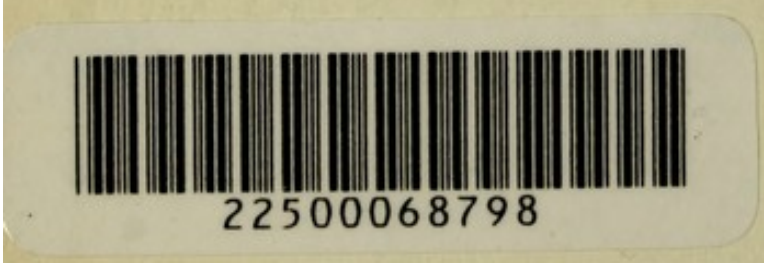
New aspects of diabetes : pathology and treatment lectures delivered at the New York Post-Graduate Medical School and published by their authority / by Carl von Noorden.

NEW ASPECTS OF DIABETES

VON NOORDEN



NEW ASPECTS OF DIABETES

PATHOLOGY AND TREATMENT

BY

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LECTURES DELIVERED AT THE NEW YORK POST-GRADUATE MEDICAL SCHOOL AND PUBLISHED BY THEIR AUTHORITY

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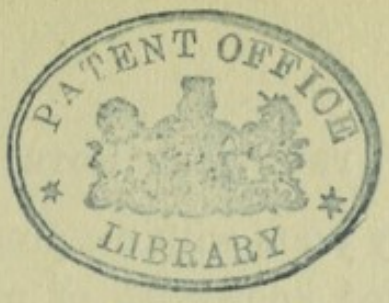

PREFATORY NOTE

One of the leading features of internal medicine, as taught and practiced in Germany at the present time, is the attention given to problems of digestion and metabolism. The advances in theoretical chemistry and their application to the studies in the physiology and pathology of nutrition have opened up most promising perspectives into the correlations of organs of the human body and have furthermore stimulated in Germany, in a most fruitful way, that art of healing which is based on scientific principles.

Our country has followed Germany very closely in the last ten years in this direction and indeed has taken an advanced independent attitude on many fundamental points. The general interest in these matters is shown by the valuable researches made upon foods which the Department of Agriculture of our government has carried out and by the interest demonstrated by our universities, scientific laboratories and the general public. The medical profession in general practice, however, has not as yet taken that interest in questions of nutrition which these problems deserve, but the interest is growing rapidly and the demands for teaching on these lines has been felt more and more in medical colleges and especially in post-graduate medical schools.

Prof. Carl von Noorden has been identified for

more than twenty years with the progress of the theoretical and applied knowledge of metabolism and is known to the American as well as to the European physician. It is therefore a source of great pleasure to the board of directors and to the faculty of the New York Post-Graduate Medical School to have had him deliver a series of lectures on such problems before the matriculates and guests of their school. This publication covers those lectures delivered in October, 1912.

It will be highly appreciated, we are sure, that these lectures have become available in this form to the progressive student of medicine in our country.

LUDWIG KAST.

New York City,
November 1, 1912.

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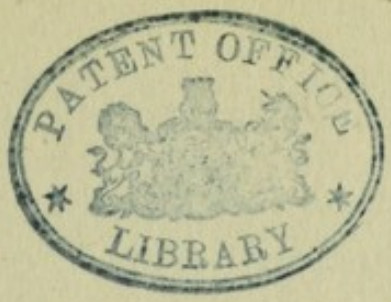
New Aspects of Diabetes

INTRODUCTION

Some years ago, I had the honor to deliver here in New York some lectures on the pathological chemistry and treatment of diabetes mellitus. I intend to speak once more upon the same subjects, since it has been represented to me that by so doing I should be meeting the wishes of a number of physicians in this country, especially as diabetes is such a many-sided and vast field, that a couple of lectures given in 1905 can scarcely be deemed sufficient to cover the whole ground. I must, however, limit myself to a few of the more interesting questions of pathological chemistry and to some of the aspects of the therapy of the disease. That which several years ago could lay claim to being new, interesting and at the same time of practical importance is already a part of the general medical knowledge. It is not necessary for me to repeat to a learned circle of experienced practitioners the elementary principles of diabetes. However during the last years many new questions concerning diabetes have been worked out; some, which seven years ago were of passing interest, have to-day entered into the arena of theoretical importance and are becoming day by day more valuable for the practical physician. Many of

the advances in the knowledge of the disease made during recent years have been carried out in my clinic and my own personal experience during the last seven years has consisted of a study of the course of treatment of more than 2000 cases of diabetes mellitus in my clinic and sanatorium. This extension of personal investigations together with the certainty of some of the results and the general progress made in all countries in a scientific study of this condition warrants me once again in addressing you upon diabetes.

We may turn first to some theoretical questions. However, I will restrict the discussion to those problems which have an immediate bearing upon the treatment of diabetes and which it is necessary to understand if the patient shall be well treated. Some of these matters were referred to in my previous lectures, but none of them could be explained with such certainty as they can to-day, and in many of the most important ones the answers are quite otherwise than what was expected seven years ago.



I. THE SOURCE OF SUGAR

A. Carbohydrates

I need only make a few remarks on carbohydrates. We know that all pure carbohydrates and the chemically related substances, present in human food, play an important part as sources of sugar. The rarer types, such as pentose and heptose, scarcely call for consideration, as they exert only a slight influence on the formation of sugar. It is very probable that in healthy men living under the usual conditions of nutrition, nearly all the absorbed carbohydrates reappear in the liver as deposits of glycogen, and that only slight traces immediately pass through the liver and reach the general circulation. The latter condition occurs in healthy men only when excessive quantities of sugar are taken and after absorption make too great demands upon rapid assimilation and fixation by the liver. The subsequent overflooding of the blood with sugar is a step towards the condition designated "alimentary glycosuria." We know that many diseases predispose to alimentary glycosuria — a knowledge that is of diagnostic as well as of theoretical importance. I will refer to this later on.

The matter is a different one when it concerns the diabetic patient. One of the most important — perhaps the predominant — of the disturbance of his me-

tabolism, lies in the fact that the hepatic cell is unable to fix the carbohydrate. This defective function varies largely in different diabetics, and in one and the same case is not always maintained at the same level. The disturbance does probably not consist of an inability to form glycogen, but owing to a tendency to decompose the just formed glycogen too rapidly, so that the excess appears in the blood as glucose. The decomposition extends more rapidly and completely as the diabetes progresses and in the same degree increases the danger of marked hyperglycaemia and glycosuria. The carbohydrates therefore constitute a source of sugar for the diabetic patient as for the healthy individual; but the tissues of the former have lost the power of storing the materials in depots and taking them out of store as demands arise. Many points of interest are bound up with this fact, and I must put them before you in their proper relation at a later stage.

B. Proteins

The question concerning the why and wherefore of protein material as a source of sugar is not so well developed.

a. The Carbohydrate Group of the Albumin Molecule

That proteins do yield sugar, however, is quite certain and it is quite clear that the majority of proteins contain a carbohydrate group. This group is split off during digestion; the cleavage occurs during

the action of the pepsin-hydrochloric acid, for the so-called albumose does not contain carbohydrates. The separated carbohydrate behaves just the same as a native carbohydrate. It is absorbed in due course and is carried to the liver. It is a remarkable fact that certain albumins which are particularly rich in carbohydrate groups, e. g. egg albumins, do not especially affect the sugar formation; the influence is relatively large when the albumin is taken raw but very slight when it is first coagulated by heat. On the other hand, some proteins act as marked excitants of the sugar production, such as muscle albumin (which contains very little carbohydrate), and casein, which hardly contains any carbohydrate.

