent.
[5] Carbohydrate range, 0.0 to 8.6 per cent.

TABLE 333.—COMPOSITION OF COMMON FOODS.—(*Continued.*)

Name and description of food.	Protein, per cent.	Fat, per cent.	Carbohydrate, per cent.	Calories, per 100 gms.
POULTRY.				
Poultry, fresh:				
Chicken, broilers, edible portion	21.5	2.5	..	109
heart, as purchased	20.7	5.5	..	132
gizzard, as purchased	24.7	1.4	..	111
liver, as purchased	22.4	4.2	2.4[1]	137
Fowls, edible portion	19.3	16.3	..	224
Goose, edible portion	16.3	36.2	..	391
Goose liver, edible portion	16.6	15.9	3.7[1]	224
Turkey, edible portion	21.1	22.9	..	291
FISH PRODUCTS.				
Fish, fresh:				
Alewife, whole, edible portion	19.4	4.9	..	122
Bass, black, edible portion	20.6	1.7	..	98
red, edible portion	16.9	0.5	..	72
sea, edible portion	19.8	0.5	..	84
striped, edible portion	18.6	2.8	..	100
Blackfish, edible portion	18.7	1.3	..	87
Bluefish, edible portion	19.4	1.2	..	88
Butterfish, edible portion	18.0	11.0	..	171
Cod, edible portion	16.7	0.3	..	70
steak, edible portion	18.7	0.5	..	79
Eels, salt water, edible portion	18.6	9.1	..	156
Flounder, edible portion	14.2	0.6	..	62
Haddock, edible portion	17.2	0.3	..	72
Halibut, edible portion	18.6	5.2	..	121
Herring, edible portion	19.5	7.1	..	142
Mackerel, edible portion	18.7	7.1	..	139
Perch, edible portion	19.0	2.4	..	98
Pickerel, edible portion	18.7	0.5	..	79
Porgy, edible portion	18.6	5.1	..	120
Salmon, edible portion	22.0	12.8	..	203
Shad, edible portion	18.8	9.5	..	161
Shad roe, as purchased	20.9	3.8	2.6	128
Smelt, edible portion	17.6	1.8	..	87
Trout, brook, edible portion	19.2	2.1	..	96
Trout, lake, edible portion	17.8	10.3	..	164
Whitefish, edible portion	22.9	6.5	..	150
Fish, preserved or canned:				
Cod, salt, "boneless," as purchased[2]	27.7	0.3	..	114
Haddock, smoked, edible portion	23.3	0.2	..	95
Halibut, smoked, edible portion[3]	20.7	15.0	..	218
Herring, smoked, edible portion[4]	36.9	15.8	..	290
Mackerel, salt, edible portion[5]	17.3	26.4	..	307
salt, canned, as purchased	19.6	8.7	..	157
salt, canned in oil, edible portion	25.4	14.1	..	229
Salmon, canned, edible portion	21.8	12.1	..	196
Sardines, canned, edible portion	23.0	19.7	..	269
Sardines, canned in mineral oil, edible portion	22.8	2.7[6]	..	116

[1] Largely, or in part, glycogen.
[2] Contains 11.0 per cent ash, largely salt.
[3] Contains 15.0 per cent ash, largely (12.1 per cent) salt.
[4] Contains 13.2 per cent ash, largely (11.7 per cent) salt.
[5] Contains 12.9 per cent ash, largely (10.4 per cent) salt.
[6] Total oil present, 13.3 per cent; approximately 20 per cent (= 2.7 per cent), digestible.

TABLE 333.—COMPOSITION OF COMMON FOODS.—(*Continued.*)

FISH PRODUCTS—*Concluded.*

Name and description of food.	Protein, per cent.	Fat, per cent.	Carbohydrate, per cent.	Calories, per 100 gms.
Fish, preserved or canned:				
Sturgeon, caviare, preserved, Russian, as purchased	30.0	19.7	7.6	328
Tunny (tuna), as purchased	21.7	4.1	..	124
canned in oil, edible portion	23.8	20.0	0.6	278
Turtle meat, canned	23.4	0.7	..	100
Shellfish, etc., fresh:				
Clams, long, in shell, edible portion	8.6	1.0	2.0[1]	51
round, in shell, edible portion	6.5	0.4	4.2[1]	46
Crabs, hard shell, whole, edible portion	16.6	2.0	1.2[1]	89
Crayfish, edible portion	16.0	0.5	1.0[1]	73
Lobster, edible portion	16.4	1.8	0.4[1]	83
Mussels, in shell, edible portion	8.7	1.1	4.1[1]	61
Oysters, in shell, edible portion	6.2	1.2	3.7[1]	50
Scallops, as purchased	14.8	0.1	3.4[1]	74
Terrapin, edible portion	21.2	3.5	..	116
Turtle, green, edible portion	19.8	0.5	..	84
Shellfish, etc., canned:				
Clams, long, as purchased	8.3	0.4	2.7[1]	48
round, as purchased	8.9	0.8	0.9[1]	46
Crabs, as purchased	15.8	1.5	0.7[1]	80
Lobster, as purchased	18.1	1.1	0.5[1]	84
Oysters, as purchased	8.8	2.4	3.9[1]	72
Shrimp, as purchased	25.4	1.0	0.2	111
AMPHIBIA.				
Frog's legs, edible portion	15.5	0.2	..	64
GELATIN.				
Gelatin	84.2[2]	0.1	None	338
EGGS.				
Eggs, fresh:[3]				
Hen, whole egg, edible portion	13.4	10.5	..	148
white	12.3	0.2	..	51
yolk	15.7	33.3	..	363
Duck, whole egg, edible portion	13.3	14.5	..	184
white	11.1	Trace	..	44
yolk	16.8	36.2	..	393
Goose, whole egg, edible portion	13.8	14.4	..	185
white	11.6	Trace	..	46
yolk	17.3	36.2	..	395
Turkey, whole egg, edible portion	13.4	11.2	..	154
white	11.5	Trace	..	46
yolk	17.4	32.9	..	366
Guinea fowl, whole egg, edible portion	13.5	12.0	..	162
white	11.6	Trace	..	46
yolk	16.7	31.8	..	353
Plover, whole egg, edible portion	10.7	11.7	..	148
Turtle, fresh water	18.1	11.1	..	172
sea	18.8	9.8	..	163

[1] Largely, or in part, glycogen.

[2] Nitrogen × 5.55.

[3] In shell eggs the shell comprises from 10 to 17 per cent of the weight of the whole egg; water content ranges from 60 to 67 per cent. Sea-turtle eggs contain about 76 per cent water.

TABLE 333.—COMPOSITION OF COMMON FOODS.—(*Continued.*)

EGGS—*Concluded.*

Name and description of food.	Protein, per cent.	Fat, per cent.	Carbohydrate, per cent.	Calories, per 100 gms.
Eggs, edible portion, cooked:				
Hen, boiled	13.2	12.0	..	161
whites	12.3	0.2	..	51
yolks	15.7	33.3	..	363
Eggs, dehydrated, average	40.0	43.7	..	556

DAIRY PRODUCTS, ETC.

Milk:				
Milk, whole	3.3	4.0	4.8	68
condensed (evaporated, concentrated)	6.9	8.2	9.9	141
sweetened, condensed (sweetened evaporated, sweetened concentrated)	7.9	9.0	54.6[1]	331
skimmed	3.4	0.3	5.1	37
sweetened, condensed	9.1	1.0	59.1[2]	282
Buttermilk	3.6	0.5	4.1	35
Kephir	3.1	2.0	1.6	37
Kumiss[3]	2.8	2.1	5.4	51
Cream, "heavy" (approximately 40 per cent)	2.1	41.0	1.5	383
"light" (approximately 20 per cent)	2.8	22.0	2.7	220
heavy, sour	4.1	41.6	1.5	397
Whey	1.0	0.3	5.0	27
Milk powder (dried milk):				
From whole milk	25.3	25.3	37.5	479
From partly skimmed milk	25.8	14.5	49.9	433
From skimmed milk, average	34.6	1.9	50.9	359
Malted milk (milk powder with malted cereal) average	13.8	6.8	71.9	404
Cheese:				
American, pale	28.8	35.9	0.3	440
red	29.6	38.3	..	463
Camembert	21.0	21.7	..	279
Cheddar	26.4	32.7	3.0	412
Cheshire	32.5	26.1	4.5	383
Cottage	20.9	1.0	4.3	110
Cottage, Jewish	27.9	9.2	None	194
Dutch	37.1	17.7	..	308
Edam	24.1	30.3	4.6	388
Full cream	25.4	30.3	2.0	382
Limburger	23.0	29.4	0.4	358
Neufchatel	18.7	27.4	1.5	327
Pineapple	29.9	38.9	2.6	480
Roquefort	22.6	29.5	1.8	363
Skimmed milk	31.5	16.4	2.2	282
Swiss	27.6	34.9	1.3	430
Ice cream, typical	3.8	12.6[4]	19.6	207

[1] Cane sugar, 40.6 per cent; milk sugar, 14 per cent.

[2] Cane sugar, 40.9 per cent; milk sugar, 18.2 per cent.

[3] According to Van Slyke (Leach: Food Inspection and Analysis, p. 174), Kumiss, from cows' milk, contains lactose, 5 per cent; protein, 4.1 per cent; fat (calculated), 1.2 per cent.

[4] Standards for fat in different States vary from 8 to 14 per cent.

TABLE 333.—COMPOSITION OF COMMON FOODS.—(*Continued.*)

Name and description of food.	Protein, per cent.	Fat, per cent.	Carbohydrate, per cent.	Calories per 100 gms.
FATS AND OILS.				
Fats and Oils:				
Butter,[1] average	1.5	84.6	None	767
Oleomargarine,[2] average	0.8	92.4	None	835
Nut margarine,[3] average	1.4	84.8	None	769
Salad oils and cooking fat, typical	Trace	99.7	None	897
SOUPS AND BROTHS.				
Soups, home-made:				
Bean	3.2	1.4	9.4	63
Beef	4.4	0.4	1.1	26
Chicken	10.5	0.8	2.4	59
Clam chowder	1.8	0.8	6.7	41
Meat stew	4.6	4.3	5.5	79
Soups, broths, etc., canned:				
Asparagus, cream of	2.5	3.2	5.5	61
Bouillon, beef	2.2	0.1	0.2	11
clam, typical	1.0	0.1	0.6	7
Celery, cream of	2.1	2.8	5.0	54
Chicken gumbo	3.8	0.9	4.7	42
soup	3.6	0.1	1.5	21
Consommé	1.4	0.1	0.4	8
Corn, cream of	2.5	1.9	7.8	58
Julienne	2.7	..	0.5	13
Mock turtle	3.0	1.0	5.7	44
Mulligatawny	3.7	0.1	5.7	39
Oxtail, edible portion	3.7	1.3	7.1	55
Pea soup	3.6	0.7	7.6	51
Pea, cream of green	2.6	2.7	5.7	58
Tomato	1.8	1.1	5.6	40
Turtle, green	6.1	1.9	3.9	57
Vegetable	2.9	..	0.5	14
Bouillon cubes:				
As purchased, average analysis[4]	11.4	1.8	5.8	85
Prepared as directed, average analysis[5]	0.2	Trace	0.1	1
Clam extract:				
As purchased	23.2	0.2	11.8	142
Prepared as directed[6]	0.5	Trace	0.3	3
Yeast extract, as purchased	31.3	0.2	12.5	177
CEREAL PRODUCTS, ETC.				
Alimentary pastes:				
Macaroni	13.4	0.9	74.1[7]	358
" cooked	3.0	1.5	15.8[7]	89
Noodles	11.7	1.0	75.2	357
Spaghetti	12.1	0.4	75.9	356
Vermicelli	10.9	2.0	72.0[7]	350

[1] Average salt content, 1.6 per cent; range, 0.2 to 4.1 per cent.
[2] Average ash content (largely salt), 0.9 per cent; range, 0.4 to 3.1 per cent.
[3] Average ash content (largely salt), 2.9 per cent; range, 1.1 to 6.1 per cent.
[4] Average salt content, 70.2 per cent.
[5] Average cube weighs 3.8 gms.; 1 cup of broth is assumed to weigh 240 gms.; salt content of prepared broth, 1.1 per cent.
[6] Salt content, 0.4 per cent.
[7] Includes fiber.

TABLE 333.—COMPOSITION OF COMMON FOODS.—(*Continued.*)

CEREAL PRODUCTS, ETC.—*Continued.*

Name and description of food.	Protein, per cent.	Fat, per cent.	Carbohydrate, per cent.	Calories, per 100 gms.
Bread, soft:				
Bread, alfalfa	10.6	1.3	64.0	310
brown	5.4	1.8	47.1[1]	226
corn (Johnnycake)	7.9	4.7	46.3[1]	259
Graham	8.9	1.8	51.0	256
peanut	33.6	12.8	19.7	328
rye	9.0	0.6	52.7	252
rye, Jewish	9.1	1.1	52.0	254
whole rye	11.9	0.6	34.7	192
rye and wheat	11.9	0.3	51.5[1]	256
wheat, average of many analyses	9.2	1.3	52.6	259
wheat, whole	9.7	0.9	48.5	241
Buns, hotcross	7.9	4.8	49.7[1]	274
Biscuit, homemade	8.7	2.6	54.6	277
Maryland	8.4	5.6	58.8	309
soda	9.3	13.7	52.6[1]	371
Rolls, all analyses	8.9	4.1	56.1	297
Bread, hard, and crackers:				
Bread, white, toasted	11.5	1.6	61.2[1]	305
Zwieback	9.8	9.9	73.5[1]	422
Crackers, Boston (split)	11.0	8.5	70.3	402
butter	9.6	10.1	71.2	414
cream	9.7	12.1	69.1	424
egg	12.6	14.0	66.2	441
flatbread	14.9	0.5	73.6[1]	359
Graham	10.0	9.4	72.3	414
oatmeal	11.8	11.1	67.1	416
oyster	11.3	10.5	70.3	421
pilot	11.1	5.0	73.9	385
pretzels	9.7	3.9	72.3	363
saltines	10.6	12.7	68.0	429
soda	9.8	9.1	72.8	412
water	11.7	5.0	75.3	393
Pastry, etc.:				
Cake, coffee	7.1	7.5	62.8	347
cup	5.9	9.0	68.2	377
frosted	5.9	9.0	64.8[1]	364
fruit	5.9	10.9	64.1	378
gingerbread	5.8	9.0	62.6	354
sponge	6.3	10.7	65.9[1]	385
Cookies	7.0	9.7	73.2	408
Doughnuts	6.7	21.0	52.4	425
Fig bars	4.6	6.6	68.1	350
Ginger snaps	6.5	8.6	75.3	405
Lady fingers	8.8	5.0	70.4	362
Macaroons	6.5	15.2	64.1	419
Pie, apple	3.1	9.8	42.8[1]	272
cream	4.4	11.4	51.2[1]	325
custard	4.2	6.3	26.1[1]	178
lemon	3.6	10.1	37.4[1]	255
mince	5.8	12.3	38.1[1]	286
raisin	3.0	11.3	47.2[1]	303
squash	4.4	8.4	21.7[1]	180

[1] Includes fiber.

TABLE 333.—COMPOSITION OF COMMON FOODS.—(*Continued.*)

CEREAL PRODUCTS, ETC.—*Continued.*

Name and description of food.	Protein, per cent.	Fat, per cent.	Carbohydrate, per cent.	Calories, per 100 gms.
Pastry, etc.—Concluded:				
Pudding, Indian meal	5.5	4.8	27.5[1]	175
rice custard	4.0	4.6	31.4[1]	183
tapioca	3.3	3.2	28.2[1]	155
Wafers, miscellaneous	8.7	8.6	74.1	409
vanilla	6.6	14.0	71.3	438
Breakfast foods:				
Barley preparations:				
Cream of Barley	11.1	1.6	76.1	363
Farwell & Rhines' Barley Crystals	11.5	1.3	75.2	359
Quaker Scotch Brand Pearled Barley	9.5	0.9	76.2	351
Corn (maize) preparations:				
Cerealine	6.9	0.4	79.9	351
E-C Corn Flakes, Toasted	6.6	0.3	78.6	344
F. S. Granulated Hominy	8.0	1.0	77.1	349
Hecker's Cream Hominy	9.8	0.4	77.3	352
H-O New Process Hominy	8.0	0.3	79.8	354
Jackson's Roman Meal	13.3	3.4	66.1	348
Jersey Corn Flakes	8.5	0.3	82.3	366
Kellogg's Toasted Corn Flakes	6.4	0.2	78.8	343
Korn Kinks	7.4	0.4	77.9	345
Nichols' Snow White Samp	7.8	0.3	77.7	345
Post Toasties	6.6	0.3	79.4	347
Quaker Best Yellow Corn Meal	7.5	0.8	78.7	352
Quaker Corn Puffs	8.7	0.3	78.5	352
Quaker Hominy Grits	7.9	0.5	77.7	347
Quaker Toasted Corn Flakes	6.8	0.4	79.9	350
Ralston Hominy Grits	9.0	2.9	75.4	364
Street's Perfection Hominy	7.9	1.3	77.9	355
Sunbeam Pearl Hominy	9.4	0.6	75.0	343
Sunseal Cream Corn Meal	8.9	1.0	77.2	353
Sunseal Hominy Grits	8.5	1.2	77.8	356
Sunseal Sunny Corn	8.3	0.4	78.2	350
Washington Corn Crisps	7.8	0.2	76.8	340
Oat preparations:				
Bestovotes	16.2	6.6	63.1	377
Bufceco Rolled Oats	15.1	6.8	64.0	378
Fruited Oats	13.1	4.9	68.2	369
Grandmother's Crushed Oats	14.9	6.5	65.4	380
Health Brand White Oats	13.8	7.8	64.5	383
Hecker's Cream Oat Meal	15.6	5.6	64.6	371
Hornby's Steam Cooked Oat Meal	16.1	6.7	64.1	381
Keen & Robinson's Granulated Scotch Oatmeal	13.7	9.1	64.1	393
Leggett's Premier 15 Minute Oat Flakes	17.2	5.4	63.7	372
McCann's Irish Oat Meal	15.1	8.7	64.9	398
Mother's Crushed Oats	15.6	6.1	64.9	377
Paw-Nee Rolled Oats	15.8	6.7	64.0	380
Purity Rolled Oats	16.3	6.1	61.1	365
Quaker Oats	15.9	6.0	64.5	376
Robinson's Patent Groats	12.8	8.6	67.7	399
Scotch Porage Oats	13.3	9.6	64.9	399
Sovereign 15 Minute Oat Flakes	16.5	5.8	64.0	374
White Rose Rolled Oats	14.3	8.0	64.8	388

[1] Includes fiber.