The first question we may ask is this: How is it, that the carbohydrate group of the albumin does not excite the sugar production so much as does the native carbohydrate? The answer lies near at hand; all native carbohydrates are absorbed quickly and so pass rapidly in large quantities into the liver. On the other hand, the digestion of the protein and the separation of its carbohydrate group requires time and absorption is slow, therefore the amount of carbohydrate entering the liver at the same time, is only small, and does not, under ordinary conditions, call for more than a slight display of energy.

b. The Aminoacids

The second constituent of the protein molecule which exerts a doubtless influence upon the sugar formation

is the aminoacid group; this makes up about 40 per cent. of the total protein molecule. If a diabetic patient, or a depancreatized dog, or a dog in which a maximum phloridzin diabetes is induced, be fed upon aminoacids, the glycosuria increases. The matter is most clear in connection with phloridzin diabetes. Equal quantities of nitrogen cause an identical increase in the glycosuria, whether isolated aminoacids such as alanin or original protein be employed. We have acquired this knowledge through the careful, laborious and painstaking investigations of your own countryman, Graham Lusk. Although it does not follow, that the aminoacids are definite and direct sources of sugar, the same result ought to follow, if these substances in ever the same proportion incite the formation of sugar, although they themselves are not the material out of which the sugar is built up. I am of the opinion that we to-day have no definite certainty that the aminoacids must be regarded as primary and consistent sugar formers, and I believe that one would stop further progress if we neglected certain difficulties, which arise on our way towards clearing these questions.

c. The Influence of Various Proteins

One of our difficulties is the extraordinary differences manifested by diabetics to vegetable and animal albumins. If in a case of severe diabetes we order a dietary which is poor in carbohydrates and of low albumin content, and at the same time suffices to exclude

glycosuria, to which we then add 100 grams of vegetable albumin, such as that useful preparation, glidin (Klopfer) the urine remains free from sugar, or almost so. If, however, we add a similar quantity of a meat albumin instead of a vegetable one, then a marked glycosuria appears and persists even after the meat albumin has been stopped.

The following table furnishes an example:

Day	Food	Additional Food	Sugar in 24 hours.
1	100 g meat, 5 eggs, 4 yolk of eggs.— 300 g thick cream. — green vegetables. — Gluten-bread.— Butter.	—	0
2	"	—	0
3	"	—	0
4	"	100 g Glidin	0
5	"	"	0
6	"	"	0
7	"	400 g Beef (raw weight)	5.6g.
8	"	"	20.8
9	"	"	26.7
10	"	0	7.2
11	"	0	2.2
12	"	0	0

I chose this example because it shows the point extremely well. I could mention some dozen of others, however, which would mirror the result. Not all cases of diabetes, however, serve to demonstrate this fact. In the slighter forms, the influence of meat albumins is not great and it is difficult to demonstrate the reaction of the patient to different forms of al-

bumin. It may be necessary to add more albumin than the patient can actually take before the glycosuric indication is reached. On the other hand, it is not always possible to obtain such results in severe cases; these patients are most susceptible to a large quantity of albumin. Once a medium amount of albumin is exceeded, say 70-80 grams, the glycosuria increases, no matter what the type of albumin is. The most favorable cases are those — as I have already mentioned — which are just under the borderline of "severe diabetes." For these, my experience has led me to formulate my views in the following manner:—

Meat is dealt with least well; namely, the glycosuria increases to the greatest extent.

Next comes casein.

Then follows egg albumin.

Finally, there is vegetable albumin; of this type *glidin* gives the best results.

As it appeared possible that the unfavorable influence of meat might be due to the presence of "extractives," we investigated the effect of meat which had been cooked so that all its extractives had passed into the water in which it was prepared. We also tried fish foods. It is known that the flesh of large and old fish is poorer in extractives than that of mammals; in young and small fish the differences are not so marked. As you know, fish has long been recognized as being specially useful to diabetics. Our clinical experience has shown that meat and fish, deprived of extractives by artificial means, or originally

poor in extractives, induce a little less output of sugar than extractive-rich foods prepared in the usual way. The differences are not great, however, except in the case of raw meats. We must admit that the extractives do exert some slight influence on the sugar output, but the extent is not sufficient to account for the differences on the effect of animal and vegetable proteins.

When we extend the inquiry further, we are not yet able to speak definitely as to the effect of the varying *quantities* of aminoacids in the animal and vegetable albumins. Here most probably the *type* of the aminoacids comes into play, for each variety of protein has its own quota of specific aminoacids. I believe that this opens a field for numerous and important investigations, whose results will be of great benefit in the treatment of diabetes.

d. The Specific Dynamic Influence of Proteins

For the moment I may advance the proposition that the influence of the protein molecule upon glycosuria does not depend only upon the fact that it contains certain atomic groups which may be utilized for the formation of sugar, but that certain fundaments of protein, or in other words, certain peptides or polypeptides, act upon the liver as powerful inciters to the formation of sugar. I refer here to an excitant or irritant that is related to, or, perhaps identical with the factor which M. Rubner some time ago designated as the specific dynamic influence of an excessive protein

dietary. Of course, to this can be opposed that increased glycosuria may follow the intake of a quantity of albumin far too small to be called excessive. This objection cannot be sustained, for Rubner's figures were derived from observations upon healthy men and animals. In severe diabetes, we have to do with sick men, in whom the energy exchange is raised, as earlier writers supposed and as the interesting works of Benedict, Falta and Joslin have confirmed. We may assume that the factors responsible for the control of the energy exchange are more liable in the case of diabetics than in healthy men, so that influences which are too slight to occasion any caloric production in normal individuals exert an effect upon those suffering from diabetes. Such an occurrence is not an isolated one. It is the same in fever and in Basedow's disease. We know that the general caloric production is increased in these conditions and it is an old observation that large quantities of albumin, and especially meat albumin, are badly borne at such times; in fever the temperature goes up and the pulse becomes more rapid, while the general disturbances such as headache, etc., are more pronounced; in Basedow's disease the sense of heat and the formation of sweat is more marked, the heart is more excited and the tremors increase; the production of calories is also apparently more excessive, for I have observed that it is more difficult to obtain a rise in body weight when much meat is given than when the meat content of the dietary is lowered. The similarity of the alterations

in the metabolism during fever, Basedow's disease and diabetes may be pushed even a little further. In all the three diseases when the caloric production is raised, hyperglycæmia follows; in fact, only seldom and if large quantities of sugar are given, a glycosuria results, although the never failing hyperglycæmia suffices to show that in these three diseases the qualitative and quantitative formations of sugar are disturbed to a certain degree.

We have in these three diseases a remarkable trio of symptoms:

1. Raised production of calories,

2. Hypersensibility to protein, especially meat protein,

3. Hyperglycæmia or glycosuria.

These coincidences are surely more than accidental. How are they connected? We cannot give a definite answer, but we can approach pretty near to the truth.

I take it for granted that the same cause which in these three conditions induces the endogenous increase of the caloric production is also responsible for the irritability of the sugar forming processes in the liver. In fever and in Basedow's disease the irritation effect is slight. However, hyperglycæmia always accompanies the raised caloric formation while with a stronger stimulus, glycosuria appears. In severe diabetes, where the irritability of the sugar manufacture is already intensified through other causes, the additional irritation will be disproportionally stronger.

How is it that this stimulus follows a protein in-

take? How is it that fat does not induce a similar result? I may here call to memory the physiological fact that all foods cause an increased caloric output; however, the amount is most marked after proteins are taken. The oxygen requirements rise to 20-25 per cent. above those during fasting; the rise following the intake of fat and carbohydrate is not so great. We ascribe the call for more oxygen to the needs of digestive processes, which in the wider sense of the term, must include hepatic processes also. The energy put forth by the liver during the assimilation of carbohydrate is very slight; with that of fat the liver has practically nothing to do, the treatment of the absorbed fat being chiefly a deposition process. It is the protein alone which is associated with energy requirements and active work on the part of the liver and I regard the cleavage of the protein therefore as a cause of the considerable physiological increase of the oxidation changes and at the same time as a stimulus for the manufacture of sugar. When this manufacture by itself is abnormally high, as in diabetes, increase of the glycosuria results.

e. The Quotient D÷N

There still remains for discussion another important question of the relation between the protein and the sugar formation. One has tried to learn from the metabolism of the diabetic, how much sugar is formed from the albumin. The question is an old one.

It has been shown long ago by v. Mering and Minkowski in their experimental pancreas diabetes, that in diabetic dogs when the carbohydrate stores are entirely used up, the relation between the urinary sugar and the urinary nitrogen — the so-called quotient D÷N remains constant whether the animal is allowed to fast or is fed with albuminous food. The quotient keeps very close to 2.8:1. Minkowski concluded from this, that this quotient showed the relative production of sugar from albumin, despite the theoretical chemical calculation that more sugar could be yielded, namely $4\frac{1}{2}$, or five parts of dextrose to one of nitrogen. The more detailed investigations upon phloridzin diabetes, for which we owe much to Graham Lusk, give the higher and more constant value of 3.6:1. In human diabetes, the quotient is less than that of Lusk in the greater number of cases. All this and the extraordinary constancy of the values in animal experiments give to this finding a marked biological significance. It is another question whether these figures have been rightly interpreted and whether they yield any indication as to the manner in which the body utilizes albumin for the formation of sugar. It would have to be assumed that after removal of the pancreas or administration of maximal doses of phloridzin the body ceases to oxidize sugar, or that the tissues have lost the capacity to utilize sugar at all, and that all the sugar which is produced reappears in the urine. This is in harmony with the views as to the type of disturbance in diabetes which I set forth in my New

York lectures some seven years ago. It has been applicable to diabetes in man also. There is however a great difficulty in bringing phloridzin diabetes into line with the other conditions and the more we learn of phloridzin diabetes the more difficult it is. To-day there seems but little doubt that phloridzin glycosuria is due to the toxic effects of the phloridzin on the renal epithelium and therefore is quite of a different origin from the pure diabetic glycosuria. There is not the slightest evidence for the assumption, that in phloridzin poisoning there is a defect in the oxidation of sugar. The objection may be advanced, that in phloridzin intoxication the sugar is so rapidly and completely removed from the blood by the kidney that none remains for the use of the tissues and that the cells are driven to draw upon the fatty substances for their demands for nitrogen-free material. This criticism would be difficult to sustain, however, for investigations have been carried out in my clinic which show definitely that the tissues, and the muscles especially, in phloridzin diabetes do not utilize and oxidize any material other than carbohydrates. Some earlier observations made in my clinic proved the same to be the case in pancreatic diabetes. I merely mention these interesting and important experiments just now; I will return to them later on.

If the tissues, in spite of the diabetic process, continue to oxidize carbohydrates, then the quotient D–÷–N does not give any reliable indication as to the conditions under which sugar is formed from albumin. It

rather shows how much sugar *remains* in proportion to the decomposed albumin after the organism has covered its total sugar requirements from the various sources (albumin and fat). It is remarkable that this quotient exhibits a certain constancy in maximal pancreas diabetes, maximal phloridzin diabetes and in human diabetes on typical diets, which is characteristic for each of the conditions. We are quite in the dark as to the principle which underlies this constancy but there is one statement we can make with safety and that is, that the proportion of the formation of sugar from albumin is not the dominant feature.

C. The Fats

There are no various views as to the formation of sugar from glycerine, which is a component of fatty substances. But the part played by fatty acids has evoked considerable discussion. Two main issues are here involved. The whole question is so important, not only from the standpoint of diabetes, but equally from that of biological chemistry in general, that we must review it at length.

a. The Circulation of Fat

We are now in position to state more confidently than heretofore, that the nitrogen-free material necessary for muscle metabolism must be supplied in the form of sugar, or sugar-free derivatives (lactic acid?), and that the liver is the place where the muscle foods

are prepared. The decomposition of albumin and the separation of its carbohydrate molecule is a matter which can be carried out most probably by any of the cells of the body. The cleavage of fat, however — if we exclude bacterial action — is an exclusive function of the liver. At least we are not aware of any evidence which points to the collaboration of other organs.

The liver receives the fat — which it has to work up — in part directly from the food, and in part — indeed preferably — from the large fat deposits of the body in which the fat is deposited with astonishing rapidity as soon as it passes from the thoracic duct into the blood stream. We do not know whether the fat which results from an excess of carbohydrate food is manufactured in the fat depots themselves. It seems probable that the liver, when its glycogen content is too abundant, builds up fat and that this fat is carried to the fat stores. On the other hand, the poverty of the liver cells in glycogen may indicate the time and season for the commencement of the manufacture of sugar out of fat. Then will follow a vigorous re-transport of fat from the fat stores to the liver cells. During inanition the blood becomes richer in fats, because the individual is living on his own body fat and it is necessary to transfer this to the liver for the process of manufacture. If in a starving animal great demands are made upon the liver for the formation of sugar, as, for instance, in phloridzin diabetes, then the fat transport is increased. Then

follows a fatty infiltration of the liver from the pressure of streams of incoming material from all quarters. When the phloridzin administration is stopped and large amounts of carbohydrates are given, then the fat returns again rapidly to the fat depots. As Rosenfeld has shown, glycogen is the antithesis of fat and fat the enemy of glycogen. In severe cases of diabetes there is visible evidence of the transport of fat in the blood to the liver in the lipaemia which often occurs; this means, that all the possible reserves are drawn upon in order to avert the extreme and dangerous stages of the diabetic process. These and many other facts in physiology and pathology appear clear and intelligible in the light of the theory advanced. I believe that the conditions may be more easily comprehended if we consider the problem from the standpoint of metabolism in starvation. Here the tissues are limited to the using up of their own substance for the production of the necessary calories. At the commencement of the hunger period there is a small quantity of glycogen available, partly in the liver and partly in the muscles. This store is soon exhausted and after about two days of hunger the body is practically devoid of glycogen. In such a case, protein and fat are the only material available for oxidation. An adult healthy man utilizes about 70 grams albumin per day; this yields about 350 calories; the 70 grams of albumin will yield at the utmost 55 grams of sugar. The starving adult man requires many more calories, at least 2000-2500 according to his size and work.

After the protein has been made to yield its calories, there still remains about 1650-2250 calories to provide for. These have to be obtained through the oxidation of fat; 180-240 grams of fat will supply the necessary calories. In support of the statement that fat is the substance used at this time and that no other material except a small amount of proteid is pressed into service, and that these bodies are carried to the end stages of oxidation, we find that the so-called "respiratory quotient" falls to 730-750, whereas with the exclusive oxidation of carbohydrates the value is 1000 and with a mixture of albumin, fat and carbohydrate, the figures vary from 800-850.

b. Does Muscle Tissue Oxidize Fat?

Up to this point there is complete unanimity on the part of all physiologists and pathologists. But from here opinions differ.

Some hold the opinion that when circumstances arise in which carbohydrates no longer are at the disposal of the body, the cells, and especially the muscle cells, alter their usual way of living and oxidize the fat brought to them by the blood stream at once, as in ordinary conditions of nutrition they oxidize predominantly or exclusively carbohydrates. This view is very difficult to maintain because the relatively simple chemistry of muscle tissue does not furnish a tittle of evidence as to type of decomposition which is undergone by fat, in the muscle cells. That there is a complete oxidation to CO_2 and H_2O is out of question,

but we could expect to find intermediary bodies formed during the fat cleavage. About this there is practically nothing known. We only know that there is an oxidation of carbohydrates and there is some evidence that muscle tissue plays a part in the attacks upon the foundation stones of the albumin molecule. O. Nasse advanced those views some forty years ago and they still form the basis of muscle chemistry to this very day. All attempts made by chemists to get a grasp of the action of the muscle cell upon fat molecules have failed signally. Nevertheless the teaching that during a period of carbohydrate deficiency the muscles oxidize fatty materials, has been clung to most stubbornly and it has exerted a powerful, and to me a highly unfavorable influence upon the progress of our knowledge of diabetic processes.