TABLE 333.—COMPOSITION OF COMMON FOODS.—*(Continued.)*

CEREAL PRODUCTS, ETC.—*Continued.*

Name and description of food.	Protein, per cent.	Fat, per cent.	Carbohydrate, per cent.	Calories per 100, gms.
Breakfast foods:—Continued.				
Rice preparations:				
Comet Cereal	7.2	0.3	80.7	354
Cook's Flaked Rice	7.8	0.1	78.9	348
Cook's Malto Rice	7.6	0.2	80.2	353
Kellogg's Toasted Rice Biscuit	10.1	0.3	80.7	366
Kellogg's Toasted Rice Flakes	10.0	0.4	81.3	369
Milk Rice	6.9	0.2	77.2	338
Quaker Puffed Rice	7.6	0.2	79.5	350
Rye preparations:				
Cream of Rye	12.0	1.6	71.8	350
Kellogg's Toasted Rye Flakes	11.4	1.5	76.2	364
Ry-Krisp	14.0	1.7	74.4	369
Wheat preparations:				
Alber's Wheat Flakes Mush	11.1	2.1	73.4	357
Cero-Vita	8.9	0.7	82.0	370
Cinnamon Rusks	10.3	7.2	71.7	393
Cream of Wheat	11.5	0.9	73.7	349
Cresco Grits	17.8	1.4	68.6	358
Crystal Wheat	11.3	2.0	73.6	358
Dieto Rusks	15.9	9.1	66.1	410
Force	10.6	1.1	73.7	347
F. S. Farina (Quaker Farina)	10.2	0.9	74.6	347
Fruited Wheat	15.6	2.3	66.2	348
Grandmother's A. & P. Farina	10.8	0.6	75.0	349
Granola	13.9	0.8	76.3	368
Granose Biscuit	10.3	1.6	71.1	340
Granose Flakes	10.3	3.9	75.4	378
Grape Nuts	11.5	0.6	74.2	348
Hecker's Farina	10.0	0.7	75.9	350
Holland Rusk	12.1	5.1	70.4	376
Jireh Frumenty	12.3	1.7	77.3	374
Jireh Whole Wheat Farina	12.9	2.3	74.6	371
Kellogg's Breakfast Toast	13.6	1.9	74.9	371
Kellogg's Krumbles	12.0	1.2	72.3	348
Kellogg's Toasted Wheat Biscuit	14.2	1.4	74.7	368
Kellogg's Toasted Wheat Flakes	9.3	1.1	80.5	369
Kellogg's Zwieback	14.3	1.6	76.1	376
Leggett's Premier Farina	11.1	0.9	73.3	346
Malt Breakfast Food	13.8	1.5	72.7	360
Manana Gluten Breakfast Food	42.6	2.0	43.6	363
Mapl-Flake	9.3	1.2	74.7	347
Mother's Wheat Hearts	10.7	1.1	74.1	349
Pettijohn's Breakfast Food	9.1	2.0	74.9	354
Pillsbury Best Cereal	11.5	0.7	75.9	356
Quaker Cracked Wheat	9.3	2.3	73.3	351
Quaker Puffed Wheat	13.1	1.8	70.2	349
Quaker Wheat Berries	14.0	2.0	71.6	360
Ralston Health Food	11.9	1.7	71.5	349
Ralston Wheat Food	11.3	1.8	73.1	354
Sanitas Granuto	10.1	1.7	81.6	382
Saxon Wheat Food	12.8	1.7	74.4	364
Shredded Wheat Biscuit	11.0	1.4	75.0	357
Street's Perfection Farina	10.3	1.1	74.9	351
Triscuit	11.0	1.4	73.9	352
Vitos	11.1	1.0	75.6	356

TABLE 333.—COMPOSITION OF COMMON FOODS.—(*Continued.*)

CEREAL PRODUCTS, ETC.—*Continued.*

Name and description of food.	Protein, per cent.	Fat, per cent.	Carbohydrate, per cent.	Calories, per 100 gms.
Breakfast food:—Concluded:				
Wheat preparations:				
Wheatena	11.3	2.8	74.2	367
Wheatlet	12.8	1.6	72.3	355
Whole Grain Wheat (prepared)	6.6	0.8	23.7	128
Zest	9.0	1.2	75.3	348
Wheat bran preparations:				
Ballard's Obelisk Sanitary Edible Bran	17.3	5.4	55.7	301
Culp's Capitol Health Bran	13.4	4.3	57.6	323
Health Food Co.'s Wheat Bran	14.3	4.1	56.2	319
Jireh Wheat Bran	16.8	4.8	56.7	337
Johnson's Educator Wheat Bran	15.4	4.7	54.4	322
Kellogg's Sterilized Wheat Bran	16.3	5.2	54.4	330
Wheat bran biscuit and other laxative preparations:				
Bran Biskue	12.1	13.1	61.0	410
Bran-eata Biscuit	9.1	0.9	72.2	333
Bran Zos	13.2	2.5	65.6	338
Brose Good Health Breakfast Food	14.4	4.3	65.5	358
Cerag	11.3	0.9	73.0	345
Cerena	27.8	11.4	46.3	399
Christian's Laxative Bread	10.0	1.4	74.6	351
Christian's Laxative Cereal Flakes	10.4	1.4	72.5	344
Colax	1.1	0.8	82.8	343
Dietetic Bran Biscuit	9.9	5.0	69.1	361
Educator Bran Cookies	8.9	14.5	64.7	425
Educator Bran Meal	12.3	2.8	66.4	340
F. B. A. Laxative Health Biscuit	6.1	1.7	77.3	349
Fruit Nut Cereal	13.5	1.2	72.4	354
Good Health Biscuit (Kellogg)	7.7	1.2	74.5	340
Health Food Wafers	10.0	7.9	65.7	374
India (Digestive) Biscuit	12.8	2.2	66.1	335
Laxa	12.4	2.8	66.6	341
Laxative Biscuit (Kellogg)	16.7	10.8	57.7	395
Mansfield's Agar Agar Wafers	7.1	12.0	69.9	416
Oval Digestive Biscuit (H. & P.)	7.8	16.3	64.5	436
Uncle Sam Health Food	21.3	24.4	40.9	468
Zim	7.4	1.7	74.2	342
Miscellaneous preparations:				
Dieto Nut Cereal	21.6	18.4	51.8	459
Dieto Wheat and Barley Cereal	11.6	2.2	75.7	369
Jireh Wheat Nuts	19.0	15.6	54.5	434
Malabar Manoca	0.6	0.1	84.1	340
Post Tavern Porridge	10.3	0.8	74.5	346
Post Tavern Special	10.9	1.1	76.9	361
Sea Moss Farina	9.1	0.3	59.9	279
Sunbeam Tapioca	0.6	0.1	85.5	345
Trix	14.5	0.2	77.3	369
Trufood (Trufood Co.)	11.5	2.5	77.1	377
Zep (Battle Creek Food Co.)	14.0	2.2	74.6	374
Flours, meals, etc.:				
Barley flour	12.3	2.4	71.3	356
Buckwheat flour	6.4	1.2	77.5	346
Corn flour	8.4	1.8	76.2	355
Corn meal	9.2	1.9	74.4	362
Oat flour	15.1	6.4	65.7	381

TABLE 333.—COMPOSITION OF COMMON FOODS.—(*Continued.*)

CEREAL PRODUCTS, ETC.—*Concluded.*

Name and description of food.	Protein, per cent.	Fat, per cent.	Carbohydrate, per cent.	Calories, per 100 gms.
Flours, meals, etc.:—Concluded.				
Potato flour	0.5	0.1	83.0	335
Rice flour	7.3	0.6	79.3	352
Rye flour	6.8	0.9	78.3	349
Rye meal	13.6	2.0	69.7	351
Soy bean flour	42.5	19.9	24.3	446
Soy bean meal	38.3	14.9	26.6	394
Wheat flour, entire	13.8	1.9	71.0	356
Wheat flour, Graham	13.3	2.2	69.5	351
Wheat flour, patent, average	11.4	1.0	74.8	354
VEGETABLES.				
Vegetables, fresh (unless otherwise stated):				
Aralia Cordata (Udo)	1.0	0.2	2.6	16
Artichokes	2.6	0.2	15.9[1]	76
Jerusalem	2.9	0.1	16.4[1]	78
cooked	2.4	0.1	16.5[1]	77
Asparagus	2.1	0.2	2.7	21
Basella	2.5	0.5	1.7	21
Beans, butter	9.4	0.6	29.1[2]	159
cranberry, young pods	0.4	None	0.6	4
medium	1.3	0.6	1.7	17
fancy	1.0	0.1	2.1	13
Lima	7.1	0.7	20.3	116
refugee, young pods	0.5	None	0.8	5
medium	1.3	0.1	3.0	18
fancy	1.1	0.1	1.4	11
string (carbohydrate range, 3.9 to 10 per cent)	2.3	0.3	5.5	34
string, cooked	0.8	1.1	1.9[2]	21
Beets (carbohydrate range, 6 to 10 per cent)	1.6	0.1	8.8	43
cooked	2.3	0.1	7.4[2]	40
Borage (salad plant)	3.0	0.4	0.4	17
Brussels sprouts	1.5	0.1	3.4	21
Burdock	4.5	0.1	7.4	49
Cabbage (carbohydrate range, 3–6.5 per cent)	1.6	0.3	4.5	27
Chinese	1.2	0.1	2.4	15
Carrots (carbohydrate range, 5.9–11.5 per cent)	1.1	0.4	8.2	41
Cassava, root	1.6	0.2	27.1	117
Cauliflower	1.8	0.5	3.7	27
Celeriac	1.8	0.2	6.0	33
Celery	1.1	0.1	3.3[2]	19
root	2.0	0.4	6.3	37
Chard (Swiss)	3.2	0.6	5.0[2]	38
Chayote (tayote)	0.9	0.1	5.9	28
Chenopodium	8.5	1.1	2.7	55
Chicory, root	..	..	15.0	..
leaves, Italian	1.9	0.4	0.8	14
Chinese vegetables:				
Kai Tsoi	1.7	0.2	1.8	16
Bak Toy	1.2	0.1	1.1	10

[1] Chiefly inulin.

[2] Includes fiber.

TABLE 333.—COMPOSITION OF COMMON FOODS.—(*Continued.*)

VEGETABLES—*Continued.*

Name and description of food	Protein, per cent.	Fat, per cent.	Carbohydrate, per cent.	Calories, per 100 gms.
Vegetables, fresh (unless otherwise stated):				
Collards	4.5	0.6	6.3[1]	49
Corn	3.1	1.1	19.2	99
Cucumbers	0.8	0.2	2.3	14
Egg plant	1.2	0.3	4.3	25
Endive	1.0	None	2.6	14
Finocchio	1.5	0.1	1.6	13
Greens, beet, cooked	2.2	3.4	3.2[1]	52
dandelion	2.4	1.0	10.6[1]	61
turnip salad	4.2	0.6	6.3[1]	47
Kale	3.0	0.4	2.1	24
sea	1.4	None	3.8	21
Kohl-rabi (carbohydrate range, 3.5–14 per cent)	2.0	0.1	4.2	26
Lambs' quarters	3.8	0.6	1.7	27
Leeks	2.9	0.1	4.0[2]	29
Lettuce	1.2	0.3	2.2	16
Mushrooms[3]	3.5	0.4	6.0	42
Mustard	2.4	0.3	0.3[2]	14
Okra	1.6	0.2	4.0	24
Onions (carbohydrate range, 4–14 per cent)	1.6	0.3	9.1	46
cooked	1.2	1.8	4.9[1]	41
Orach	4.6	0.4	0.2[2]	23
Oyster plant	1.2	0.1	7.0	34
Palmetto cabbage	3.3	0.6	6.1	43
cooked	2.9	0.5	5.6	39
Parsnips (carbohydrate range, 6–14 per cent)	1.6	0.5	11.0	55
Patience (Rumex Patientia)	2.1	0.2	0.1[2]	11
Peas, green, cooked	6.7	3.4	14.6[1]	116
marrowfat, first grade	5.1	..	12.4	..
second grade	6.7	..	11.0	..
third grade	5.9	..	14.5	..
petits pois, first grade	3.4	..	7.0	..
second grade	4.2	..	10.4	..
third grade	4.4	..	10.3	..
sifted, first grade	5.3	..	12.2	..
second grade	5.7	..	13.1	..
third grade	5.6	..	15.5	..
Peppers, Neapolitan	1.1	0.3	5.7	30
sweet, green	0.8	0.1	4.1	21
Potatoes	2.2	0.1	18.0	82
air (tropical Asia)	1.9	0.4	16.3	76
boiled	2.5	0.1	20.3	92
cooked, chips	6.8	39.8	46.7[1]	572
mashed and creamed	2.6	3.0	17.8[1]	109
sweet (carbohydrate range, 16.5–44.5 per cent)	1.8	0.7	26.1	118
cooked	3.0	2.1	42.1[1]	199
Pumpkins (carbohydrate range, 3–14 per cent)	1.0	0.1	4.0	21

[1] Includes fiber.
[2] Starch and sugar.
[3] Protein and carbohydrates largely unassimilable (E. P. J.).

TABLE 333.—COMPOSITION OF COMMON FOODS.—(*Continued.*)

VEGETABLES—*Continued.*

Name and description of food.	Protein, per cent.	Fat, per cent.	Carbohydrate, per cent.	Calories per 100 gms.
Vegetables, fresh (unless otherwise stated):				
Radishes (carbohydrate range, 2.7–7.5 per cent)	1.3	0.1	5.1	27
Rhubarb	0.6	0.7	2.5	19
Roquette (Rocket salad)	0.7	0.4	0.3[1]	8
Rutabagas (carbohydrate range, 3–12 per cent)	1.3	0.2	7.3	36
Sauerkraut	1.7	0.5	3.8[2]	27
Sorrel	2.1	0.2	0.1[1]	11
Spinach	2.1	0.3	2.3	20
cooked	2.1	4.1	2.6[2]	56
Squash	1.4	0.5	8.2	43
Tomatoes, green	1.2	0.2	2.8	18
ripe	0.9	0.4	3.3	20
Truffles	9.1	0.5	7.0	69
Turnips (carbohydrate range, 2.3–18 per cent)	1.3	0.2	6.8	34
Vegetable marrow	0.5	0.1	4.0	19
cooked	0.4	0.1	4.1	19
Watercress	0.7	0.5	3.7	22
Yams	1.6	0.2	23.6	103
Yautia (Tanier)	4.2	0.4	53.0	232
Vegetables, dried:				
Beans	22.5	1.8	55.2	327
carob	6.3	0.6	80.7	353
frijoles	21.9	1.3	65.1[2]	360
Lima	18.1	1.5	65.9[2]	350
mesquite	12.2	2.5	77.1[2]	380
soy	38.3	14.9	26.6[3]	394
Carrots, evaporated	7.7	3.6	80.3[2]	384
Lentils	25.7	1.0	59.2[2]	349
Peas	24.6	1.0	57.5	337
cow	21.4	1.4	56.7	325
Peppers, green	15.5	8.5	63.0[2]	391
red	9.4	7.7	70.0[2]	387
Potatoes, evaporated	8.5	0.4	80.9[2]	361
Tomatoes	12.9	8.1	62.3[2]	374
Vegetables, canned:				
Artichokes (carbohydrate range, 3.2–6.1 per cent)	0.8	..	4.4	21
Asparagus (carbohydrate range, 1.6–3.3 per cent)	1.5	0.1	2.3	16
Beans, baked	6.9	2.5	17.1	119
haricots verts	1.1	0.1	2.0	13
flageolets (carbohydrate range, 9.8–12.4 per cent)	4.6	0.1	11.5	65
Lima (carbohydrate range, 9.6–16.5 per cent)	4.0	3.0	13.4	97
little green	1.2	0.1	2.8	17
red kidney	7.0	0.2	17.3	99
string (carbohydrate range, 1.5–4.5 per cent)	1.1	0.1	3.3	19
wax	1.0	0.1	2.5	15

[1] Starch and sugar.