The second hypothesis is that sugar serves the muscle cell as food only, and what is more, also then if the food contains hardly any carbohydrate and the glycogen stores are used up. In this category must be placed every individual who consumes protein and fat alone and this is the ordinary diet of many tribes of the far North and of all beasts of prey. The individual undergoing starvation comes under the same heading; while diabetics on restricted dietaries and those suffering from severe diabetes who excrete more sugar than the amount represented by the intake of carbohydrates must be similarly classed.

O. Nasse in his time put forward the view, that when carbohydrates were absent the muscle cell con-

tinued to burn sugar and sugar only, but he did not develop the hypothesis very fully, and it did not therefore make any lasting impression upon physiologists. I. Seegen pushed the question more vigorously, and to-day we recognize that his findings very closely approached what we now consider as the right standpoint. Unfortunately, Seegen supported his contentions with so imperfect and unreliable methods, that his experiments would not stand criticism, and the critics who rightly condemned his experiments, cast also his conclusions and his theories to the winds.

Already twenty years ago I supported Seegen's hypothesis, that when starving men, or men living on protein and fat only, undertake muscular work and burn up a certain quantity of fat the decomposition of the fat does not occur in the muscle cell itself, and I went further, and said, that it was necessary for the fat to be worked up into sugar elsewhere before it could serve as food for the muscle cells. The liver was suggested as the place where the change took place; it was elsewhere thought, that the change was a facultative one, that is to say, that this was not the case at all times and seasons, but only when the liver did not command sufficient glycogen to provide the requirements of the blood and tissues for sugar.

The formation of sugar from fat is closely associated with two factors:

c. Limits of Sugar Formation from Fat

Glycogen is not formed during the process. One has

fed animals with the various forms of fat and transfused various fatty acids and their salts through the portal veins of isolated and surviving livers, and also mixed fresh emulsions of liver cells with fatty acids; in not a single instance has the smallest quantity of glycogen been demonstrable. These findings have been used as an argument against the formation of sugar from fat; such a contention goes, however, too far. The experiments show only, that after flooding the liver with fatty acids, glycogen is not deposited in the cells. That leaves the question of sugar formation an open one. To my mind, the results of the experiments may be stated differently: The normal healthy liver only forms carbohydrates out of fat when it is necessary to do so to maintain the normal content of the blood and supply the needs of the tissues. This comes practically to what I have said before, namely, that the formation of sugar from fat is a facultative process. It puts it into the position of an act of necessity when other material is unavailable; it does not overstep the bounds of necessity. Whether the formation of sugar from fat is a direct one without passing through the glycogen stage or whether glycogen is formed and rapidly broken up and passed into the blood as dextrose must be left an open question. I consider the first to be the more likely process. The fact that in the healthy individual a large quantity of sugar exceeding the amount required does not originate from fat is of general biological interest. The liver does not receive the fat which it utilizes directly from the fat contained in

food, or at all events, only to a slight extent. The fat of the food streams through the thoracic duct into the blood and disappears rapidly from the blood into the large fat depots. The liver receives only a very small fraction.

If the liver manufactures sugar in unlimited quantities from the fat present in the food, or from the fat streaming in from the fat stores, then it becomes necessary for the organism immediately to transform the carbohydrate again into fat. For the use of sugar by the tissues is a limited one; it is one of the best recognized principles of physiology that any excess of carbohydrates is quickly converted into fat. We overfeed animals and men with carbohydrates and we gain fat. All these chemical changes call for work and energy exchange. It would be a squandering of potential energy if fat were first changed into stored glycogen and then reconverted into fat, while it is an economy that the manufacture of sugar from fat is carried on only to provide for the immediate needs.

d. Decomposition of Fat and Acetone Bodies

A second characteristic of the hepatic formation of sugar from fat is the appearance of acetone bodies as by-products. This process is not restricted to the decomposition of fat alone, for it plays a part also in the cleavage of the aminoacids from the albumin molecule. This was first demonstrated by G. Embden and his colleagues in my Frankfurt laboratory. It is prob-

able that certain parts of the fatty acid molecule may be amidised before they are broken down further. If this supposition be confirmed, then we shall be able to state the formation of acetone bodies from albuminates and fatty acids in uniform chemical formulæ. There seems little doubt to-day but that acetone bodies occur during normal intermediate metabolism, but most probably in limited bounds only. Under ordinary conditions they are at once further decomposed. If we review the entire circumstances under which acetone and B-oxybutyric acid appear, we meet always one important fact: under all these conditions is glycogen absent, or nearly absent, from liver cells; we shall not be going too far if we venture the sentence — the presence of glycogen in liver cells hinders the formation of acetone bodies or hastens their further decomposition. Embden's experiments go far to verify this statement.

e. Arguments for and against the Formation of Sugar from Fat

In the above we accepted the formation of sugar from fat as an established principle. This is by no means, however, generally recognized. When, twenty years ago, I found new grounds for supporting the older teaching of Seegen I was quite alone in my contentions and together with my pupils had to defend this principle, so equally important for both physiology and pathology. First some time later, E. Pflüger lent the

theory his strong support; in spite of this, the view has not to-day gained wide recognition; in fact, with a few exceptions—Th. Rumpf, Lenné—all the modern workers upon diabetes dissent from it. I have to complain, that although many facts have been brought forward in support of the above-mentioned theory, yet always the same old reasons have been opposed to it. I must deal with the several objections and arguments in further detail.

(1) It is argued that chemistry has not been able to show a way by which a fatty molecule may yield sugar. This is quite right, but the opposite is also true. We do not know the chemical means by which sugar is converted into fatty acids and yet the formation of fat from carbohydrates is one of the fundamental facts of biology. This so impressed itself upon the minds of observers and investigators, that already in the early days of biology it became a fundamental axiom. Still to-day we know little more of the details of the chemical processes than did the first workers. If then in the organism sugar is transformed into fat by an unknown chemical method, may we not with safety accept that a transformation in the opposite direction is equally possible? All the fermentative processes occurring in animals and plants which serve to bring about molecular changes, are reversible in nature. We see this in the building-up and breaking-down of albumins, purin bodies and carbohydrates, while in plant life there is the convincing and satisfactory process of the interchange between fat and carbohydrate. At all

events, in denying the occurrence of the transformation it is an entirely unscientific attitude to do this solely because we are ignorant of the exact chemical details of the process.

(2) It has been urged that fat does not yield glycogen. This statement is also correct. As we have already observed, it does not follow therefore that fat does not yield sugar. I have shown that from the standpoint of the energy exchange it is an intelligible act of economy, if fat is used only for the immediate needs and not for the purpose of building up a reserve-stock of carbohydrates.

(3) One has referred to the quotient D÷N and insisted, that in the urine of a patient upon a carbohydrate-free diet there occurs no more sugar than would be expected from the decomposition of albumin according to chemical calculations. (Index: the amount of nitrogen in the urine.) No further source for the sugar be therefore required.

This view, that the urinary sugar corresponds to the maximal quantity, which according to theory, may be derived from albumin, is unconditionally right for phloridzin diabetes. for experimental pancreas diabetes, and for all slight, as well as for some of the severe forms of human diabetes. It is not correct, however, for a certain number of severe cases. As we have shown, the maximal amount of sugar obtainable from albumin corresponds to one part of nitrogen to five parts of glucose. Now there are records of a number of cases, and mostly from my clinic, in which

the quotient D÷N not only temporarily but for a long time reached a higher level than 5:1, in spite of starch-free food. As under these conditions there is no other source for the sugar, the extra sugar must be ascribed to a fatty origin. Against the precision and reliability of these clinical experiments many objections have been made, but the overscrupulous critic is bound to admit that consequently the later observations have been carried out with even much greater exactness and care than the earlier ones. Even if we accept the criticism upon some of the observations, there still remain a sufficient number of cases in which it is safe to assume the necessity for a source of sugar other than that of the carbohydrates and albumin.

As I have already mentioned, all the conclusions drawn from a consideration of the quotient D÷N postulate, that the sugars which are formed in diabetics — animal or human — are excreted in the urine, and that the tissues have lost the property of sugar oxidation. One regards this assumption as a correct one, because in severe diabetes the respiratory quotient falls very low and approaches the value which would express the total oxidation as from fat. In reality, however, this proves only that fat was the primary material attacked by the oxidation process; it does not in the slightest degree indicate what is the type of cleavage of the atomic groups of the fatty molecule in the intermediary metabolism. The respiratory quotient does not teach us whether certain parts of the fat molecule were

transformed into sugar before the oxidation to carbonic acid and water was finished.

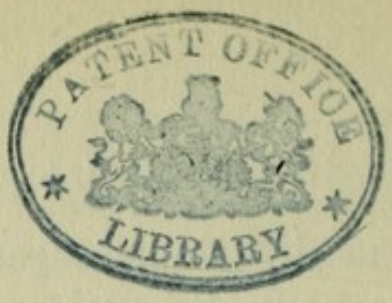
Here I may mention some recent experiments which have been carried out in my laboratory by H. Salomon and O. Porges. As a basis we accepted the statement that the change of fat into sugar occurs in the liver alone. If this is correct, thn the exclusion of the liver from the circulation would remove the influence which the fat exchange in the liver exerts upon the respiratory quotient. We hoped then to discover what materials were oxidized in the other tissues. Should the tissues, and especially the muscles, be able to combine directly with the fatty acid molecule and to oxidize it after the abdominal organs had been excluded from the domination of the respiratory exchanges, then the respiratory quotient would remain at a low level. As a matter of fact, immediately the liver is cut off from the circulation, the quotient reaches 1, which is practically the figure yielded by the oxidation of sugar. This was first obtained with a healthy animal, and later with animals the subjects of pancreas diabetes and maximal phloridzin diabetes. On the other hand, control experiments were made with an Eck's fistula. In this instance also, the respiratory quotient rose, although not to the same height as in the previously cited experiments. This is what would be expected, as an Eck's fistula does not exclude the liver from the circulation entirely, but only in part. The experiments gave results which were the same in healthy animals or in animals with severe diabetes. We find therefore

that after the exclusion of the liver the muscle cells oxidize carbohydrates only and that this characteristic is not altered even in severe diabetes. These experimental results are important both for physiology and science of diabetes. It is apparent, therefore, that all conclusions based upon the effect of the quantitative relations of albumin and sugar formation on the quotient D÷N must fall to the ground.

D. Summary

These arguments and facts so far brought forward tend to show, that in addition to carbohydrates, proteins and fats contribute to the formation of sugar. The share of the protein and fat is not, however, an equal one. Quantitatively, the part played by the albumin itself in the formation of sugar is not great. About 100 grams is an average daily albumin exchange in man; at the most this would only yield 60-70 grams of sugar and probably the amount is very much less. This is a small quantity for the metabolic needs of a resting adult, let alone that of a man in full work. In addition, proteins exert an irritant action upon the sugar-forming organs; some proteins act more intensely than others; they may be looked upon as a whip to the diastatic processes. In the healthy, the well-regulated mechanism of the sugar production is not affected by this irritation, but when the mechanism is not well regulated there is a definite response to the smart. This has been quoted at full length. Fats, on

the other hand, do not irritate the sugar-producing centers; they do not incite the liver to manufacture sugar. The liver uses fats for the purpose of forming sugar only when the poverty of other materials makes it necessary.



II. THE RISE IN CALORIC PRODUCTION AND ITS CAUSES

It is generally accepted that in severe diabetes the processes of oxidation, or, in other words, the production of calories is increased. Why is this the case? To-day we are accustomed to regard endogenous factors as the cause of this increase in:

1. Basedow's disease, feeding with thyroid gland, and spontaneous and artificial hyperthyroidism.
2. In severe diabetes in man.
3. In experimental diabetes and pancreatic ablation.
4. In high pyrexia (man and animals).
5. In some cases of acromegaly.

Do the causes of the increased oxidation differ in these five cases or is there a bridge by means of which we may connect them together? I am of the opinion that the latter is probable. The advances made in our knowledge of the internal secretions have shown that certain inter-relations come into play. The investigations made by my assistants, Eppinger and Falta, revealed, among other things, the inter-actions of the pancreas and the thyroid gland. Both exhibit a type of opposition to one another, for instance, in hyperthyroidism the function of the pancreas is depressed and alimentary glycosuria is easily brought about. On the other hand, in atrophy or hypoplasia of the thyroid gland the pancreatic powers are increased and patients

suffering from these diseases — for instance, myxœdema — can take large quantities of glucose without the slightest glycosuria. The influence of the thyroid gland is seen also in the alterations of the external secretions of the pancreas, although this is less common. In Basedow's disease, there is often a "fatty diarrhœa" due to the insufficiency of pancreatic ferments. In all these cases there is either a spontaneous glycosuria, or at least a spontaneous hyperglycæmia and a tendency to glycosuria. When the Basedow's condition improves, the fatty diarrhœa and glycosuria disappear; in two cases we were able to diminish the size of the thyroid by Röntgen rays; the evidences of Basedow's disease became less prominent and the alimentary glycosuria was no more demonstrable.

The relations between the glands possessing internal secretions are many-sided. The thyroid can be influenced by the pancreas, and so we are not surprised to find that the moment the pancreas is ablated the thyroid functions gain the upper hand; there is increased oxidation, that typical symptom of hyperthyroidism. Thus the thyroid acts upon oxidation as a pair of bellows rejuvenates a fire. That the principles which determine the important effects following extirpation of the pancreas may be applied to the condition of severe diabetes in man goes without saying. We may assign the increases in the caloric production in the disease to the loss or diminution of the inhibitory factors, radiating into the thyroid through the chemical correlation of the pancreas.

We may perhaps also attribute the increased oxidation which we often — though not always — meet with in pyrexia to a chemical irritation of the thyroid gland, in other words, to a toxogenous (or pyogenous) hyperthyroidism. In febrile infectious diseases there are many symptoms which also occur in Basedow's disease; tendency to sweating, abnormal irregularity of the cardio-vascular nerves, increased frequency of pulse, and above all, that cardinal symptom of Basedow's disease, the augmented oxidation processes. In spite of a precise and almost primeval acquaintance with the symptoms of fever, the pathogenesis of the condition is not yet sufficiently clear, and we can to-day only put into the form of hypothesis the thought, that the symptom-complex of fever, and especially the raised caloric production, is intimately associated with a toxic irritation of the thyroid tissues. This hypothesis gains support from the fact that in fever there occurs regularly a demonstrable hyperglycæmia and very frequently a tendency to alimentary glycosuria. During an attack of pneumonia or of erysipelas patients sometimes excrete 8 to 12 grams of sugar after an intake of 100 grams of glucose, while at the end of the attack large quantities of carbohydrates and sugar can be consumed without a slightest trace of glycosuria. This surely indicates a febrile insufficiency of the pancreas and we have to consider: 1, whether the infectious intoxication irritates the thyroid first; or 2, whether the pancreas is the first to be damaged, and as a result of this defect there is a marked excitation of the thy-

roid; or 3, whether both organs are affected at the same time, although independently, the thyroid in the sense of an irritation, the pancreas in such of a paralysis.

That the pancreas will be damaged in various ways by the several infections is quite natural; the hurt most probably takes the form of a degeneration such as is generally met with in glandular organs in infectious diseases.

For many years I have held, that the marked alimentary hyperglycæmia and glycosuria in fever must be regarded from this standpoint, and now we come more and more in our findings in diabetes to see that the connection between diabetes and the acute infectious conditions, such as angina, influenza, measles and scarlet fever is so direct and evident that we cannot deny the possibility of some intermediate ætiological factor.

We commenced these remarks with the discussion upon the formation of sugar from albumin. We have seemed to get wide off our theme, but it is only an apparent extension. In reality, this apparently simple question is very complicated. We soon get into a blind alley, if we regard our theme from a purely chemical aspect alone and only considered the chemical conditions which determine the pathway of aminoacids to carbohydrates. We do not know to-day what the details of these processes are; on the other hand, I have shown, that the increased formation of sugar which follows the ingestion of proteins and aminoacids is

bound up with important questions of metabolism, and that the anomalies observed in diabetic metabolism are only placed in their right light when analogous metabolic changes in other diseases are investigated at the same time.