[2] Includes fiber.

[3] About one-fourth available.

TABLE 333.—COMPOSITION OF COMMON FOODS.—(*Continued.*)

VEGETABLES—*Concluded.*

Name and description of food.	Protein, per cent.	Fat, per cent.	Carbohydrate, per cent.	Calories, per 100 gms.
Brussels sprouts	1.5	0.1	2.9	19
Corn[1] (carbohydrate range, 11.7–25.1 per cent)	2.8	1.2	18.2	95
and tomatoes	1.6	0.4	9.1	46
Macedoine (mixed vegetables)	1.4	..	3.9	21
Okra[2]	0.7	0.1	2.9	15
Peas[3] (carbohydrate range, 4.3–17.2 per per cent)	3.6	0.2	8.6	51
Potatoes, sweet	1.9	0.4	40.6	174
Pumpkins (carbohydrate range, 3.6–7.3 per cent)	0.8	0.2	5.6	27
Squash (carbohydrate range, 3.6–12.8 per cent)	0.9	0.5	9.8	47
Succotash (carbohydrate range, 13.9–21.3 per cent)	3.6	1.0	17.7	94
Tomatoes (carbohydrate range, 1–4.5 per cent)	1.2	0.2	3.5	21
Pickles, condiments, etc.:				
Capers	3.2	0.5	5.0	37
Catsup, tomato (carbohydrate range, 3–26 per cent)	1.8	0.2	10.0	49
Chili sauce (carbohydrate range, 14–28 per cent)	..	..	20.0	..
Horseradish	1.4	0.2	10.5[4]	49
Olives, green, edible portion (10 samples)[5]	1.3	12.1	2.5	124
ripe, edible portion (8 samples)[6]	1.4	18.0	2.0	176
Mustard, prepared	4.7	4.1	5.0	76
cereal added (carbohydrate range, 4– 15 per cent)	3.5	1.9	7.0	59
Pickles, cucumber	0.5	0.3	2.7[4]	16
mixed	1.1	0.4	4.0[4]	24
spiced	0.4	0.1	21.0	87
Vinegar, cider (carbohydrate range, 0.3–1.5 per cent)	None	None	0.3	1
distilled	None	None	None	..
malt	..	..	0.5[7]	..
spiced salad	..	..	10.0	..
Tarragon	..	..	0.2[7]	..
wine	..	..	0.4	..

FRUITS, BERRIES, ETC.

(*Analyses are of edible portion.*)

Fruits, berries, etc., fresh:				
Apples (carbohydrate range, 9–21 per cent)	0.4	0.5	13.0	58
Apricots	1.0	..	13.4[4]	58
Avocados (alligator pears)	1.1	13.7	7.1[4]	156
Bananas	1.3	0.6	21.0	95
Blackberries	1.3	1.0	8.4	48
Cherries	1.0	0.8	16.5	77
Citrang juice	1.3	..	6.9	33
Cranberries	0.4	0.6	8.4	41

[1] Average, 0.4 per cent salt (NaCl).
[2] Average, 1.1 per cent salt (NaCl).
[3] Average, 0.7 per cent salt (NaCl).
[4] Includes fiber.
[5] Salt, 5.9 per cent.
[6] Salt, 2.1 per cent.
[7] Manufacturer's analysis.

TABLE 333.—COMPOSITION OF COMMON FOODS.—(*Continued.*)

FRUITS, BERRIES, ETC.—*Continued.*

Name and description of food.	Protein, per cent.	Fat, per cent.	Carbohydrate, per cent.	Calories, per 100 gms.
Fruits, berries, etc., fresh:—Concluded:				
Currants	1.5	..	12.8[1]	57
Egg fruit	3.4	1.9	41.0	195
Figs	1.5	..	18.8[1]	..
Gooseberries	0.4	..	12.0	..
Grapes	1.3	1.6	14.9	79
Grapejuice (carbohydrate range, 11–20 per cent)	..	..	15.0	..
Grapefruit[2]	0.8	..	8.6	36
Huckleberries	0.6	0.6	16.6[1]	74
Lemons	1.0	0.7	7.4	40
juice	..	..	9.8	..
Loganberries[3]	4.6	0.6	7.2[4]	53
juice[3]	0.6	..	6.8	..
Loquat	0.3	..	23.0	..
Mangoes	..	..	13.0	..
Mulberries	0.3	..	12.0	..
Muskmelons	0.6	0.3	7.2	34
Nectarines	0.6	..	15.9[1]	..
Oranges[6]	0.8	0.2	11.6[1]	51
Orange-lemon juice	0.6	..	1.8	..
Papaya (papaw)	0.8	0.1	6.3	29
Peaches	0.7	0.1	5.8	27
Pears	0.6	0.5	11.4	53
Persimmons	0.8	0.7	29.7	128
Pineapple	0.4	0.3	9.3	42
Plums	1.0	..	20.1[1]	..
Pomegranates	1.5	1.6	16.8	88
Prunes	0.9	..	18.9[1]	..
Quince	0.3	0.1	13.2	55
Raspberries, black	1.7	1.0	12.6[1]	66
red	1.0	..	9.7	..
Sapodilla	0.6	1.4	19.4	93
Sour sop	0.8	0.1	17.2	73
Strawberries	1.0	0.6	6.0	33
Tangelo juice	0.7	..	9.0	..
Watermelons	0.4	0.2	6.7[1]	30
Whortleberries	0.7	0.3	10.0	46
Fruits, berries, etc., dried:				
Apples	1.6	2.2	66.1[1]	291
Apricots	4.7	1.0	62.5[1]	278
Citron	1.5	1.5	78.1[1]	332
Currants	2.4	1.7	74.2[1]	322
Dates	2.1	2.8	78.4[1]	347
Figs	4.3	0.3	74.2[1]	317
Prunes	2.1	..	73.3[1]	..
Raisins	2.6	3.3	76.1[1]	345
Raspberries	7.3	1.8	80.2[1]	366

[1] Includes fiber.

[2] Florida, California and Porto Rico, carbohydrate range, 6.6–8.2 per cent (E. M. Frankel).

[3] Jour. Ind. and Eng. Chem., 1918, **10**, 30.

[4] Invert sugar.

[5] Jour. Ind. and Eng. Chem., 1917, **9**, 1043.

[6] Florida, average of seven analyses, carbohydrate 8 per cent; California, eight analyses, carbohydrate 8.3 per cent (E. M. Frankel).

TABLE 333.—COMPOSITION OF COMMON FOODS.—(*Continued.*)

FRUITS, BERRIES, ETC.—*Concluded.*

Name and description of food.	Protein, per cent.	Fat, per cent.	Carbohydrate, per cent.	Calories, per 100 gms.
Fruits, berries, etc., canned; jellies and preserves:[1]				
Apples, crab	0.3	2.4	54.4[2]	240
Apple sauce	0.2	0.8	37.2[2]	157
Apricots	0.9	..	17.3[2]	..
Apricot sauce	1.9	1.3	48.8[2]	215
Blackberries	0.8	2.1	56.4[2]	248
Blueberries	0.6	0.6	12.8[2]	59
Cherries	1.1	0.1	21.1[2]	90
Cherry jelly	1.1	..	77.2[2]	..
Figs, stewed	1.2	0.3	40.9[2]	171
Grape butter	1.2	0.1	58.5[2]	240
Grapefruit	0.5	0.1	8.3	36
Marmalade, orange	0.6	0.1	84.5[2]	341
Peaches	0.7	0.1	10.8[2]	47
Pears	0.3	0.3	18.0[2]	76
Pineapple	0.4	0.7	36.4[2]	154
Prune sauce	0.5	0.1	22.3[2]	92
Strawberries, stewed	0.7	..	24.0[2]	..
Tomato preserves	0.7	0.1	57.6[2]	234

NUTS.

(*Analyses are of edible portion.*)

Nuts:				
Almond	21.0	54.9	15.3	639
Almond butter	22.1	61.5	7.9	674
Beechnuts	21.9	57.4	13.2[2]	657
Brazil nuts	16.8	69.4	5.0	712
Butternuts	27.9	61.2	3.5[2]	676
Cashew nuts	19.1	47.1	26.2	605
Chestnuts	6.2	5.4	40.3	235
Cocoanuts	5.7	50.6	27.9[2]	590
Cocoanut milk	0.4	1.5	4.6	34
prepared	6.3	57.4	31.5[2]	668
Filberts	15.6	65.3	13.0[2]	702
Hickory nuts	15.4	67.4	11.4[2]	714
Lichi nuts	2.9	0.2	77.5[2]	323
Peanuts	25.8	38.6	21.9	538
Peanut butter	29.3	46.5	17.1[2]	604
Pecans	9.6	70.5	15.3[2]	734
Pine nuts, Pignolias	36.5	47.9	4.8	596
Piniones	6.5	60.7	26.2[2]	677
Pinon	14.6	61.9	17.3[2]	685
Sabine	28.1	53.7	8.4[2]	629
Pistachios	24.3	51.1	14.3	614
Walnuts, California	18.4	64.4	11.6	700
black	27.6	56.3	10.0	657
soft shell	16.6	63.4	13.5	691

[1] Jams, jellies, preserves and marmalade contain 47 per cent or more carbohydrate. There is a wide variation in the sugar content of canned fruits. Pie peaches are packed in water while other grades may be found in 30, 40 or even 50 per cent syrup.

[2] Includes fiber.

TABLE 333.—COMPOSITION OF COMMON FOODS.—(*Concluded.*)

ALCOHOLIC BEVERAGES.

Name and description of food.	Protein, per cent.	Fat, per cent.	Carbohydrate, per cent.	Calories, per 100 gms.
Distilled liquors[1] (whisky, gin, rum, brandy)	..	..	None or trace	..
Wines,[2] dry (carbohydrate range, trace to 3.6 per cent)	..	..	0.3	..
sweet (carbohydrate range 0.1–40.7 per cent)	..	..	8.0	..
Cordials[3] (creme de menthe, kümmel, benedictine, anisette, chartreuse	..	..	30.0	..
Beer,[4] near (average of several brands)	..	..	5.0	..
Ale[5]	..	..	5.1	..
Malt extract, commercial	..	..	10.6	..
true, concentrated	..	..	71.3	..
Cider[6] (carbohydrate range, 0–13.5 per cent)	..	..	4.5	..

OTHER BEVERAGES.

Tea (0.5 oz. to 1 pt. water)	..	..	0.6	..
Coffee (1 oz. to 1 pt. water)	..	..	0.7	..
Cocoa (0.5 oz. to 1 pt. water)	..	..	1.1	..
(0.5 oz. to 1 pt. milk)	..	..	6.0	..
Carbonated drinks (bottled soda, sarsaparilla, birch beer, root beer, gingerale)	..	..	8.0	..
Chocolate[7]	12.4	52.2	24.8[8]	619
Cocoa[7]	18.3	26.7	37.5[9]	464

[1] Sugar is sometimes added to brandy. One sample examined was sensibly sweet and contained 33.5 per cent of sugar (Connecticut Exp. Sta. Bull. 227, 1920, p. 232). Range of alcohol content, 35 to 50 per cent.

[2] Natural wines contain 6 to 12 per cent alcohol; "fortified" wines, 15 to 20 per cent.

[3] Range of alcohol content, 35 to 50 per cent.

[4] Range of alcohol content for beer, generally 3 to 5 per cent; for prohibition beer (near beer), not over 0.5 per cent.

[5] Range of alcohol content, same as for beer.

[6] Range of alcohol content, generally 2.5 to 6 per cent.

[7] Analysis of food itself; not as prepared for drinking. Sweetened chocolate contains from 50 to 60 per cent of sugar; sweetened cocoa contains from 25 to 50 per cent of sugar.

[8] Starch and sugars, about 10 per cent; availability of remainder doubtful or undetermined.

[9] Starch and sugars, about 14 per cent; availability of remainder doubtful or undetermined.

TABLE 334.—COMPOSITION OF SPECIAL FOODS.

Date of analysis.	Manufacturer or agent and name of product.	Protein, per cent.	Fat, per cent.	Carbohydrate.		Calories, per 100 gm.
				Starch, per cent.	Other carbohydrate, per cent.	
	FLOURS AND MEALS.					
	Herman Barker, Somerville, Mass.:					
1919	Barker's Gluten Food "A"	77.0	0.4	2.6	9.8	361
1919	Barker's Gluten Food "B"	74.0	0.5	5.2	10.1	362
1919	Barker's Gluten Food "C"	73.0	0.4	6.4	9.8	360
	Battle Creek Sanitarium Co., Battle Creek, Mich.:					
1916	Gluten Meal	26.3	1.0	55.0	8.7	369
1916	Gluten Meal	39.3	0.9	41.1	10.1	370
1916	Gluten Meal, 80 per cent	76.6	..	5.8	..	..
	Battle Creek Food Co., Battle Creek, Mich.:					
1925	Gluten Flour	43.2	1.8	39.3[1]	6.4	372
	Callard, Stewart & Watt, London:					
1909	Casoid Flour	82.5	1.6	None	3.1[2]	357
1916	Gluten Flour	73.4	..	None	..	..
	Canada Cereal & Flour Co.:					
1919	Gluten Flour	18.6	4.5	43.9	16.9	358
	Cereal Meal Corporation, St. Louis, Mo.:					
1923	Cereal Meal	19.2	6.6	34.8[1]	23.4	368
	Cereo Co., Tappan, N. Y.:					
1919	Soy Bean Gruel Flour	46.1	18.6	0.9	21.9	443
	Cheltine Food Co., Cheltenham, England:					
1923	Cheltine Diabetic Food	57.9	10.1	16.4[1]	3.3	401
	Curdolac Food Co., Waukesha, Wis.:					
1924	Curdolac Flour	41.1	12.4	4.6[1]	22.5	384
	The Dieto Food Co., New York:					
1914	Pure Whole Wheat Flour	13.5	2.1	62.4	12.0	371
	Efficiency Products Co., Somerville, N. J.:					
1926	Hoffman's Casein Flour	73.0	1.0	0.7[1]	2.5	314
	Empire Flour Mills:					
1919	Gluten Flour	13.1	1.1	59.1	15.5	361
	Farwell & Rhines, Watertown, N. Y.:					
1913	Cresco Flour	18.1	1.0	57.2	10.2	351
1923	Gluten Flour	40.5	1.4	43.2[1]	5.1	368
1925	Gluten Flour	42.1	1.4	41.0[1]	6.3	370
1913	Special Diabetic Food	27.5	2.8	40.0	16.6	362
	Federal Mill & Elevator Co., Lockport, N. Y.:					
1923	Gluten Flour	38.5	1.8	42.3[1]	6.9	367
	Gericke, Potsdam:					
1910	Aleuronat	76.0	3.3	10.5[2]		376
	Golden Rod Milling Co., Portland, Ore.:					
1919	Acme Special Flour	15.1	1.8	61.5	8.6	356
1916	Gluten Flour	14.1	1.3	67.0	..	..

[1] Includes soluble carbohydrate.
[2] Includes fiber.

TABLE 334.—COMPOSITION OF SPECIAL FOODS.—(*Continued.*)

Date of analysis.	Manufacturer or agent and name of product.	Protein, per cent.	Fat, per cent.	Carbohydrate.		Calories, per 100 gm.
				Starch, per cent.	Other carbohydrate, per cent.	
	FLOURS AND MEALS—*Continued.*					
	O. B. Gilman, Boston, Mass.:					
1913	Gluten Flour	43.2	2.0	31.4	13.1	369
	The Health Food Co., New York:					
1919	Almond Meal	50.3	15.4	None	18.0	412
1919	Bran Biskue, Gluten Bran	27.7	10.5	33.8	13.9	396
1919	Diabetic Casein Flour (self-raising)	72.3	0.8	None	5.7	319
1919	Gluten Flour, 40 per cent	39.2	1.1	37.3	13.0	368
1919	Glutosac Gluten Flour	41.5	1.7	36.2	9.1	362
1919	Pronireu (Gluten Griddle Cake Flour)	37.9	1.2	36.6	9.1	345
1914	Protosac Gluten Flour	41.9	2.0	31.5	14.8	370
1919	Protosoy Soy Flour	39.4	18.6	1.9	25.1	433
1919	Pure Washed Gluten Flour	74.9	2.0	3.8	10.0	373
1919	Snow Flake Diabetic Casein Flour	79.2	1.2	None	3.2	340
	Hudon Hebert (Furn'r.):					
1919	Gluten Flour	14.4	2.2	52.2	16.8	354
	Jireh Diabetic Food Co., New York:					
1919	Diabetic Flour	14.8	2.0	50.1	20.7	360
1919	Gluten Flour	14.4	2.1	50.0	21.9	364
1913	Patent Barley	11.4	1.6	67.8	12.4	381
1913	Patent Cotton Seed Flour	49.1	12.7	6.0	15.3	396
1913	Patent Lentils Flour	27.3	1.2	42.6	17.2	359
1913	Protein Flour	31.4	2.0	48.5	8.2	370
1925	"Starch-treated" Flour	13.4	2.1	66.0[1]	7.9	368
1913	Soja Bean Flour	42.3	18.2	None	25.8	435
1924	Soycasein Flour	75.8	3.0	1.4[1]	4.6	354
1906	Wheat and Barley Flour	11.8	1.9	66.2[1]	7.3	358
	Johnson Educator Food Co., Boston, Mass.:					
1911	Educator Standard Gluten Flour	36.6	1.4	40.9	12.8	374
	The Kellogg Food Co., Battle Creek, Mich.:					
1916	Gluten Meal, 20 per cent	24.7	0.9	51.2	14.2	369
1919	Gluten Flour, 40 per cent	47.2	1.0	30.7	10.2	361
1919	Gluten Meal, thoroughly cooked, 40 per cent	43.0	1.5	33.4	12.0	367
1912	Gluten, 80 per cent	74.2	0.9	6.2	8.8	365
1919	Pure Gluten Meal	79.1	0.7	2.6	8.7	368
	La Societe l'Aliment "Essential," Nanterre, France:					
1921	Heudebert, Surazotized Gluten Flour	61.3	2.3	14.0[1]	10.9	366
1921	Heudebert, Gluten Flour with Cacao	53.6	5.8	13.8[1]	14.7	381
	Lister Bros., New York:					
1919	Lister's Diabetic Flour, self-rising	68.3	1.0	None	9.7	321
	Lyster Bros., Whitefield, N. H.:					
1915	Casein Flour	84.5	3.6	None	0.4	372
1916	Diabetic Flour	79.3	3.0	None	..	..
	Loeb's Diabetic Food Bakery, New York:					
1919	Gluten Cracker Meal	36.7	10.9	30.7	11.5	414
1923	Pure Gluten Flour	41.5	2.2	39.7[1]	7.4	374
1923	Special Gluten	73.2	2.0	9.4[1]	8.7	383

[1] Includes soluble carbohydrate.