III. THE CONTROL OF SUGAR FORMATION AND ITS DISTURBANCES—THEORY OF DIABETES

A. The Liver as the Place of Control

The control of sugar formation and its distribution takes place in the liver. The other organs elaborate and consume sugar, but do not share in its production. The cells of the glands, and still more those of the muscles, have a certain local controlling power, in so far as they are able, when there is over-production, to take up a small reserve of glycogen. It is left to the liver, however, to supply the organism in general with sugar. The following processes occur in the liver:

1. The taking up of carbohydrates streaming in from the intestinal canal through the portal vein.

2. Their conversion into glycogen, and perhaps into fat, when there is a great excess. As we have said, it is not certain whether the liver can form fat out of carbohydrates, or whether this is the only organ in which this process takes place.

3. When there is a very rapid and extensive supply of sugar to the liver, a portion escapes conversion into glycogen and this leads to hyperglycæmia and eventually to alimentary glycosuria.

4. Intra-hepatic decomposition of protein leads to sugar formation. The details of this chemical process are unknown. Perhaps it is more a stimulus to sugar

formation which occurs, and not a direct conversion of the protein nuclei into sugar.

5. If the remaining materials, the available carbohydrates, and in the last resort, the protein nuclei, are insufficient for the needs of the moment, sugar is formed from fat.

6. A diastatic process by which the glycogen in the liver is re-converted into sugar. Glucose is formed, and leaves the liver by the hepatic vein.

Which particular material gives rise to sugar is not important from our present point of view. We must regard sugar formation in the liver as a single process, which has for its object the maintenance of the sugar content of the blood at a constant height, and likewise the supplying of sugar to the tissues. The amount of sugar metabolized in the tissues varies enormously. During complete rest it is at its minimum; work increases it two or three times over, or more. The sugar content of the blood nevertheless remains at about the same level, namely about 70 to 90 centigrams of glucose in one liter of blood. It falls a little (to about 50 to 60 centigrams) only as a result of prolonged and laborious muscular work. Then the sugar is so rapidly used up that the production cannot keep pace with the loss. This synchronizes with a feeling of actual bodily fatigue, and a desire for rest. All investigations of working men and animals, and of the isolated hearts of cold- and warm-blooded animals, show that carbohydrates, and especially sugar, are the best materials for retarding or abolishing muscular fa-

tigue. It is easy to understand the prophylactic influence of sugar food. It is the material most easily absorbed, and most easily and quickly converted into blood sugar by the liver, whilst the formation of sugar from protein and fat must certainly take up more energy and probably also more time.

The normal control of sugar formation results in a small supply during rest and a copious supply during work, as it has to adapt the amount yielded to the blood to the amount required by the tissues. We do not know the signal by which the liver is informed as to how much sugar it ought to set free. Possibly the sugar content of the hepatic artery provides the signal; possibly the metabolic products of the cells of the muscles and glands perform this duty. But the process is very likely far more complicated. The signals, that is to say, are not transmitted directly to the liver, but are first passed through the pancreas or suprarenals, both of which exert a controlling influence on the sugar production of the liver. Whatever path these signals take, however, we can state with certainty that normally they originate in the tissues; in other words, it is the *requirements of the tissues* which form the supreme and perhaps the only factor in regulating in amount of sugar formation.

For these processes to maintain their normal course, we must assume a normal degree of excitability in the sugar factory in the liver. The general expression "sugar factory," or sugar mechanism, will be employed henceforth, because it commits us to nothing,

and because the words "diastatic process," commonly used, do not cover the entire extent of the sugar-forming activities of the liver.

The excitability of the sugar factory is not uniformly great, and only depends to a very small degree on the condition of the liver itself. One might imagine, that so delicately adjusted a mechanism as the control of the sugar production must be seriously damaged when the organ in which it takes place is diseased. This, however, is not the case — on the contrary — carbohydrate metabolism usually goes on pretty well normally in most diseases of the liver. The only abnormality which we can detect is a stronger tendency to alimentary glycosuria, which sometimes affects glucose and sometimes lævulose or galactose. This may be easily explained by supposing that the damaged, or numerically decreased, liver cells cannot take up so much glycogen as in times of health, and that therefore more sugar passes directly from the portal vein into the general circulation. It is only the most severe diseases of the parenchyma of the liver which seriously disturb sugar formation. This happens, for instance, in acute yellow atrophy and phosphorus poisoning; but the actual disturbances which these bring about in the elaboration of carbohydrates are at present obscure. Perhaps they are confined to total inability to store up glycogen. In other conditions it is surprising with what tenacity the liver clings to its controlling function in spite of severe disease. Assuredly this extraordinary power of resistance is no chance occurrence. We must regard it as an impor-

tant acquisition in the struggle for existence. Were it otherwise, and were every disease of the liver to impair its power of sugar production, the continuance of life would be threatened, as muscular work, and still more the work of the heart cannot go on without the production and supply of sugar.

B. The Influence of Other Organs on the Liver

I have remarked that the sugar factory does not depend entirely on the degree of excitability of the liver. Two guards are set over the liver which influence its excitability and whose forces are normally equally balanced.

a. The Pancreas

One guard is the pancreas; it acts as a break to the sugar factory. As was first shown by your own countryman, Opie, it is probably the so-called islands of Langerhans which liberate the active stuff into the portal blood. When the pancreas is removed, or when the islands of Langerhans are atrophied, this inhibitory action fails. The excitability of the sugar factory is enormously raised; the control no longer exists which equalizes sugar production to sugar requirements; more sugar is formed than is wanted. The blood is flooded with it, and valuable material escapes in the urine. In experimental pancreatic diabetes and in severe diabetes in man the liver is always found to be free from glycogen. This may be explained in various ways:

1. The absence of glycogen depends on the over excitability of the sugar factory. Even in health glycogen is the least stable of substances, and is converted into blood sugar more easily than any other. Absence of glycogen in the liver springs from increased sugar production in pancreatic diabetes, just as it does in healthy animals when exhausted by muscular work; only with this difference, that in an animal at work the large amount of sugar formed is *required* and *used* by the tissues, whereas in pancreatic diabetes the absence of impediment allows a high sugar production which is absolutely *useless*. In this connection we must remember that it is possible to furnish the liver with a certain amount of glycogen in spite of pancreatic diabetes, by using lævulose. Recent work has established the hypothesis which I put forward a long time ago, that lævulose-glycogen is not identical with dextrose-glycogen. The former has shown itself much more resistant to all attacks on the glycogen stock of the liver. Different names have been given to these two glycogens — dextrogen and fructogen. Unfortunately, we can only make small therapeutic use of this observation, which is, however, most interesting theoretically. This is because the differences almost completely disappear after lævulose has been given for any length of time.

2. The second explanation of the absence of glycogen in the liver is, that owing to the failure of the internal secretion of the pancreas, the organ loses the power of forming and storing glycogen. Naunyn

coined the word " dyszoamylia " for this condition, and saw in it the intrinsic virtue of the disease known as diabetes. In my earlier publications in New York, I have tried to refer some of the metabolic disturbances in diabetes to this, for their orginal cause. You see where the difference between these two conceptions lies. In the first, the absence of glycogen is the result of increased sugar production, and in the second it is its cause.

Probably it is not correct to place one theory in antagonism to the other. There are many reasons for believing that many factors unite in producing a single result — namely, the absence of glycogen in the organs. One factor is a prodigality in sugar production, with the result of impoverishing the glycogen reserves in the liver; the other is a specific stimulation of the diastatic processes, which involves not only the liver, but the muscles also.

b. The Chromaffin System

We must pass on to consider the relation of the suprarenals and the rest of the chromaffin system to sugar production. The suprarenals constitute the second of the guards placed over the liver which regulate the excitability of the sugar factory. Its influence, in contradistinction to that of the pancreas, is one of stimulation. Adrenalin causes a rapid expulsion of glycogen from the liver; the blood is flooded with sugar, and glycosuria results. The blood sugar, on the other hand, falls markedly (to 0.5 per mille and below) after

extirpation of the suprarenals, and in severe cases of Addison's disease. A moderate dose of adrenalin produces a glycosuria lasting for some hours. After that, normal conditions are restored. A second injection of adrenalin soon afterwards again produces glycosuria. But if the injection is repeated several times, glycosuria does not reappear, but only moderate hyperglycæmia. A much larger dose of adrenalin is required to produce again sugar in the urine. As the pancreas and the suprarenals can be regarded as antagonistic in their action on the liver, the inhibition of the action of adrenalin may be explained by supposing that the pancreas was taken by surprise by the first stimulating doses of adrenalin, and consequently could not prevent the disturbance of sugar control. But the repetition of the stimulus puts the pancreas into a strong defensive condition. Its inhibitory influence makes itself felt, and a stop is put to the disturbance in the regulating mechanism produced by the adrenalin. It is probable that a similar intensification of the pancreatic functions also accounts for the fact, that in conditions of chronic overaction of the suprarenals, such as we so often meet with in hypertonic arteriosclerosis and granular kidney, there is no glycosuria, but at most a moderate hyperglycæmia. Possibly, too, another hitherto unexplained clinical phenomenon is connected with this. All of you know of cases of diabetes which have gone on for a long time, and then, on the development of chronic granular kidney, get much better or clear up completely. We find that marked hypertension and

hypertrophy of the heart are much more usually present in these cases than in other forms of granular kidney. The blood also is richer in adrenalin. The adrenalin not only whips up the liver, but also the pancreas, causing it to hyperactivity, perhaps especially to hypertrophy of the still unhurt activating islands of Langerhans. Of course, there is much in this explanation which is hypothetical; but I think it is more profitable to rely upon a theory for what it is worth, and to make it the basis for further studies, than to content myself with the meaningless expression, "acquired tolerance of adrenalin." Let us next see what pathological anatomy has to say. We must see whether, in cases of simple hypertension, of hypertonic nephritis, and of post-diabetic and vascular kidney, hypertrophy of the islands of Langerhans occurs. This must be specially looked for in cases where there has been hyperglycæmia without glycosuria during life. Such cases are not rare. The hypothesis also stimulates us to therapeutic experiments.

So far as the liver is concerned, the injection of adrenalin causes rapid expulsion of glycogen; the expression is often used, "adrenalin mobilizes glycogen." No glycosuria is produced by small doses of adrenalin, if the liver is previously rendered free of glycogen; larger doses, however, stimulate the whole mechanism of sugar production. They produce glycosuria in animals which have been freed from glycogen by starvation. Proteins or fats must therefore be employed for the formation of sugar. When the inhibitory action

of the pancreas fails, as in extirpation of the pancreas and in severe diabetes in man, the liver is especially susceptible to stimulation by adrenalin. Quite small doses, which would be inoperative in healthy persons, send up the sugar excretion by leaps and bounds. This fact illustrates most beautifully the antagonism between the two glands, as it shows how one obtains a predominance as soon as the other is excluded. But the pancreas and the chromaffin system have not the supreme control of the hepatic sugar production. Their power of action can be influenced by remote organs.

c. The Nervous System — Neurogenous Diabetes

The chromaffin system is the one in which this is most clearly shown. It is undoubtedly under the influence of the nervous system. It has been shown in Professor H. Meyer's laboratory in Vienna that the nervous influence passes down by way of the left splanchnic nerve to the left suprarenal and from thence is carried across to the right one. Stimulation of the sympathetic mobilizes the adrenalin, and this then increases the sugar production in the liver. Claude Bernard's famous experiment of the "piqûre" demonstrates the same thing. The stimulation of the medulla oblongata is passed on to the suprarenal by the sympathetic. Piqûre glycosuria is nothing else than adrenalin glycosuria. Claude Bernard's center can undoubtedly be excited not only by gross mechanical lesions but also by numerous stimuli of psychical and somatic

origin. We now understand why and how it is that certain excitable, nervous individuals can exhibit transitory nervous glycosuria after mental or physical pain and the like. We understand why, in true diabetes, the intensity of the glycosuria is so very dependent on the condition of the entire nervous system: why psychical stimuli, mental or bodily overstrain, loss of sleep, etc., are often so certain to set up glycosuria. The same process is again set going: passage of the stimulus to the center in the medulla, its transference through the sympathetic to the suprarenals, mobilization of the adrenalin, an increased sugar production. Investigations in my clinic by Dr. H. Eppinger, have shown that individuals exist with a highly strung vagus system, and others in whom it is entirely outweighed by the tonus of the sympathetic system which antagonizes it. We can show, that those with a highly strung sympathetic system are much more sensitive to adrenalin, and exhibit a quite considerable glycosuria after even one milligram of adrenalin; whereas those with a highly strung vagus system have to take much larger doses to produce the same result. Generally speaking the vagus system predominates in hysterical persons, and the sympathetic in neurastheniacs. We also find the vagal and sympathetic types among diabetics and we may expect that stimuli of the most varied kind will excite more easily through the sympathetic nerves and so reach the suprarenals and increase diabetic glycosuria in the latter class than in the former. A preliminary list of the nervous constitutions of our dia-

betics, and especially as regards their response to vagotropic and sympatheticotropic drugs, has confirmed the correctness of this explanation. When we remember that in the large majority of persons the tonus of the autonomic and sympathetic nervous systems are equally balanced, and that it is only in a minority that the one outweighs the other to any great extent, we shall easily see that the same nervous stimulus will not always produce the same effect on the diabetic patient. There are, in fact, diabetics whose glycosuria is extraordinarily unaffected by any kind of nervous excitement, and others in whom the glycosuria is in the highest degree sensitive to all sorts of nervous stimuli. And between these two classes come many transitional forms. We must now deal with a cognate question, namely whether the facts already ascertained are indicative of the existence of a true neurogenous diabetes. In my opinion, they are not. I think we can only say at present (1) that there is a transitory non-diabetic glycosuria or nervous origin; and (2) that true diabetic glycosuria may be temporarily increased by nervous influence. It is quite another question, whether continuous and progressive irritation either in the sympathetic nervous system or in the suprarenals can, by the exclusion of the pancreas, set up a chronic diabetes in man. In this connection we must remember that long-continued neurogenous glycosuria implies long-continued excess of adrenalin in the blood. The blood of diabetics has many a time been examined for excess of adrenalin. This has often been done in my clinic,

but always with negative results. We only know of one disease in which excess of adrenalin certainly exists, namely, the hypertonic form of granular kidney, and this is, as we have said, to a certain extent antagonistic to diabetes mellitus. We know moreover from experiment that it is only a sharp, sudden poisoning with adrenalin which causes glycosuria; rapid and considerable increases in dosage are required in order to prolong it. We have suggested that this is due to a compensatory stimulation of the pancreas. Experimentally, no chronic adrenalin-glycosuria is known. From all we know of adrenalin, it is certain, that chronic overaction of the suprarenals must very soon become manifest in serious changes in vascular system. But there is no indication of this in those young or middle-aged people in whom " neurogenous diabetes " is most frequently diagnosed. Clinical observation, also, tells against the existence of a chronic neurogenous diabetes. First, the glycosuria must be shown to be entirely independent of alimentary conditions. Now there are cases of diabetes which are so slight that at first they seem independent of diet. When they occur in persons with a very excitable, highly strung sympathetic nervous system, the glycosuria may at first only appear when the mechanism for sugar formation happens to be damaged by nervous influence. More accurate tests, and especially long and careful clinical observation will, however, make clear the alimentary factor in the glycosuria. Let us follow these cases a little further. Year by year the hope that they are of nerv-

ous origin and can be cured by placing the nervous system under favorable conditions becomes less and less in nearly all instances; finally the sad conclusion is reached that the original diagnosis of "neurogenous diabetes" was premature and false. In the course of the last twenty years I have had under clinical treatment more than 4,000 diabetics. Moreover, I have seen most of the patients again and again, year after year, so that I could estimate all the factors controlling their glycosuria. Among this large number of diabetics there are hardly twenty whose glycosuria was permanently independent of alimentary conditions; but on the other hand there are many whose diabetes remained for a long time but slightly developed and in a quite harmless stage; owing to rational and systematic diabetic treatment. In these cases sugar only reappeared in the urine owing to careless neglect of diabetic rules, or severe nervous excitement. There are, however, many cases in which from the beginning the nervous factor in the glycosuria appeared to predominate so strongly that in spite of every care and the conscientious observance of instructions, day by day and year by year the characteristic picture of diabetes developed. I have given a short account of the details of a most instructive case of this kind in another place (*Medizinische Klinik, 1912,* No. 1).