TABLE 334.—COMPOSITION OF SPECIAL FOODS.—(*Continued.*)

Date of analysis	Manufacturer or agent and name of product	Protein, per cent.	Fat, per cent.	Carbohydrate. Starch, per cent.	Carbohydrate. Other carbohydrate, per cent.	Calories, per 100 gm.
	FLOURS AND MEALS—*Continued.*					
	MacDowell Bros., Ogdensburg, N. Y.:					
1925	Diaban Diabetic Flour	28.0	18.1	32.1[1]	6.5	429
1925	Diaban Diabetic Flour	26.1	17.4	33.2[1]	10.0	434
	Maple Leaf Milling Co.:					
1919	Gluten Flour	12.7	1.2	61.5	11.5	354
	Thos. Martindale & Co., Phila., Pa.:					
1919	Special Gluten Flour	36.8	1.5	41.4	11.2	371
	Mayflower Mills, Fort Wayne, Ind.:					
1919	Gluten Flour	48.0	1.7	28.6	10.2	363
	A. McFarlane Co.:					
1919	Gluten Flour	12.1	1.4	60.3	14.3	359
	P. McIntosh Co.:					
1919	Gluten Flour	15.1	1.0	63.3	9.3	360
	Theo. Metcalf Co., Boston, Mass.:					
1913	Soja Bean Meal, 18 per cent starch	41.0	20.0	25.0		444
1913	Vegetable Gluten, 8.1 per cent starch	73.3	1.5	5.9	11.0	374
	Northwestern Cereal Co., London, Ont.:					
1919	Gluten Flour	17.1	5.0	42.1	22.0	370
1919	Gluten Flour, 40 per cent	14.2	5.3	38.7	25.6	361
	Phospho Food Co., Los Angeles, Calif.:					
1914	Phospho D & D Special	13.7	2.2	58.6	14.4	367
	Plasmon Co., London, Eng.:					
1922	Arrowroot	19.8	0.1	62.2[1]	2.5	339
	Pieser-Livingston Co., Chicago, Ill.:					
1919	Genuine Gluten Flour	41.4	1.4	36.3	9.8	363
1925	Gluten Flour	42.0	1.7	39.4[1]	7.0	369
	Potter & Wrightington, Boston, Mass.:					
1919	Diet-Ease Gluten Flour	39.6	2.3	36.2	11.8	371
1925	Diet-Ease Gluten Flour	40.6	2.6	38.4[1]	8.9	375
1925	Diet-Ease Gluten Flour	40.1	2.8	40.6[1]	6.5	374
	Pure Gluten Food Co., New York:					
1919	Hoyt's Gluten Flour, over 40 per cent protein	41.8	1.1	33.2	12.1	359
1925	Hoyt's Gluten Flour	43.1	1.9	40.4[1]	5.2	372
1919	Hoyt's Gluten Self-raising Flour, over 40 per cent protein	41.5	0.9	33.4	9.7	346
1919	Hoyt's Gluten Special Flour, 80 per cent protein	77.2	1.2	2.8	10.6	373
	Schulenburg Oil Mill, Schulenburg, Texas:					
1919	Baumgarten Process Allison Flour	50.0	10.0	1.1	21.6	381
1921	Allison Flour (Cotton Seed)	50.4	7.9	8.8[1]	15.2	369
	Soy Bean Food Products Co., San Francisco, Calif.:					
1919	Soy Bean Flour A	41.8	19.4	0.3	24.1	440
1919	Soy Bean Flour B	44.0	14.2	0.8	26.0	411
	Sprague, Warner & Co., Chicago, Ill.:					
1919	Richelieu Gluten Flour	45.3	1.2	31.6	12.5	368

[1] Includes soluble carbohydrate.

TABLE 334.—COMPOSITION OF SPECIAL FOODS.—(*Continued.*)

Date of analysis.	Manufacturer or agent and name of product.	Protein, per cent.	Fat, per cent.	Carbohydrate.		Calories, per 100 gm.
				Starch, per cent.	Other carbohydrate, per cent.	
	FLOURS AND MEALS—*Concluded.*					
	Still Rock Spa, Waukesha, Wis.:					
1919	Curdolac Flour	56.6	2.4	5.1	17.9	340
	G. Van Abbott & Sons, London:					
1913	Almond Flour	24.6	58.6	None	7.9	657
1913	Gluten Flour	68.5	0.9	12.4	6.8	359
1913	Gluten Semola	46.9	2.9	28.2	8.7	361
	Vitæ Health Food Co., Seattle, Wash.:					
1924	Soya Manna	41.1	19.0	None	25.2[1]	436
	Waukesha Health Products Co., Waukesha, Wis.:					
1917	Ayos, the Improved Soja Bean Flour	41.4	16.9	0.6	24.4	418
1919	Hepco Flour	44.0	19.1	0.9	21.4	438
	White Swan Spice Co., Toronto, Can.:					
1919	Diet Flour	8.7	1.3	61.3	16.1	356
1919	Gluten Flour	9.8	1.5	62.3	16.0	366
	Wilson Bros., Rochester, N. Y.:					
1919	Genteel Brand Flour	29.4	2.4	49.2	6.2	361
1913	Gluten Flour, 4/7 Standard	19.0	2.1	54.6	11.8	361
1913	Gluten Flour, Self-raising, 4/7 Standard	15.8	2.0	51.8	13.3	342
1919	Gluten Flour	45.8	2.0	28.6	11.9	364
	"NON-NUTRITIVE" FLOURS, FILLERS, ETC.					
	Dietetic Cellulose Co., Chicago:					
1920	Cellu Flour	None	Trace	None	36.9[2]	..
	Efficiency Products Co., Summerville, N. J.:					
1924	Ecmo Flour	4.1	0.6	None	80.4[2]	..
1926	Hoffmann's Non-nutritive Flour	4.0	0.5	None	80.7[2]	..
	Lister Bros., Inc., New York:					
1924	Lister's Low Caloric Flour	3.9	0.6	None	76.6[2]	..
	Nutrivoid Diabetic Flour Co., Brooklyn, N. Y.:					
1924	Nutrivoid Flour	4.3	0.9	None	78.2[2]	..
	Vitæ Health Food Co., Seattle, Wash.:					
1925	Cellulose Flour	11.6	2.8	None	39.2[2]	..
	PROTEIN PREPARATIONS.					
	Cheltine Food Co., Cheltenham, Eng.:					
1923	Milk Protein	84.5	1.0	None	2.4[3]	357
	Glogau & Co., Chicago, Sole Agents:					
1923	Aleuronat	71.0	5.6	10.7[4]	3.6	391
	Menley & James, New York:					
1913	Glidine	83.3	0.8	None	9.1	377

[1] Includes 10.7 per cent soluble carbohydrate.
[2] Probably largely unavailable.
[3] Lactose.
[4] Includes soluble carbohydrate.

TABLE 334.—COMPOSITION OF SPECIAL FOODS.—(*Continued.*)

Date of analysis.	Manufacturer or agent and name of product.	Protein, per cent.	Fat, per cent.	Carbohydrate.		Calories, per 100 gm.
				Starch, per cent.	Other carbohydrate, per cent.	
	PROTEIN PREPARATIONS—*Concluded.*					
	Norton-Truax, Chicago, Ill.:					
1919	Diaprotein	79.4	1.5	None	1.1[1]	336
1922	Diaprotein, No. 2	79.3	1.6	None	1.2[1]	336
	Plasmon Co., London:					
1923	Milk Proteid	75.9	0.7	None	3.3[1]	322
	SOFT BREADS.[2]					
	American System of Bakeries, Hartford, Conn:					
1921	Gluten Bread	26.2	6.0	23.8[3]	6.8	281
1921	Gluten Bread A	27.8	5.9	27.6[3]	6.1	299
1921	Gluten Bread B	28.5	5.4	27.5[3]	5.7	295
	Barker System of Bakeries, Hartford, Conn.:					
1925	Gluten Bread	16.7	3.6	32.3[3]	6.5	254
	Beroth Bread Shop, Hartford, Conn.:					
1925	Gluten Bread	28.6	4.6	23.3[3]	7.1	278
	Bibeau, Meriden, Conn.:					
1925	Gluten Bread	8.6	1.4	41.8[3]	6.1	239
	Canada Bread Co., Toronto, Can.:					
1919	Gluten Bread	9.9	1.1	34.8	16.5	255
	Community Bake Shop, Norwich, Conn.:					
1925	Gluten Bread	30.9	4.8	22.3[3]	5.8	279
	The Dieto Food Co., New York:					
1914	Dieto Bread, Pure Whole Wheat	8.8	0.4	36.6	11.4	231
	Ferguson Bakery, Boston, Mass.:					
1913	Gluten Bread	22.1	3.1	25.2	10.5	259
	H. and R. Diabetic Foods, Bronx, N. Y.:					
1924	Bread of Low Food Value	9.5	23.3[4]	1.7[3]	27.9	...
	Hallinan's Bakery, New Britain, Conn.:					
1925	Gluten Bread	27.5	5.8	23.4[3]	7.5	287
	The Health Food Co., New York:					
1919	Glutosac Bread	29.8	2.6	29.5	12.3	309
1919	Protosac Bread, No. 1	36.0	4.0	20.5	7.4	292
1919	Protosac Bread, No. 2	27.0	3.5	30.5	8.4	295
	J. Heinbockel & Co., Baltimore, Md.:					
1914	Diabetic Bread for Diabetes	8.6	1.5	40.4	11.7	256
	Jireh Diabetic Food Co., New York:					
1913	Whole Wheat Bread (not fresh)	11.3	0.7	44.9	18.2	304
	Keney Tower Bakery, Hartford, Conn.:					
1925	Gluten Bread	20.6	5.0	29.8[3]	3.3	260
	Levine Bros., New Haven, Conn.:					
1923	Gluten Bread	17.5	3.8	25.7[3]	11.7	254

[1] Lactose.

[2] It should be remembered that ordinary wheat bread contains protein, 9.2 per cent; fat, 1.3 per cent; carbohydrate, 52.6 per cent. (See Table 333, page 931.)

[3] Includes soluble carbohydrate.

[4] About three-fourths of the fat is unavailable.

TABLE 334.—COMPOSITION OF SPECIAL FOODS—(*Continued*).

Date of analysis.	Manufacturer or agent and name of product.	Protein, per cent.	Fat, per cent.	Carbohydrate.		Calories, per 100 gm.
				Starch, per cent.	Other carbohydrate, per cent.	
	SOFT BREADS—*Concluded.*					
	Loeb's Diabetic Food Bakery, New York:					
1919	Casein Bread	40.8	10.8	None	3.4	274
1919	Casein Muffins	45.7	11.4	None	7.0	313
1919	Genuine Gluten Bread	28.4	2.1	28.6	6.9	275
1923	Genuine Gluten Bread	32.6	3.6	27.2[1]	4.4	289
1914	P & L Genuine Glubetic Bread	35.3	4.1	19.2	10.0	294
	Lyster Bros., Whitefield, N. H.:					
1915	Casein Bread	36.6	18.4	None	2.5	322
	Mory's Bakery, New Haven, Conn.:					
1925	Gluten Bread	28.1	3.9	24.0[1]	4.3	260
	Mrs. Root's Food Shop, New Haven, Conn.:					
1925	Gluten Bread	28.9	5.1	23.9[1]	5.1	277
	Schaeffer Bros., Inc., Middletown, Conn.:					
1925	Gluten Bread	27.8	4.5	25.1[1]	5.3	273
	Slinn-Schouldis Co.:					
1919	Gluten Bread	9.2	2.6	39.0	13.4	269
	Washburn-Crosby Co., Minneapolis, Minn.:					
1925	Gluten Bread	23.6	19.5	10.2[1]	13.5	365
	Weston Bakery, Boston, Mass.:					
1915	Gluten Bread	19.0	..	28.2	..	..
	HARD BREAD AND BAKERY PRODUCTS.					
	James Aird:					
1916	Gluten Bread	13.1	0.7	59.8	15.9	362
	Arnaud, Inc., New York:					
1921	Cassava Cakes	1.8	0.2	69.5[1]	11.1	331
	Brusson, Jeune, Villimur, France:					
1921	Gluten Bread	33.8	3.8	45.0[1]	0.4	351
	Callard & Co., London:					
1923	Almond Biscuits, No. 15	34.1	48.6	3.5[1]	2.8	599
1925	Bran and Agar Biscuits ("Cellulon")	10.9	7.0	None	51.5[2]	..
1923	Bran and Almond Biscuits, No. 13	24.4	57.5	2.8[1]	3.8	642
1923	Casoid Biscuits, No. 17	58.3	24.6	0.3[1]	1.7	463
1923	Casoid Rusks, No. 8	54.3	26.6	0.5[1]	4.9	478
1925	Chocolate Biscuits ("Casoid")	23.0	51.6	5.4[1]	9.4	616
1923	Gluten and Almond Biscuits, No. 11	65.4	23.3	3.1[1]	None	484
1923	Gluten Biscuits, No. 9	60.4	23.9	3.4[1]	3.9	486
1923	Gluten Cracknells, No. 7	68.7	14.7	3.4[1]	4.7	440
1923	Gluten Dinner Rolls, No. 6	73.8	7.1	5.2[1]	5.4	402
1923	Kalari Batons, No. 5*a*	44.2	42.5	1.2[1]	0.1	565
1923	Parmesan Cheese Straws, No. 17	31.2	48.9	3.5[1]	6.6	606
1923	Ponos Biscuits, No. 14	60.6	19.2	1.3[1]	2.6	431
1923	Prolacto Biscuits, No. 12	59.8	20.5	0.3[1]	4.7	444
1923	Soup Sippets	54.1	28.7	0.5[1]	7.0	505
1925	Starchless Ginger Biscuits	27.4	56.9	None	7.2	651

[1] Includes soluble carbohydrate.

[2] Probably largely unavailable.

TABLE 334.—COMPOSITION OF SPECIAL FOODS.—(*Continued.*)

Date of analysis.	Manufacturer or agent and name of product.	Protein, per cent.	Fat, per cent.	Carbohydrate.		Calories, per 100 gm.
				Starch, per cent.	Other carbohydrate, per cent.	
	HARD BREAD AND BAKERY PRODUCTS —*Continued.*					
	Canada Bread Co., Toronto, Can.:					
1916	Gluten Health Bread	15.4	3.4	57.9	13.2	376
	Charrasse, Marseilles, France:					
1926	Biscuits au Gluten	35.3	4.8	35.6	17.5	397
	Cheltine Food Co., Cheltenham, Eng.:					
1923	Assorted Biscuits	18.3	16.0	51.5[1]	5.3	444
1923	Brown Rusks	18.2	9.7	51.0[1]	10.8	407
1923	White Rusks	22.7	14.8	48.0[1]	4.6	434
1923	Manhu Diabetic Biscuits	12.9	12.0	61.7[1]	5.6	429
	Chicago Dietetic Supply House:					
1925	Bran Agar Agar Wafers	11.9	5.7	Trace	56.1[2]	..
1925	Cellu Bran Wafers	4.1	24.2[2]	None	41.7[2]	..
1925	Cellu Cheese Wafers	7.8	30.6[2]	None	33.8[2]	..
1925	Cellu Chocolate Wafers	6.5	28.3[2]	2.1	36.3[2]	..
	The Dieto Food Co., New York:					
1914	Dieto Crackers	13.4	9.2	54.8	13.9	411
1914	Dieto Rusks	15.9	9.1	52.1	14.0	410
	Energen Foods Co., Inc., New York:					
1923	Energen New Natural Gluten Bread	33.1	10.1	44.0[1]	4.2	416
	Fougeron, Paris:					
1925	Pain Anti-diabetique	20.9	20.1	34.3	14.6	460
	Fromm & Co., Dresden:					
1913	Almond-form Wafers with Chocolate	4.8	29.0	14.0	48.3	529
1913	Butterbrezeln	12.3	16.5	43.1	19.6	449
1914	Conglutin Drops	50.8	1.1	29.2	6.9	358
1914	Conglutin-Zwieback	14.3	21.3	29.7	27.9	479
1913	Crackers	12.9	7.7	58.2	10.2	395
1913	Eierbiscuit	18.8	11.4	37.5	23.1	420
1913	Haselnuss-Stangen	13.4	16.0	None	60.8	441
1913	Luft Bread	50.9	1.0	23.4	7.3	335
1913	Makronen	14.1	19.4	None	56.2	456
1913	Salt-Stangen	13.0	15.6	39.1	22.1	437
1913	Stangenin	14.0	13.0	51.6	12.8	431
1913	Uni Bread	71.7	1.7	2.9	6.5	340
	Karl Goldscheider, Karlsbad:					
1914	Aleuronat-Conglutin Cakes	26.6	15.6	31.7	19.6	452
1914	Butter-Brezeln	10.5	14.9	43.9	23.6	446
1914	Feinste Cocosnuss-Biskuits für Diabetiker "3.6 per cent carbohydrates"	34.4	45.4	None	13.9	602
1914	Feinste Vanille-Biskuits für Diabetiker, "3.6 per cent carbohydrates"	46.4	30.3	None	16.8	525
1914	Honigküchen für Diabetiker, "3.6 per cent carbohydrates"	40.3	38.8	None	13.9	566
1914	Saccharin-Oblaten ohne Zucker	16.5	22.6	33.5	17.6	474
1914	Tee-Gebäck	7.0	27.3	18.0	42.8	517
1914	Zwieback	21.3	3.6	51.7	13.6	379

[1] Includes soluble carbohydrate.
[2] Probably largely unavailable.
[3] Availability not determined.

TABLE 334.—COMPOSITION OF SPECIAL FOODS.—(*Continued.*)

Date of analysis.	Manufacturer or agent and name of product.	Protein, per cent.	Fat, per cent.	Carbohydrate.		Calories, per 100 gm.
				Starch, per cent.	Other carbohydrate, per cent.	
	HARD BREAD AND BAKERY PRODUCTS —*Continued.*					
	H. and R. Diabetic Foods, Bronx, N. Y.:					
1924	Bran Biscuit	6.6	12.5	2.2[1]	57.0[2]	375
1924	Bran Biscuit, spiced and sweetened	7.6	18.4	2.2[1]	55.6[2]	427
1924	Cellu Lemon Cookies	7.8	27.5	4.0[1]	45.1[2]	475
	Health Food Co., New York:					
1919	Alpha	68.6	8.4	1.0	6.4	380
1919	Alpha No. 1 Best Diabetic Wafer, Casein	48.4	33.5	None	4.9	515
1919	Alpha No. 2 Best Diabetic Wafer	70.5	4.0	1.1	6.3	348
1914	Diabetic Biscuit	35.9	8.8	39.8	6.8	409
1919	Gluten Cracker Dust	44.5	8.8	23.2	11.8	398
1919	Gluten Nuggets	28.8	12.3	32.2	15.4	417
1919	Glutona Bread Sticks	33.4	11.1	30.6	14.1	412
1919	Glutosac Butter Wafers	31.1	8.0	40.4	7.9	390
1919	Glutosac Rusk	34.7	5.6	34.3	12.5	376
1919	Glutosac Wafers, Plain	41.0	7.5	25.1	12.1	380
1919	Glutosac Zwieback	28.8	10.5	33.3	15.2	405
1919	No. 1 Proto Puffs	69.1	4.7	3.3	10.7	375
1914	No. 2 Proto Puffs	53.6	2.1	20.7	11.5	362
1919	Protosac Rusk	32.7	5.0	39.3	7.8	364
1919	Protosoy Diabetic Wafer	46.5	15.5	10.6	14.2	425
1919	Salvia Almond Sticks	32.1	26.1	21.4	9.1	485
	Heintz Food Co., Chicago, Ill.:					
1913	Gluten Biscuits	11.7	18.3	21.4	37.4	447
	Huntley & Palmer, London:					
1916	Akoll Biscuits	53.6	28.3	Trace	6.2	493
	Jacob & Co., Dublin, Ireland:					
1923	Plasmon Oat Biscuit	15.4	20.7	49.3[1]	6.1	470
1923	Plasmon Plain Biscuit	18.6	15.8	52.5[1]	3.9	443
1923	Plasmon Sweet Biscuit	17.8	15.2	53.6[1]	4.6	441
1923	Plasmon Wholemeal Biscuit	20.0	16.8	47.2[1]	6.6	446
	Jireh Diabetic Food Co., New York:					
1913	Diabetic Biscuit	13.2	7.4	49.6	21.2	403
1913	Diabetic Rusks	14.9	8.7	47.0	21.0	410
	Johnson Educator Food Co., Boston, Mass.:					
1913	Educator Gluten Bread Sticks	32.7	7.2	37.5	11.5	392
1919	Gluten Cookies	29.0	11.6	36.5	13.5	422
	The Kellogg Food Co., Battle Creek, Mich.:					
1913	Potato Gluten Biscuit	37.9	0.5	39.5	12.1	363
1919	Pure Gluten Biscuit	78.4	1.5	2.9	6.5	365
1919	40 per cent Gluten Biscuit	40.9	1.6	35.6	10.9	364

[1] Includes soluble carbohydrate.
[2] Probably largely unavailable.

TABLE 334.—COMPOSITION OF SPECIAL FOODS.—(*Continued.*)

Date of analysis.	Manufacturer or agent and name of product.	Protein, per cent.	Fat, per cent.	Carbohydrate.		Calories, per 100 gm.
				Starch, per cent.	Other carbohydrate, per cent.	
	HARD BREAD AND BAKERY PRODUCTS —*Continued.*					
	Laboratoire E. Storage, Marsailles, France (Hygienic Food Co., New York, Distributors):					
1924	Madeleins Lucullus	8.8	23.4	46.9[1]	14.2	490
1924	Vichy Goufrettes	14.8	50.9	13.4[1]	12.9	623
1924	Goufrettes Vanillees	8.8	1.2	81.3[1]		371
1924	Nougatines de Vichy	10.0	28.4	41.0[1]	15.1	520
	Laporte & Gauthier, Somerset, Manitoba, Can.:					
1921	Croustils, Dechloridized	16.6	6.1	64.8[1]	3.3	394
1921	Croustils, Simple	17.1	3.4	66.0[1]	3.8	378
1921	Croustils, Glutenized	30.3	6.7	49.9[1]	3.3	394
	La Societe l'Aliment "Essential," Nanterre, France:					
1921	Heudebert, Bread of Gluten	61.8	6.2	13.2[1]	7.5	386
1921	Heudebert, Aleurone Bread	64.0	5.1	11.5[1]	7.5	378
1921	Heudebert, Special Diabetic Bread	55.5	5.9	19.3[1]	6.6	379
1921	Heudebert, Rolls of Gluten	9.7	8.8	66.1[1]	5.2	403
1921	Heudebert, Rusks of Gluten	10.8	7.6	67.4[1]	5.6	404
	Loeb's Diabetic Food Bakery, New York:					
1919	Aërated Gluten Bread	47.8	11.1	26.8	3.2	411
1923	Aërated Gluten Bread	49.8	12.2	23.6[1]	7.0	431
1919	Diabetic Almond Macaroons	30.4	46.3	0.6	10.5	583
1919	Diabetic Bread Sticks	41.8	3.8	35.4	6.9	371
1919	Diabetic Bread Sticks, Almond	39.4	11.7	31.2	7.1	416
1919	Diabetic Butter Cookies	36.5	12.0	31.1	8.4	412
1919	Diabetic Lady Fingers	47.8	34.1	1.9	3.5	519
1919	Diabetic Sponge Cookies	49.7	33.8	1.9	1.4	516
1919	Gluten Almond Zwieback	41.3	7.8	32.6	7.0	394
1919	Gluten Bread	42.5	11.1	27.7	8.8	416
1916	Gluten Luft Bread	40.6	9.8	29.9	11.3	415
1919	Gluten Zwieback	38.7	3.0	36.1	10.6	368
	Nutrivoid Diabetic Flour Co., Brooklyn, N. Y.:					
1925	Nutrivoid Bran Wafers	5.8	31.1[2]	None	43.2[3]	..
	Pure Gluten Food Co., New York:					
1914	No. 1 Dainty Fluffs	79.9	0.5	10.7	0.5	370
1914	No. 2 Dainty Fluffs	66.3	0.5	21.9	3.0	369
1916	Dainty Fluffs	80.0	0.8	7.7	3.0	370
1914	Gum Gluten Biscuit Crisps	48.1	0.5	31.2	11.5	368

[1] Includes soluble carbohydrate.
[2] Largely mineral oil, unavailable.
[3] Largely unavailable.

TABLE 334.—COMPOSITION OF SPECIAL FOODS.—(*Continued.*)

Date of analysis.	Manufacturer or agent and name of product.	Protein, per cent.	Fat, per cent.	Carbohydrate.		Calories, per 100 gm.
				Starch, per cent.	Other carbohydrate, per cent.	
	HARD BREAD AND BAKERY PRODUCTS —*Continued.*					
	Rademann's Nahrmittelfabrik, Frankfurt:					
1926	Brusson, Jeune Mignonettes	50.8	3.4	36.9[1]	2.8	393
1913	Diabetiker-Biscuit	29.6	19.6	25.9	18.6	473
1926	Diabetiker Casoid Biscuits	57.3	26.9	1.0[1]	3.9	491
1913	Diabetiker-Bretzel	31.4	8.5	40.7	9.4	402
1913	Diabetiker-Cakes	29.6	13.5	39.1	8.1	429
1913	Diabetiker-Dessert-Gebäck	22.2	42.4	5.9	21.6	580
1926	Diabetiker Keks	32.1	15.2	36.0[1]	7.6	440
1913	Diabetiker-Makronen	23.2	48.0	3.0	17.6	607
1913	Diabetiker-Stangen	17.7	44.2	21.4	8.1	586
1926	Diabetiker Zwieback	25.4	12.6	48.1[1]	7.2	436
1913	Käsestangen	9.3	33.7	38.0	8.4	526
1926	Ohneko Biscuits	61.6	22.6	4.2[1]	3.1	479
	R. M. Scott, Ltd., Ipswich:					
1922	Gluten and Almond Biscuit	23.8	19.9	44.5[1]	3.2	465
	James Strachen:					
1916	Gluten Bread	16.9	0.6	52.7	21.3	369
	Therapeutic Foods Co., Inc., New York:					
1924	Aleurone Bread	62.0	1.7	15.4[1]	7.5	355
1923	Charrasse Gluten Bread	42.7	5.8	36.0[1]	5.3	388
1923	Charrasse Gluto-Kola Bread	45.9	6.0	37.3[1]	None	387
1923	Charrasse Gluto-Soja Bread	48.6	6.9	33.3[1]	0.7	393
1923	Charrasse Supreme Bread	45.6	6.9	35.9[1]	0.6	391
1924	Bread of Gluten	71.6	1.5	6.3[1]	7.7	356
1924	Brusson, Jeune Gluten Bread	39.3	1.0	12.8[1]	36.0	361
1925	Gluten Bread	73.0	3.7	5.9[1]	6.9	377
1924	Special Diabetic Bread	63.0	1.1	15.0[1]	8.4	356
	G. Van Abbott & Sons, London:					
1913	Caraway Biscuits for Diabetics	35.6	37.5	8.6	7.3	544
1913	Diabetic Rusks for Diabetics	70.9	0.8	12.6	3.4	355
1913	Euthenia Biscuit	35.8	40.7	6.9	6.3	562
1913	Gluten Biscottes or Rolls	47.1	2.3	29.8	7.7	359
1913	Gluten Bread or Slices	49.4	2.2	27.4	8.2	361
1913	Gluten Butter Biscuit for Diabetics	40.2	33.2	9.0	7.6	526
1913	Ginger Biscuit for Diabetics	34.6	39.4	10.9	5.8	560
1913	Midolia Biscuit	17.6	36.4	13.4	18.2	524
1923	Soya Biscuit	39.2	25.0	11.4[1]	11.8	475
1913	Walnut Biscuits for Diabetics	20.9	57.2	Trace	12.3	648
	Waukesha Health Products Co., Waukesha, Wis.:					
1919	Hepco Dodgers	42.4	16.7	1.0	21.6	411
	Weston's Bakery, Boston, Mass.:					
1915	Gluten Cookies	27.7	..	19.6	..	..

[1] Includes soluble carbohydrate.

TABLE 334.—COMPOSITION OF SPECIAL FOODS.—(*Continued.*)

Date of analysis.	Manufacturer or agent and name of product.	Protein, per cent.	Fat, per cent.	Carbohydrate.		Calories, per 100 gm.
				Starch, per cent.	Other carbohydrate, per cent.	
	HARD BREAD AND BAKERY PRODUCTS —*Concluded.*					
	Woman's Baking Co., Boston, Mass.[1]					
1921	Bran Cookies, Anice	7.4	25.9	5.2[2]	..	..
1921	Bran Cookies, Caraway	8.1	24.2	5.0[2]	..	..
1921	Bran Cookies, Cocoa Nib	8.2	26.9	8.7[2]	..	..
1921	Bran Cookies, Spice	6.6	22.7	9.3[2]	..	..
1921	Bran Muffins	7.3	5.9	5.6[2]	..	..
1921	Cellu Biscuits	3.2	13.2	3.9[2]	..	..
1921	Cellu Cookies, Caraway	5.6	22.5	3.8[2]	32.0	..
1921	Cellu Cookies, Lemon	4.2	24.4	3.9[2]	..	..
1921	Cellu Cookies, Vanilla	4.3	21.3	4.1[2]	..	..
1921	Cellu Kisses	23.0	0.2	2.5[2]	25.2	..
1921	Cellu Muffins	3.8	13.6	3.5[2]	..	..
1921	Cellu Nuts	5.4	28.7	3.6[2]	23.8	..
1921	Cellu Soup Wafers	3.7	25.6	4.2[2]	..	..
	BREAKFAST FOODS.					
	Arnaud, Inc., New York:					
1921	Starchless Breakfast Food	2.0	0.2	70.9[2]	10.3	335
	Battle Creek Food Co., Battle Creek, Mich.:					
1924	Cooked Bran	15.3	4.7	59.2		340
	Brusson, Jeune, Villimur, France:					
1913	Farina au Gluten	30.9	0.6	48.8	8.0	356
	Callard & Co., London:					
1925	Washed Bran	10.4	6.5	2.3[2]	46.4	293
	Curdolac Food Co., Waukesha, Wis.:					
1924	Krinkles	10.8	14.4	4.8[2]	45.5	374
	Dieto Food Co., New York:					
1914	Dieto Nut Cereal	21.6	18.4	39.5	12.3	459
1914	Wheat and Barley Cereal	11.6	2.2	61.4	14.4	369
	Efficiency Products Co., Somerville, N. J.:					
1924	Nut Flakes	4.4	1.0	2.8[2]	75.6[3]	..
1926	Ecmo Breakfast Food	6.4	1.1	2.6[2]	69.1[3]	..
1926	Starch-free Bran	16.7	4.4	2.4[2]	40.8	279
	Farwell & Rhines, Watertown, N. Y.:					
1913	Barley Crystals	11.5	1.3	62.7	12.5	359
1913	Cresco Grits	17.8	1.4	54.1	14.5	358
	Health Food Co., New York:					
1919	Manana Gluten Breakfast Food	44.8	8.7	22.0	12.5	396
1919	Protosoy (Cereal)	40.1	18.2	Trace	24.9	424
	Jireh Diabetic Food Co., New York:					
1913	Whole Wheat Farina	11.7	2.3	59.5	16.3	371
1913	Frumenty	12.3	1.7	65.4	11.9	374

[1] The fat in these products is largely or entirely mineral oil and unassimilable.
[2] Includes soluble carbohydrate.
[3] Largely unavailable.

TABLE 334.—COMPOSITION OF SPECIAL FOODS.—(*Continued.*)

Date of analysis.	Manufacturer or agent and name of product.	Protein, per cent.	Fat, per cent.	Carbohydrate.		Calories, per 100 gm.
				Starch, per cent.	Other carbohydrate, per cent.	
	BREAKFAST FOODS—*Concluded.*					
	Kellogg's Toasted Corn Flake Co., Battle Creek, Mich.:					
1923	Kellogg's Bran Cooked and Krumbled	14.4	3.4	68.5[1]		362
	Kramer Surgical Stores, New York:					
1926	Breakfast Cereal	32.8	1.3	3.5[2]	47.0[2]	..
	Lister Bros., Inc., New York:					
1924	"Starch-free" Bran	16.4	4.0	1.6[2]	44.4	286
	Loeb's Diabetic Food Bakery, N. Y.:					
1919	Casein Breakfast Cereal	36.6	42.5	0.7	11.0[1]	576
1919	Gluten Breakfast Cereal	29.2	19.4	25.5	17.8	464
	S. S. Pierce Co., Boston:					
1926	Deshell Starchless Agar Flakes	1.9	0.2	None[2]	83.3[2]	..
	Plasmon Co., London:					
1922	Oats	17.3	8.1	57.4[2]	5.9	395
	Pure Gluten Food Co., New York:					
1919	Gluten Breakfast Food	40.8	0.7	35.7	12.3	361
1924	Gluten Flakes (av. of two analyses)	42.5	3.7	14.7[2]	23.1	355
1916	Gum Gluten Granules	39.3	0.9	40.5	11.4	373
1919	Hoyt's Gluten Breakfast Food, 40 per cent protein	46.0	1.8	31.4	10.2	366
1923	Hoyt's Gluten Flakes	44.7	4.4	16.5[2]	18.9	360
1919	Hoyt's Gluten Granules, over 40 per cent protein	43.8	2.6	32.2	10.1	368
1924	Hoyt's Protein Cereal	79.4	1.6	2.9[2]	8.9	379
1924	Hoyt's Special Gluten Flakes	74.1	1.9	5.9[2]	8.1	370
	The Spa, Waukesha, Wis.:					
1924	Malted Bran	9.8	5.6	2.0[2]	58.6	332
	Vitæ Health Food Co., Seattle, Wash.:					
1925	Starch-free Bran[4]	22.4	8.9	5.8[2]	27.8	304
	Gerda H. Wagner, Brooklyn, N. Y.:					
1924	Diabetic Cereal	10.1	4.6	1.4[2]	58.8	323
	Waukesha Health Products Co., Waukesha, Wis.:					
1919	Hepco Grits	40.3	16.4	0.9	23.9	408
	Woman's Baking Co., Boston:					
1921	Washed Bran	11.2	7.4	4.6[2]	..	..
	MACARONI, NOODLES, ETC.					
	Brusson, Jeune, Villimur, France:					
1913	Petites Pates au Gluten	17.0	1.0	61.2	10.8	365
	Callard & Co., London:					
1922	Casoid Flakes	78.5	3.1	1.2[2]	None	347
1922	Casoid Vermicelli	80.0	2.7	0.5[2]	None	346
	The Dieto Food Co., New York:					
1914	Whole Wheat Brand Macaroni	13.9	1.1	58.7	15.0	361

[1] Includes fiber.
[2] Includes soluble carbohydrate.
[3] Largely unavailable.
[4] Soy bean product.

TABLE 334.—COMPOSITION OF SPECIAL FOODS.—(*Continued.*)

Date of analysis.	Manufacturer or agent and name of product.	Protein, per cent.	Fat, per cent.	Carbohydrate.		Calories, per 100 gm.
				Starch, per cent.	Other carbohydrate, per cent.	
	MACARONI, NOODLES, ETC.—*Concluded.*					
	Jireh Diabetic Food Co., New York:					
1913	Macaroni	16.9	0.9	58.8	12.6	361
	Kramer Surgical Stores, New York:					
1926	Broad Noodles	41.3	5.1	5.6[1]	33.8	369
1926	Fine Noodles	41.7	5.1	4.7[1]	34.6	370
1926	Macaroni	41.8	4.8	4.5[1]	32.9	360
	Eugene Loeb, New York:					
1913	Home Made Noodles	41.8	5.5	36.7	5.0	384
	Loeb's Diabetic Food Bakery, N. Y.:					
1919	Gluten Noodles	37.3	3.6	36.8	10.3	370
	Pure Gluten Food Co., New York:					
1914	Hoyt's Gum Gluten Noodles	36.9	1.2	41.8	10.8	369
	NUTS AND NUT PREPARATIONS.					
	Dieto Food Co., New York:					
1914	Pine Nuts	39.7	50.0	None	2.8	620
	Chas. Lawrence Co., Boston, Mass.:					
1913	California Paper Shell Almonds, edible portion	18.4	55.3	None	16.3	637
	Christian National Food Co., Kenilworth, N. J.:					
1916	Christian's Protoid Nuts	37.6	48.2	Trace	5.7[1]	607
	Jireh Diabetic Food Co., New York:					
1913	Diabetic Pine Nuts (Pignolias)	39.7	49.4	None	3.4	617
	The Kellogg Food Co., Battle Creek, Mich.:					
1913	Nut Bromose (Meltose and Nuts)	17.1	26.8	3.2	36.2	467
1913	Pine Nuts	38.0	49.6	4.2		615
	Nashville Sanitarium Food Co., Nashville, Tenn.:					
1913	Malted Nut Food	24.7	42.7	3.4	24.1[1]	593
1913	Nut Butter	28.0	52.6	3.8	9.2	637
1913	Nutcysa	12.9	21.0	Trace	6.3	266
1913	Nutfoda	20.8	8.0	Trace	6.8	182
	CHOCOLATE AND CHOCOLATE PREPARATIONS.					
	Brusson, Jeune, Villimur, France:					
1913	Chocolate and added Gluten a la Vanille	15.9	49.7	9.2	17.2	617
	Callard & Co., London:					
1923	"Casoid" Chocolates	22.9	38.8	5.0[2]	23.0	553
1923	"Casoid" Dessert Chocolate	24.9	46.1	7.9[2]	11.3	591
1923	"Casoid" Nut Chocolate	23.9	46.4	8.6[2]	11.3	593
1923	Chocolate Biscuits	26.1	49.8	5.6	9.2	612
1923	Sugarless Chocolate	14.0	44.3	14.0[2]	17.3	580
1925	"Casoid" Chocolate Creams	21.8	21.6	4.8[2]	35.8[3]	443

[1] Includes fiber. [2] Includes soluble carbohydrate. [3] Glycerin present.

TABLE 334.—COMPOSITION OF SPECIAL FOODS.—(*Continued.*)

Date of analysis.	Manufacturer or agent and name of product.	Protein, per cent.	Fat, per cent.	Carbohydrate.		Calories, per 100 gm.
				Starch, per cent.	Other carbohydrate, per cent.	
	CHOCOLATE AND CHOCOLATE PREPARATIONS—*Concluded.*					
1925	"Casoid" Chocolate Peppermints	22.3	20.5	4.1[1]	36.0	434
1925	"Casoid" Chocolate Truffles	27.8	46.7	5.2[1]	9.3	589
1925	"Casoid" Marzipan Chocolate	24.8	37.2	4.2[1]	21.2[2]	536
	Fritz, Vienna:					
1924	Cakes with Chocolate Icing	24.9	31.3	25.6[1]	9.5	521
1924	Dr. Fromm's Conglutin Schokolade	18.2	36.7	3.8	29.4	536
1924	Ferment-Scho-Kolade	6.3	48.8	26.7[1]	15.1	631
1924	Nut Chocolate	19.2	54.4	4.9[1]	13.0	638
1924	Saccharin-Schokolade	17.3	42.7	12.7[1]	18.0	576
	Fromm & Co., Dresden:					
1913	Conglutin-Diabetiker-Schokolade	17.6	39.1	4.3	28.4	553
	Karl Goldscheider, Karlsbad:					
1914	Feinste Dessert-Schokolade für Diabetiker, "9.98 per cent carbohydrates"	11.4	57.6	5.0	20.4	665
1914	Feinste Mocca-Schokolade für Diabetiker, "10.26 per cent carbohydrates"	10.2	60.2	4.1	19.4	677
1914	Feinste Nuss-Schokolade für Diabetiker, "11.32 per cent carbohydrates"	14.6	54.4	6.9	16.4	641
1914	Feinste Orange-Schokolade für Diabetiker, "9.98 per cent carbohydrates"	11.4	57.6	5.0	19.9	664
	Laboratoire E. Storage, Marseilles, France (Hygienic Food Co., New York, Distributors):					
1924	Croquetts de Chocolate Sucre	22.1	26.5	29.9[1]	10.6	488
1924	Pastilles de Chocolate	21.0	25.9	30.7[1]	12.0	488
	Loeb's Diabetic Food Bakery, New York:					
1919	Almond Chocolate Bars	14.9	53.2	5.3	15.6	622
1919	Diabetic Chocolate	14.7	51.7	7.3	15.5	615
	Plasmon Co., London:					
1923	Plasmon Chocolate	13.8	29.4	38.5[1]	14.4	531
	Rademan's Nahrmittelfabrik, Frankfurt:					
1913	Diabetiker-Chokolade	17.5	57.6	3.8	13.1	656
1926	Schokolade Dessert for Diabetiker	12.3	55.4	10.1[1]	14.9	648
	COCOA.					
	Callard & Co., London:					
1923	Biogene Cocoa	33.1	17.9	11.1[1]	19.8	417
	Cheltine Food Co., Cheltenham, Eng.:					
1923	Cheltine Milk Cocoa	47.1	15.9	8.9[1]	13.1	420
	The Dieto Food Company, New York:					
1914	Dieto Cocoa	23.6	22.9	12.4	26.6	456

[1] Includes soluble carbohydrate.

[2] Glycerin present.

TABLE 334.—COMPOSITION OF SPECIAL FOODS.—(*Continued.*)

Date of analysis.	Manufacturer or agent and name of product.	Protein, per cent.	Fat, per cent.	Carbohydrate.		Calories, per 100 gm.
				Starch, per cent.	Other carbohydrate, per cent.	
	COCOA—*Concluded*					
	H. & R. Diabetic Foods, Bronx, N. Y.:					
1924	Cellu Cocoa Nibs	8.3	30.1	4.2[1]	42.8	492
	Loeb's Diabetic Food Bakery, New York:					
1923	Diabetic Cocoa	25.4	20.9	16.0[1]	23.1	446
	Gustav Müller, New York:					
1913	Charrasse Gluto-Cacao	21.5	22.2	16.3	23.8	446
	Plasmon Co., London:					
1921	Cocoa	50.4	11.6	6.0[1]	13.1	382
	Rademan's Nahrmittelfabrik, Frankfurt:					
1913	Diabetiker-Cacao	17.6	23.6	10.7	34.0	462
	SUGAR-FREE MILK.					
	Gustav Müller & Co., New York:					
1913	Dr. Bouma Sugar-free Milk	2.4	5.3	..	..	57
	D. Whiting & Sons, Boston, Mass.:					
1919	Sugar-free Milk	6.4	9.3	..	0.2[2]	110
1922	Sugar-free milk	6.6	8.6	..	0.5[2]	106
	FRUITS AND VEGETABLES (CANNED).					
	Callard & Co., London:					
1925	Cranberries, Sugarless	0.3	..	1.3[1]	..	..
1925	Plums, Sugarless	0.3	..	1.5[1]	..	..
	The Diaprotein Co., Columbus, Ohio:					
	"Dieta" Brand Products:					
1921	Apple Sauce	0.2	0.6	5.8[1]	3.7	44
1921	Blackberries	0.7	0.5	2.6[1]	2.4	27
1921	Cherries, Red, Pitted	0.5	0.1	5.1[1]	3.4	37
1921	White	0.7	0.1	3.8[1]	3.5	33
1921	Peaches, Yellow	0.5	0.1	2.9[1]	2.5	25
1921	Pears, Bartlett	0.3	0.1	2.5[1]	2.7	23
1921	Raspberries, Red	0.9	0.7	3.0[1]	4.0	38
1921	Strawberries	0.6	0.4	2.0[1]	2.4	24
1921	Beans, Cut, Wax	0.8	0.1	1.2[1]	0.5	11
1921	Refugee, Green	1.0	0.1	1.4[1]	0.8	14
1921	Peas, Green	3.2	0.4	3.9[1]	2.2	41
1921	Rhubarb	0.4	0.1	0.3[1]	1.9	11
1921	Spinach	3.1	0.6	0.6[1]	1.0	24
1921	Tomatoes	1.0	0.2	1.5[1]	1.3	17
	The Poms Co., Sarasota, Fla.:					
1924	Grapefruit (Poms)	0.5	0.1	4.2[1]	4.1	36
	The John Sexton & Co., Chicago, Ill.:					
1924	Apricots, Edelweiss	0.4	0.1	4.9[1]	3.8	35
1924	Apricots, Pride of the West	0.4	0.1	4.8[1]	3.3	35
1924	Blackberries, Alp Rose	1.0	0.7	5.6[1]	4.8	52
1924	Blueberries, Alp Rose	0.4	0.3	7.6[1]	4.5	53
1924	Cherries, Edelweiss	0.6	0.1	4.2[1]	4.9	39
1924	Cherries, Pride of the West	0.6	0.1	4.9[1]	5.2	43
1925	Cherries, Alp Rose Black	0.6	0.3	10.0[1]	6.0	69
1925	Cherries, Alp Rose Red Pitted	0.5	0.3	7.0[1]	4.9	52

[1] Includes soluble carbohydrate.

[2] Lactose.

TABLE 334.—COMPOSITION OF SPECIAL FOODS.—(*Continued.*)

Date of analysis.	Manufacturer or agent and name of product.	Protein, per cent.	Fat, per cent.	Carbohydrate.		Calories, per 100 gm.
				Starch, per cent.	Other carbohydrate, per cent.	
	—FRUITS AND VEGETABLES (CANNED) *Concluded.*					
1924	Cherries, Alp Rose Royal Anne	0.6	0.1	7.6[1]	5.1	54
1924	Grape Fruit, Alp Rose	0.7	0.1	4.9[1]	3.3	36
1924	Logan Berries, Alp Rose	1.0	0.7	5.6[1]	5.1	53
1924	Peaches, Edelweiss	0.4	0.1	4.0[1]	3.2	31
1924	Peaches, Pride of the West	0.4	Trace	4.8[1]	2.6	31
1924	Pears, Alp Rose Bartlett	0.3	0.1	4.3[1]	5.3	40
1924	Pears, Edelweiss	0.2	0.1	3.7[1]	4.8	36
1924	Pears, Pride of the West	0.2	0.1	3.6[1]	4.7	35
1924	Pineapple, Alp Rose Hawaiian, Sliced	0.4	0.1	8.5[1]	4.6	55
1924	Pineapple, Pride of the West	0.4	0.1	9.7[1]	3.2	54
1924	Plums, Alp Rose Japan	0.3	0.1	2.8[1]	2.9	25
1924	Plums, Alp Rose Prune	0.3	0.1	6.9[1]	3.5	44
1924	Plums, Pride of the West Prune	0.4	0.1	4.8[1]	5.3	43
1925	Raspberries, Alp Rose Black	0.8	1.1	3.3[1]	3.8	42
1924	Raspberries, Alp Rose Red	0.7	0.5	4.8[1]	3.0	34
1925	Strawberries, Alp Rose	0.4	0.3	2.0[1]	2.4	22
1924	Asparagus, Alp Rose Peeled, White	1.2	0.1	1.5[1]	0.8	15
1924	Asparagus Tips, Alp Rose White	1.7	0.1	1.6[1]	1.0	18
1925	Beans, Alp Rose Refugee (small green)	1.0	0.1	1.4[1]	1.4	16
1925	Beets, Alp Rose (small)	1.3	0.1	8.4[1]	4.6	58
1925	Peas, Alp Rose (sifted early June)	2.6	0.2	4.2[1]	1.5	34
1925	Sauerkraut, Edelweiss	1.1	0.2	0.4[1]	2.3	17
1925	Spinach, Alp Rose	2.9	0.5	1.0[1]	1.9	28
1925	Sweet Corn, Alp Rose	2.1	1.1	10.3[1]	2.5	69
	Washington County Co., Dennysville, Me.:					
1925	Aunty's Mountain Cranberries	0.5	0.8	3.3[1]	11.4	68
1925	Aunty's Blueberries	0.7	0.9	8.0[1]	7.2	72
	MISCELLANEOUS PRODUCTS.					
	Callard & Co., London:[2]					
1925	Sugarless Jam, Apricot	3.9[3]	..	3.3[1]	..	..
1925	Sugarless Jam, Green Gage Plum	5.0[3]	..	2.8[1]	..	..
1925	Sugarless Jam, Plum	5.0[3]	..	1.7[1]	..	..
1925	Sugarless Marmalade, Orange	5.8[3]	..	1.2[1]	..	..
1925	Sugarless Jelly, Pineapple	6.8[3]	..	..	..	..
1925	Ponos Marzipan	20.1	34.7	3.1[1]	23.8	500
1925	Ponos Marzipan (Creme de Menth)	21.8	45.4	2.7[1]	15.9	570
	Manual Freres:					
1917	Longuets de Lausanne	14.2	5.5	49.2	16.9	371
	Health Food Co., New York:					
1913	Kaffeebrod	12.9	1.5	10.1	62.4	355
	Jell-O Company, Le Roy, N. Y.:					
1924	D-Zerta[3]	72.8[4]	0.1	None[1]	..	..

[1] Includes soluble carbohydrate.

[2] The jams, jellies and marmalades made by this company for diabetic diets are packed with from 10 to 45 per cent of glycerin.

[3] Ash, 1.7 per cent; undetermined (chiefly water and organic acids), 25.4 per cent.

[4] Gelatin (N × 5.55).

TABLE 334.—COMPOSITION OF SPECIAL FOODS.—(*Concluded.*)

Manufacturer or agent and name of product.	Protein, per cent.	Fat, per cent.	Carbohydrate.		Calories, per 100 gms.
			Starch, per cent.	Other carbohydrate, per cent.	
LAXATIVE FOODS.					
Bran Products, etc.:					
Bran (so-called "health bran" for dietetic use), average of six commercial brands	15.6	4.8	55.8		329
Bran Biskue	12.1	13.1	61.0		410
Bran Zos	13.2	2.5	65.6		338
Bran-eata Biscuit	9.1	0.9	72.2		333
Brose Good Health Breakfast Food	14.4	4.3	65.5		358
Cerag	11.3	0.9	73.0		345
Christian's Laxative Bread	10.0	1.4	74.6		351
Colax	1.1	0.8	82.8		343
Dietetic Bran Biscuit	9.9	5.0	69.1		361
Educator Bran Cookies	8.9	14.5	64.7		425
Educator Bran Meal	12.3	2.8	66.4		340
F.B.A. Health Biscuit	6.1	1.7	77.3		349
Fruit Nut Cereal	13.5	1.2	72.4		354
Good Health Biscuit (Kellogg)	7.7	1.2	74.5		340
Health Food Wafers	10.0	7.9	65.7		374
India (Digestive) Biscuit	12.8	2.2	66.1		335
Laxa	12.4	2.8	66.6		341
Laxative Biscuits (Kellogg)	16.7	10.8	57.7		395
Mansfield's Agar-Agar Wafers	7.1	12.0	69.9[1]		416
Oval Digestive Biscuit (H and P)	7.8	16.3	64.5		436
Uncle Sam Health Food	21.3	24.4	40.9		468
Zim	7.4	1.7	74.2		342
DiaBiskit (Jackson)	17.6	4.8	6.1[2]	47.2[3]	..

[1] Carbohydrate of agar-agar largely unavailable.
[2] Includes soluble carbohydrate.
[3] Carbohydrate largely unavailable.

SECTION XX.

HARRIS AND BENEDICT PREDICTION TABLES.

THE Harris and Benedict formula employed for men is:

$$h = 66.473 - 13.752w - 5.003s - 6.755a$$

in which h represents the heat-production per twenty-four hours, w the nude body weight in kilograms, s the height without shoes in centimeters, and a the age in years. For a male, aged twenty-four years, height 170 cm., and weight 63 kilograms, and assuming the metabolism obtained by observation to be 1783 calories, the calculation would therefore be as follows:

$h = 66.473 - (13.752 \times 63) - (5.003 \times 170) - (6.755 \times 24) = 1621$ calories;

$$\frac{\text{observed metabolism (1783)} - \text{predicted metabolism (1621)}}{1621} = 10 \text{ per cent H. and B.}$$

For women the formula is:

$$h = 655.096 - 9.563w - 1.85s - 4.676a$$

Making use of the Harris and Benedict Prediction Table, see pp. 961 to 966, the calculation of basal metabolism is as follows:

Sex	Male	Factor for height and age in cm.[1]	688
Age in years	24	Factor for weight in kg.[2]	933
Height in centimeters	170		
Weight in kilograms	63	Basal metabolism	1621

The DuBois method is based upon his formula for calculating the body-surface. Having obtained this, it is multiplied by the calories computed by him to be standard for square meter body-surface for age and sex.

[1] See page 961.

[2] See page 966.

The DuBois formula for ascertaining body-surface of men and women is as follows:

$$\text{Area (sq. cm.)} = \text{Weight}^{0.425} \times \text{Height}^{0.725} \times 71.84$$

in which the product of the weight in kilograms raised to the power 0.425 and the height in centimeters raised to the power 0.725 is multiplied by the factor 71.84.

The DuBois table for estimation of calories per square meter body-surface is reproduced in Table 335.

TABLE 335.—CALORIES PER SQUARE METER OF BODY-SURFACE (HEIGHT-WEIGHT FORMULA) PER HOUR FOR AGE AND SEX.

Age in years.	Males.	Females.	Age in years.	Males.	Females.
14–16	46.0	43.0	40–50	38.5	36.0
16–18	43.0	40.0	50–60	37.5	35.0
18–20	41.0	38.0	60–70	36.5	34.0
20–30	39.5	37.0	70–80	35.5	33.0
30–40	39.5	36.5			

The calculation is as follows:

Sex, male; age in years, twenty-four; height in centimeters, 170; weight in kilograms, 63.

$$\text{Area (sq. cm.)} = (\text{Weight } 63)^{0.425} \times (\text{Height } 170)^{0.725} \times 71.84 = 17{,}305 \text{ sq. cm.}$$

$$= 1.73 \text{ square meters}$$

$$1.73 \times 39.5 = 68.3 \text{ calories per hour}$$

$$68.3 \times 24.0 = 1639 \text{ calories per twenty-four hours}$$

Thus, by the Harris and Benedict Standards the basal metabolism of a male, twenty-four years of age, 63 kilograms in weight, and 170 cm. in height would be 1621 calories and by the DuBois Standard, 1639 calories.

In the original publication of Harris and Benedict the figures are given for the nearest tenth of a kilogram, and the nearest centimeter. It is felt that for practical purposes in the clinic, data with sufficient accuracy are obtained if calculated to the nearest kilogram and the nearest 2 cm. For example, the weight of a patient may easily vary half a kilogram, according to whether water has been drunk or the rectum and bladder evacuated. As records are not kept of such data, it appears to be a false refinement of accuracy to attempt to calculate the metabolism more closely than to $\frac{1}{2}$ kilogram. Similarly, it is extremely difficult to measure an individual to within less than a centimeter. However, should more intimate data be desired, it is a simple matter to interpolate the intervening figures in the tables, as has in fact been done in the following example.

Harris and Benedict Prediction Tables. The use of these tables is better shown by example than by description.

Man, aged twenty-seven years; height, 172 cm.; weight, 77.2 kg.		Woman, aged twenty-two years; height, 166 cm.; weight, 77.2 kg.		Woman, aged sixty-six years; height, 162 cm.; weight, 62.3 kg.	
From Table 336	678	From Table 337	204	From Table 337	−9
From Table 338	1128	From Table 338	1393	From Table 338	1251
Predicted cals.	1806	Predicted cals.	1597	Predicted cals.	1242

TABLE 336.—FACTORS FOR STATURE AND AGE IN MEN.

Cm.	21	22	23	24	25	26	27	28	29	30
151	614	607	600	593	587	580	573	566	560	553
153	624	617	610	603	597	590	583	576	570	563
155	634	627	620	613	607	600	593	586	580	573
157	644	637	630	623	617	610	603	596	590	583
159	654	647	640	633	627	620	613	606	600	593
161	664	657	650	643	637	630	623	616	610	603
163	674	667	660	653	647	640	633	626	620	613
165	684	677	670	663	657	650	643	636	630	623
167	694	687	680	673	667	660	653	646	640	633
169	704	697	690	683	677	670	663	656	650	643
171	714	707	700	693	687	680	673	666	660	653
173	724	717	710	703	697	690	683	676	670	663
175	734	727	720	713	707	700	693	686	680	673
177	744	737	730	723	717	710	703	696	690	683
179	754	747	740	733	727	720	713	706	700	693
181	764	757	750	743	737	730	723	716	710	703
183	774	767	760	753	747	740	733	726	720	713
185	784	777	770	763	757	750	743	736	730	723
187	794	787	780	773	767	760	753	746	740	733
189	804	797	790	784	777	770	763	756	750	743
191	814	807	800	794	787	780	773	766	760	753
193	824	817	810	804	797	790	783	776	770	763
195	834	827	820	814	807	800	793	787	780	773
197	844	837	830	824	817	810	803	797	790	783
199	854	847	840	834	827	820	813	807	800	793

Cm.	31	32	33	34	35	36	37	38	39	40
151	546	539	533	526	519	512	506	499	492	485
153	556	549	543	536	529	522	516	509	502	495
155	566	559	553	546	539	532	526	519	512	505
157	576	569	563	556	549	542	536	529	522	515
159	586	579	573	566	559	552	546	539	532	525
161	596	589	583	576	569	562	556	549	542	535
163	606	599	593	586	579	572	566	559	552	545
165	616	609	603	596	589	582	576	569	562	555
167	626	619	613	606	599	592	586	579	572	565
169	636	629	623	616	609	602	596	589	582	575
171	646	639	633	626	619	612	606	599	592	585
173	656	649	643	636	629	622	616	609	602	595
175	666	659	653	646	639	632	626	619	612	605
177	676	669	663	656	649	642	636	629	622	615
179	686	679	673	666	659	652	646	639	632	625
181	696	689	683	676	669	662	656	649	642	635
183	706	699	693	686	679	672	666	659	652	645
185	716	709	703	696	689	682	676	669	662	655
187	726	719	713	706	699	692	686	679	672	665
189	736	729	723	716	709	702	696	689	682	675
191	746	739	733	726	719	712	706	699	692	685
193	756	749	743	736	729	722	716	709	702	695
195	766	759	753	746	739	732	726	719	712	705
197	776	769	763	756	749	742	736	729	722	715
199	786	779	773	766	759	752	746	739	732	725

TABLE 336.—FACTORS FOR STATURE AND AGE IN MEN.—*Continued.*

Cm.	41	42	43	44	45	46	47	48	49	50
151	479	472	465	458	452	445	438	431	425	418
153	489	482	475	468	462	455	448	441	435	428
155	499	492	485	478	472	465	458	451	445	438
157	509	502	495	488	482	475	468	461	455	448
159	519	512	505	498	492	485	478	471	465	458
161	529	522	515	508	502	495	488	481	475	468
163	539	532	525	518	512	505	498	491	485	478
165	549	542	535	528	522	515	508	501	495	488
167	559	552	545	538	532	525	518	511	505	498
169	569	562	555	548	542	535	528	521	515	508
171	579	572	565	558	552	545	538	531	525	518
173	589	582	575	568	562	555	548	541	535	528
175	599	592	585	578	572	565	558	551	545	538
177	609	602	595	588	582	575	568	561	555	548
179	619	612	605	598	592	585	578	571	565	558
181	629	622	615	608	602	595	588	581	575	568
183	639	632	625	618	612	605	598	591	585	578
185	649	642	635	628	622	615	608	601	595	588
187	659	652	645	638	632	625	618	611	605	598
189	669	662	655	648	642	635	628	621	615	608
191	679	672	665	658	652	645	638	631	625	618
193	689	682	675	668	662	655	648	641	635	628
195	699	692	685	678	672	665	658	651	645	638
197	709	702	695	688	682	675	668	661	655	648
199	719	712	705	698	692	685	678	671	665	658

Cm.	51	52	53	54	55	56	57	58	59	60
151	411	404	397	391	384	377	370	364	357	350
153	421	414	407	401	394	387	380	374	367	360
155	431	424	417	411	404	397	390	384	377	370
157	441	434	428	421	414	407	400	394	387	380
159	451	444	438	431	424	417	410	404	397	390
161	461	454	448	441	434	427	420	414	407	400
163	471	464	458	451	444	437	431	424	417	410
165	481	474	468	461	454	447	441	434	427	420
167	491	484	478	471	464	457	451	444	437	430
169	501	494	488	481	474	467	461	454	447	440
171	511	504	498	491	484	477	471	464	457	450
173	521	514	508	501	494	487	481	474	467	460
175	531	524	518	511	504	497	491	484	477	470
177	541	534	528	521	514	507	501	494	487	480
179	551	544	538	531	524	517	511	504	497	490
181	561	554	548	541	534	527	521	514	507	500
183	571	564	558	551	544	537	531	524	517	510
185	581	574	568	561	554	547	541	534	527	520
187	591	584	578	571	564	557	551	544	537	530
189	601	594	588	581	574	567	561	554	547	540
191	611	604	598	591	584	577	571	564	557	550
193	621	614	608	601	594	587	581	574	567	560
195	631	624	618	611	604	597	591	584	577	570
197	641	634	628	621	614	607	601	594	587	580
199	651	644	638	631	624	617	611	604	597	590

TABLE 336.—FACTORS FOR STATURE AND AGE IN MEN.—*Continued.*

Cm.	61	62	63	64	65	66	67	68	69	70
151	343	337	330	323	316	310	303	296	289	283
153	353	347	340	333	326	320	313	306	299	293
155	363	357	350	343	336	330	323	316	309	303
157	373	367	360	353	346	340	333	326	319	313
159	383	377	370	363	356	350	343	336	329	323
161	393	387	380	373	366	360	353	346	339	333
163	403	397	390	383	376	370	363	356	349	343
165	413	407	400	393	386	380	373	366	359	353
167	423	417	410	403	396	390	383	376	369	363
169	434	427	420	413	406	400	393	386	379	373
171	444	437	430	423	416	410	403	396	389	383
173	454	447	440	433	426	420	413	406	399	393
175	464	457	450	443	437	430	423	416	409	403
177	474	467	460	453	447	440	433	426	419	413
179	484	477	470	463	457	450	443	436	429	423
181	494	487	480	473	467	460	453	446	440	433
183	504	497	490	483	477	470	463	456	450	443
185	514	507	500	493	487	480	473	466	460	453
187	524	517	510	503	497	490	483	476	470	463
189	534	527	520	513	507	500	493	486	480	473
191	544	537	530	523	517	510	503	496	490	483
193	554	547	540	533	527	520	513	506	500	493
195	564	557	550	543	537	530	523	516	510	503
197	574	567	560	553	547	540	533	526	520	513
199	584	577	570	563	557	550	543	536	530	523

TABLE 337.—FACTORS FOR STATURE AND AGE IN WOMEN.

	21	22	23	24	25	26	27	28	29	30
151	181	176	172	167	162	158	153	148	144	139
153	185	180	175	171	166	161	157	152	147	143
155	189	184	179	174	170	165	160	156	151	146
157	192	188	183	178	173	169	164	159	155	150
159	196	191	187	182	177	173	168	163	158	154
161	199	195	190	186	181	176	172	167	162	158
163	203	199	194	189	185	180	175	171	166	161
165	207	202	198	193	188	184	179	174	170	165
167	211	206	201	197	192	187	183	178	173	169
169	214	210	205	200	196	191	186	182	177	172
171	218	213	209	204	199	195	190	185	181	176
173	222	217	212	208	203	198	194	189	184	180
175	225	221	216	211	207	202	197	193	188	183
177	229	225	220	215	210	206	201	196	192	187
179	233	228	224	219	214	210	205	200	195	191
181	237	232	227	223	218	213	209	204	199	195
183	240	236	231	226	222	217	212	208	203	198
185	244	239	235	230	225	221	216	211	207	202
187	248	243	238	234	229	224	220	215	210	206
189	251	247	242	237	233	228	223	219	214	209
191	255	250	246	240	236	232	227	222	218	213
193	259	254	249	245	240	235	231	226	221	217
195	262	258	253	248	244	239	234	230	225	220
197	266	262	257	252	247	243	238	233	226	224
199	270	265	261	256	251	247	242	237	232	228

TABLE 337—FACTORS FOR STATURE AND AGE IN WOMEN.—*Continued.*

Cm.	31	32	33	34	35	36	37	38	39	40
151	134	130	125	120	116	111	106	102	97	92
153	138	133	129	124	119	115	110	105	101	96
155	142	137	132	128	123	118	114	109	105	100
157	145	141	136	131	127	122	117	113	108	103
159	149	144	140	135	130	126	121	116	112	107
161	153	148	143	139	134	129	125	120	115	111
163	157	152	147	143	138	133	128	124	119	114
165	160	156	151	146	142	137	132	128	123	118
167	164	159	155	150	145	141	136	131	127	122
169	168	163	158	154	149	144	140	135	130	126
171	171	167	162	157	153	148	143	139	134	129
173	175	170	166	161	156	152	147	142	138	133
175	179	174	169	165	160	155	151	146	141	137
177	182	178	173	168	164	159	154	150	145	140
179	186	181	177	172	167	163	158	153	149	144
181	190	185	180	176	171	166	162	157	152	148
183	194	189	184	180	175	170	165	161	156	151
185	197	193	188	183	179	174	169	165	160	155
187	201	196	192	187	182	178	172	168	164	159
189	205	200	195	191	186	181	177	172	167	163
191	208	204	199	194	190	185	180	176	171	166
193	212	207	203	198	193	189	184	179	175	170
195	216	211	206	202	197	192	188	183	178	174
197	219	215	210	205	201	196	191	187	182	177
199	223	218	214	209	204	200	195	190	186	181

	41	42	43	44	45	46	47	48	49	50
151	88	83	78	74	69	64	60	55	50	46
153	91	87	82	77	73	68	63	59	54	49
155	95	90	86	81	76	72	67	62	58	53
157	99	94	89	85	80	75	71	66	61	57
159	102	98	93	88	84	79	74	70	65	60
161	106	101	97	92	87	83	78	73	69	64
163	110	105	100	96	91	86	82	77	72	68
165	113	109	104	99	95	90	85	81	76	71
167	117	113	108	103	98	94	89	84	80	75
169	121	116	112	107	102	98	93	88	83	79
171	125	120	115	111	106	101	97	92	87	83
173	128	124	119	114	110	105	100	96	91	86
175	132	127	123	118	113	109	104	99	95	90
177	136	131	126	122	117	112	108	103	98	94
179	139	135	130	125	121	116	111	107	102	97
181	143	138	134	129	124	120	115	110	106	101
183	147	142	137	133	128	123	119	114	109	105
185	150	146	141	136	132	127	122	118	113	108
187	154	150	145	140	135	131	126	121	117	112
189	158	153	149	144	139	134	130	125	120	116
191	162	157	152	148	143	138	134	129	124	119
193	165	161	156	151	147	142	137	133	128	123
195	169	164	160	155	150	146	141	136	132	127
197	173	168	163	159	154	149	145	140	135	131
199	176	172	167	162	158	153	148	144	139	134

TABLE 337—FACTORS FOR STATURE AND AGE IN WOMEN.—*Continued.*

Cm.	51	52	53	54	55	56	57	58	59	60
151	41	36	31	27	22	17	13	8	3	−1.2
153	45	40	35	31	26	21	16	12	7	2
155	48	44	39	34	30	25	20	16	11	6
157	52	47	43	38	33	29	24	19	15	10
159	56	51	46	42	37	32	28	23	18	14
161	59	55	50	45	41	36	31	27	22	17
163	63	58	54	49	44	40	35	30	26	21
165	67	62	57	53	48	43	39	34	29	25
167	70	66	61	56	52	47	42	38	33	28
169	74	69	65	60	55	51	46	41	37	32
171	78	73	68	64	59	54	50	45	40	36
173	82	77	72	67	63	58	53	49	44	39
175	85	81	76	71	67	62	57	52	48	43
177	89	84	80	75	70	66	61	56	52	47
179	93	88	83	79	74	69	65	60	55	51
181	96	92	87	82	78	73	68	64	59	54
183	100	95	91	86	81	77	72	67	63	58
185	104	99	94	90	85	80	76	71	66	62
187	107	103	98	93	89	84	79	75	70	65
189	111	106	102	97	92	88	83	78	74	69
191	115	110	105	101	96	91	87	82	77	73
193	119	114	109	104	100	95	90	86	81	76
195	122	118	113	108	104	99	94	89	85	80
197	126	121	117	112	107	103	98	93	89	84
199	130	125	120	116	111	106	102	97	92	88

	61	62	63	64	65	66	67	68	69	70
151	−6	−11	−15	−20	−25	−29	−34	−39	−43	−48
153	−2	− 7	−12	−16	−21	−26	−30	−35	−40	−44
155	1	− 3	− 8	−13	−17	−22	−27	−31	−36	−41
157	5	1	− 4	− 9	−14	−18	−23	−28	−32	−37
159	9	4	− 0	− 5	−10	−15	−19	−24	−29	−33
161	13	8	3	− 1	− 6	−11	−15	−20	−25	−30
163	16	12	7	2	− 2	− 7	−12	−16	−21	−26
165	20	15	11	6	1	− 3	− 8	−13	−17	−22
167	24	19	14	10	5	0	− 4	− 9	−14	−18
169	27	23	18	13	9	4	− 1	− 5	−10	−15
171	31	26	22	17	12	8	3	− 2	− 6	−11
173	35	30	25	21	16	11	7	2	− 3	− 7
175	38	34	29	24	20	15	10	6	1	− 4
177	42	37	33	28	23	19	14	9	5	0
179	46	41	37	32	27	22	18	13	8	4
181	50	45	40	36	31	26	22	17	12	8
183	53	49	44	39	35	30	25	21	16	11
185	57	52	48	43	38	34	29	24	20	15
187	61	56	51	47	42	37	33	28	23	19
189	64	60	55	50	46	41	36	32	27	22
191	68	63	59	54	49	45	40	35	31	26
193	72	67	62	58	53	48	44	39	34	30
195	75	71	66	61	57	52	47	43	38	33
197	79	74	70	65	60	56	51	46	42	37
199	83	78	74	69	64	59	55	50	45	41

TABLE 338.—FACTOR FOR BODY WEIGHT.

	Men.		Women.			Men.		Women.	
	0.0	0.5	0.0	0.5		0.0	0.5	0.0	0.5
Kg.					Kg.				
25	410	417	894	899	75	1098	1105	1372	1377
26	424	431	904	909	76	1112	1118	1382	1387
27	438	445	913	918	77	1125	1132	1391	1396
28	452	458	923	928	78	1139	1146	1401	1406
29	465	472	932	937	79	1153	1160	1411	1415
30	479	486	942	947	80	1167	1173	1420	1425
31	493	500	952	956	81	1180	1187	1430	1435
32	507	513	961	966	82	1194	1201	1439	1444
33	520	527	971	975	83	1208	1215	1449	1454
34	534	541	980	985	84	1222	1228	1458	1463
35	548	555	990	995	85	1235	1242	1468	1473
36	562	568	999	1004	86	1249	1256	1478	1482
37	575	582	1009	1014	87	1263	1270	1487	1492
38	589	596	1019	1023	88	1277	1283	1497	1501
39	603	610	1028	1033	89	1290	1297	1506	1511
40	617	623	1038	1042	90	1304	1311	1516	1521
41	630	637	1047	1052	91	1318	1325	1525	1530
42	644	651	1057	1062	92	1332	1338	1535	1540
43	658	665	1066	1071	93	1345	1352	1544	1549
44	672	678	1076	1081	94	1359	1366	1554	1559
45	685	692	1085	1090	95	1373	1380	1564	1568
46	699	706	1095	1100	96	1387	1394	1573	1578
47	713	720	1105	1109	97	1400	1407	1583	1588
48	727	733	1114	1119	98	1414	1421	1592	1597
49	740	747	1124	1128	99	1428	1435	1602	1607
50	754	761	1133	1138	100	1442	1449	1611	1616
51	768	775	1143	1148	101	1455	1462	1621	1626
52	782	788	1152	1157	102	1469	1476	1631	1635
53	795	802	1162	1167	103	1483	1490	1640	1645
54	809	816	1172	1176	104	1497	1504	1650	1654
55	823	830	1181	1186	105	1510	1517	1659	1664
56	837	843	1191	1195	106	1524	1531	1669	1674
57	850	857	1200	1205	107	1538	1545	1678	1683
58	864	871	1210	1215	108	1552	1559	1688	1693
59	878	885	1219	1224	109	1565	1572	1698	1702
60	892	898	1229	1234	110	1579	1586	1707	1712
61	905	912	1238	1243	111	1593	1600	1717	1721
62	919	926	1248	1253	112	1607	1614	1726	1731
63	933	940	1258	1262	113	1620	1627	1736	1741
64	947	953	1267	1272	114	1634	1641	1745	1750
65	960	967	1277	1281	115	1648	1655	1755	1760
66	974	981	1286	1291	116	1662	1669	1764	1769
67	988	995	1296	1301	117	1675	1682	1774	1779
68	1002	1008	1305	1310	118	1689	1696	1784	1788
69	1015	1022	1315	1320	119	1703	1710	1793	1798
70	1029	1036	1325	1329	120	1717	1724	1803	1807
71	1043	1050	1334	1339	121	1730	1737	1812	1817
72	1057	1063	1344	1348	122	1744	1751	1822	1827
73	1070	1077	1353	1358	123	1758	1765	1831	1836
74	1084	1091	1363	1368	124	1772	1779	1841	1846

TABLE 339.—HEIGHTS AND WEIGHTS OF MEN AND WOMEN OF FIFTEEN OR MORE YEARS OF AGE (WITH CLOTHES).[1]

MEN.

Age.	Feet and inches with shoes.																	
	5–0	5–1	5–2	5–3	5–4	5–5	5–6	5–7	5–8	5–9	5–10	5–11	6–0	6–1	6–2	6–3	6–4	6–5
16 . .	109	111	114	117	120	124	128	132	136	140	144	149	154	159	164	169	174	179
18 . .	113	115	118	121	124	128	132	136	140	144	148	153	158	163	168	173	178	183
20 . .	117	119	122	125	128	132	136	140	144	148	152	156	161	166	171	176	181	186
22 . .	119	121	124	127	131	135	139	142	146	150	154	158	163	168	173	178	183	188
24 . .	121	123	126	129	133	137	141	144	148	152	156	160	165	171	177	182	187	192
26 . .	123	125	127	130	134	138	142	146	150	154	158	163	168	174	180	186	191	196
28 . .	125	127	129	132	135	139	143	147	151	155	159	164	170	176	182	188	193	198
30 . .	126	128	130	133	136	140	144	148	152	156	161	166	172	178	184	190	196	201
32 . .	127	129	131	134	137	141	145	149	154	158	163	168	174	180	186	192	198	203
34 . .	128	130	132	135	138	142	146	150	155	160	165	170	176	182	188	194	200	206
36 . .	129	131	133	136	139	143	147	151	156	161	166	171	177	183	190	196	202	208
38 . .	130	132	134	137	140	144	148	152	157	162	167	173	179	185	192	198	204	210
40 . .	131	133	135	138	141	145	149	153	158	163	168	174	180	186	193	200	206	212
42 . .	132	134	136	139	142	146	150	154	159	164	169	175	181	187	194	201	208	214
44 . .	133	135	137	140	143	147	151	155	160	165	170	176	182	188	195	202	209	215
46 . .	134	136	138	141	144	148	152	156	161	166	171	177	183	189	196	203	210	216
48 . .	134	136	138	141	144	148	152	156	161	166	171	177	183	190	197	204	211	217
50 . .	134	136	138	141	144	148	152	156	161	166	171	177	183	190	197	204	211	217
52 . .	135	137	139	142	145	149	153	157	162	167	172	178	184	191	198	205	212	218
54 . .	135	137	139	142	145	149	153	158	163	168	173	178	184	191	198	205	212	219

Allow 1 inch for shoes and 10 pounds for clothes.

WOMEN.

Age.	Feet and inches with shoes.																
	4–8	4–9	4–10	4–11	5–0	5–1	5–2	5–3	5–4	5–5	5–6	5–7	5–8	5–9	5–10	5–11	6–0
16 . . .	102	104	106	108	109	111	114	117	120	124	128	132	136	139	143	148	153
18 . . .	104	106	108	110	112	114	117	120	123	126	130	134	138	141	145	150	155
20 . . .	106	108	110	112	114	116	119	122	125	128	132	136	140	143	147	151	156
22 . . .	107	109	111	113	115	117	120	123	126	129	133	137	141	145	149	153	157
24 . . .	109	111	113	115	117	119	121	124	127	130	134	138	142	146	150	154	158
26 . . .	110	112	114	116	118	120	122	125	128	131	135	139	143	147	151	155	159
28 . . .	111	113	115	117	119	121	123	126	130	133	137	141	145	149	153	156	160
30 . . .	112	114	116	118	120	122	124	127	131	134	138	142	146	150	154	157	161
32 . . .	113	115	117	119	121	123	125	128	132	136	140	144	148	152	155	158	162
34 . . .	115	117	119	121	123	125	127	130	134	138	142	146	150	154	157	160	163
36 . . .	116	118	120	122	124	126	128	131	135	139	143	147	151	155	158	161	164
38 . . .	117	119	121	123	125	127	130	133	137	141	145	149	153	157	160	163	166
40 . . .	119	121	123	125	127	129	132	135	138	142	146	150	154	158	161	164	167
42 . . .	120	122	124	126	128	130	133	136	139	143	147	151	155	159	162	166	169
44 . . .	122	124	126	128	130	132	135	138	141	145	149	153	157	161	164	168	171
46 . . .	123	125	127	129	131	133	136	139	142	146	150	154	158	162	165	169	172
48 . . .	124	126	128	130	132	134	137	140	143	147	152	156	160	164	167	171	174
50 . . .	125	127	129	131	133	135	138	141	144	148	152	156	161	165	169	173	176
52 . . .	125	127	129	131	133	135	138	141	144	148	152	157	162	166	170	174	177
54 . . .	125	127	129	131	133	135	138	141	144	148	153	158	163	167	171	174	177

Allow 1½ inches for shoes and 6 pounds for clothes.

[1] Association of Life Insurance Directors and Actuarial Society of America, New York, 1912, pp. 38 and 67.

TABLE 340.—HEIGHTS AND WEIGHTS OF CHILDREN BETWEEN ONE AND FOUR YEARS OF AGE (WITHOUT CLOTHES).[1]

5602 boys			4821 girls	
Height, inches.	Weight, pounds.	Age, months.	Height, inches.	Weight, pounds.
26.5	18.0	6	25.9	16.8
27.3	19.1	7	26.5	17.4
27.6	19.8	8	27.0	18.3
28.1	20.4	9	27.6	19.1
28.5	20.9	10	27.9	19.5
29.0	21.4	11	28.4	20.1
29.4	21.9	12	28.9	20.8
29.9	22.9	13	29.4	21.0
30.3	23.0	14	29.5	21.6
30.8	23.6	15	30.1	21.9
31.1	24.1	16	30.5	22.6
31.4	24.5	17	30.8	22.9
31.8	24.6	18	31.1	23.4
32.3	25.5	19	31.5	23.8
32.6	25.8	20	32.0	24.1
32.9	25.8	21	32.3	24.8
33.3	26.9	22	32.6	25.3
33.6	27.0	23	32.9	25.6
33.8	27.1	24	33.4	26.4
34.0	27.9	25	33.8	26.9
34.1	28.3	26	33.9	27.3
34.8	29.0	27	33.9	27.3
35.1	29.1	28	34.6	27.8
35.4	29.3	29	34.8	27.8
35.4	29.5	30	34.9	28.3
35.5	30.5	31	35.1	28.8
36.0	30.6	32	35.4	29.0
36.1	30.6	33	35.6	29.1
36.5	31.1	34	36.5	30.1
36.8	31.9	35	36.5	30.3
37.1	32.3	36	36.8	30.5
37.4	32.3	37	36.8	30.8
37.5	32.4	38	37.0	31.0
37.9	33.1	39	37.3	31.6
38.5	33.5	40	37.5	32.0
38.6	33.6	41	37.8	32.3
38.6	33.8	42	38.0	32.5
38.8	33.8	43	38.3	32.8
38.9	34.3	44	38.5	33.0
39.0	34.5	45	38.5	33.5
39.0	34.8	46	38.8	33.5
39.3	35.8	47	38.9	33.5
39.5	35.9	48	39.0	33.8

[1] Crum, F. S.: Quarterly Publication of the American Statistical Association, Boston, September, 1916, N. S., No. 115, **15**, 332.

TABLE 341.—HEIGHTS AND WEIGHTS OF BOYS BETWEEN FIVE TO FOURTEEN YEARS (WITHOUT CLOTHES).[1]

BOYS

	Weight in Pounds	Without Clothes
	Height in Feet and Inches	Without Shoes

AGE	3-3	3-4	3-5	3-6	3-7	3-8	3-9	3-10	3-11	4	4-1	4-2	4-3	4-4	4-5	4-6	4-7	4-8	4-9	4-10	4-11	5	5-1	5-2	5-3	5-4	5-5	5-6	5-7	5-8	5-9	5-10	5-11	6	6-1
5	35	38	39	41	42	46																													
6		38	39	41	42	44	46	48																											
7					42	43	46	48	49	54																									
8							45	46	50	53	54	57	59																						
9									50	53	55	56	60	62	65																			
10									55	56	56	60	62	65	69	69	71																	
11												61	61	65	69	71	77	77	76															
12												63	67	70	75	78	79	84	84	85														
13													67	71	75	78	80	85	90	91	96	99	99	100										
14													67	71	76	79	92	98	90	94	97	103	105	114	122									
15																79	93	97	91	96	99	106	112	116	119	121	129	133						
16																					96	99	104	115	120	122	125	129	133	134	136			
17																						104	110	117	122	125	128	130	136	140	140			
18																							115	120	120	126	131	136	139	143	140			
19																								120	126	129	134	136	139	144	146	149		
20																									125	130	132	134	139	145	148	154	155	

TABLE 342.—HEIGHTS AND WEIGHTS OF GIRLS BETWEEN FIVE TO FOURTEEN YEARS (WITHOUT CLOTHES).[1]

GIRLS

	Weight in Pounds	Without Clothes
	Height in Feet and Inches	Without Shoes

AGE	3-3	3-4	3-5	3-6	3-7	3-8	3-9	3-10	3-11	4	4-1	4-2	4-3	4-4	4-5	4-6	4-7	4-8	4-9	4-10	4-11	5	5-1	5-2	5-3	5-4	5-5	5-6	5-7	5-8	5-9	5-10	5-11	6	6-1
5		34	37	39	41	43	45																												
6			35	37	39	41	43	45	49																										
7					39	42	44	45	47	50																									
8							42	45	47	49	51	53	56																						
9										49	51	53	56	59	63																			
10											54	57	58	62	64	69																		
11													60	62	63	68	70	73																
12													63	66	69	71	75	78	83	88	94													
13														65	65	73	76	80	86	89	94	99	104											
14																	76	83	86	93	98	100	104	107	112	114								
15																		89	95	100	102	106	109	110	113	119								
16																			100	104	109	111	116	116	121									
17																				109	109	110	116	117	125									
18																				103	106	107	112	114	120									
19																				99	106	111	113	119	120									
20																				99	111	114	114	118	125									

[1] Wood, T. D.: The ninth yearbook of the National Society for the Study of Education, Part I, Health and Education, Chicago, 1910, p. 34.

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18	188, 541
19	712
22	580
30	110
34	731
36	712
38	417
44	742
46	712
56	742
68	742
75	742
90	897
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206	742
208	433
209	742
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252	373, 374
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306	869, 871
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341	806
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348	714, 778, 806
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353	742
354	189
355	793, 794
356	416
358	712
359	698
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404	742
406	159
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543	742
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552	545, 582
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560	582
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608	869, 871
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4634	742
4652	706
4664	866, 869, 871
4665	382
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4858	866, 867, 869, 871
4859	866, 869, 871
4862	704
4873	742
4882	732
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4941	866, 869, 871
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5029	697
5036	875
5045	52
5049	827
5063	866, 869, 871
5079	697, 733
5095	147
5105	752
5110	742
5114	697
5121	653
5122	869, 871
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5143	892
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5152	697
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5181	586
5186	793
5188	866, 869, 871
5200	742
5229	697
5231	742
5250	793
5257	863, 865, 866, 869, 871
5277	586
5288	742
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5348	736
5384	697
5385	803
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5396	697
5397	697
5398	697
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5582	586	5823	537	6050	586
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