When we discuss therapeutics we shall once more briefly revert to this question. In the meanwhile I feel bound to say that the practical physician ought to be extremely cautious in diagnosing "neurogenous dia-

betes," otherwise he will not attach sufficient importance to the regulation of the diet, and will thus throw away the only means by which cure or improvement may be attained, or at any rate the downward progress of the disease be postponed.

As in the case of the suprarenals, the pancreas is to a certain extent subject to outside influences. It has not yet been possible to trace the connection with the nervous system, but there is much to be said for the view that the vagus has some relation to the internal secretion of the pancreas, just as it controls its external secretion. The experiments, however, are difficult and inconclusive, and it would be premature to give a definite opinion.

d. The Thyroid System

In the second place we must mention the thyroid gland. Here we are in no doubt whatever. The thyroid and pancreas have antagonistic actions, the former inhibits the excitability of the latter. The more powerful the action of the thyroid, the more marked the inhibition. A similar action can be obtained by thyroid feeding. Glycosuria can be invariably induced both in man and animals on a mixed diet, the time of its appearance being merely a question of the amount of thyroid given; on the other hand it is almost impossible to set up glycosuria in animals after extirpation of the thyroid or in human beings suffering from myxœdema, as the functional activity of the pancreas is increased by the absence of thyroid influ-

ence. Probably the parathyroids also stand in metabolic relationship to the pancreas. These glands have not yet been sufficiently studied, and the only thing that can be said is that the extirpation of the epithelial bodies (parathyroids) weakens the functions of the pancreas and favors the onset of glycosuria. This then is an antagonistic action to that of the thyroids.

e. Diagram Illustrating the Regulation

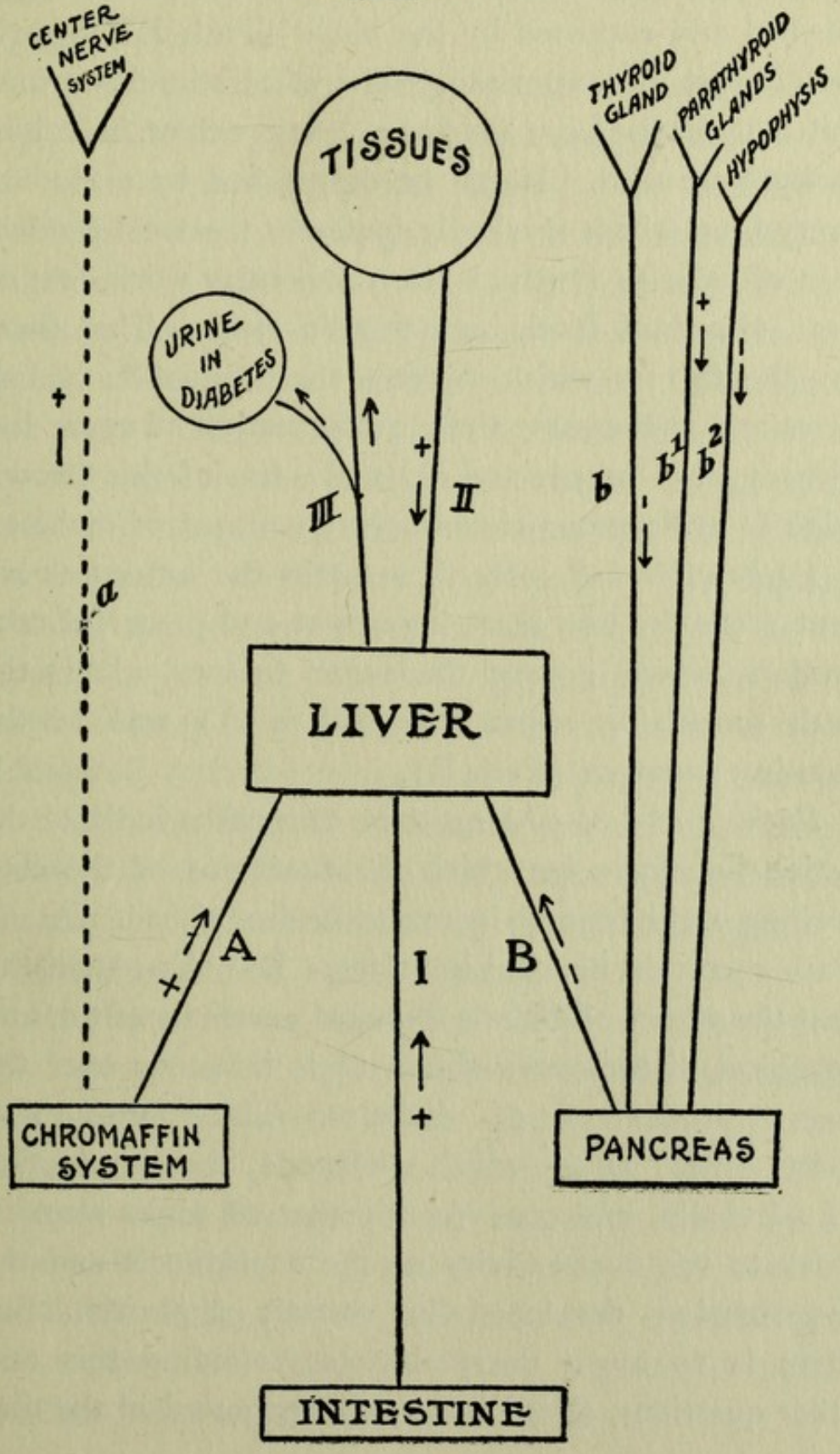
Two years ago I devised a diagram to illustrate the metabolic relationship of the organs which I have described.

The dotted lines indicate "nervous paths," the continuous lines "blood paths"; the arrows show the direction of the stimulus; and the plus or minus signs behind them show whether the stimulus increases or inhibits the power of the organ which is influenced.

Paths I, II and III.—The normal metabolism of the carbohydrates is concerned only with Paths I, II and III.

Path I shows that material, inciting an increased activity of the sugar-forming mechanism, streams up from the intestine to the liver. This path in diabetes corresponds to the "alimentary factor" in glycosuria. We can, at will, control the stimuli passing up by this way. The conscientious carrying out of this is the aim and object of diabetic cures.

Paths II and *III* show the action of the metabolic processes as a whole. Along Path II are transmitted the requirements of the tissues (especially the muscles)



and to their extent corresponds to the amount of sugar formed and exported by the blood (Path III, hepatic vein, heart and arteries). The total stimulus transmittal by Path II can also, to a certain extent, be voluntarily controlled. It can be diminished by excluding everything which markedly increases the total production of calories (such as heavy muscular work, loss of heat, abundant food, high protein diet). That these are the factors which increase the production of calories and at the same time the formation of sugar has already been noted; and we make use of this knowledge to achieve our aims in the treatment of diabetes.

Paths A and B.—By these paths the influences are sent from the two most important and powerful controllers, which govern the sugar factory. It is the path sensitizing suprarenals (Path A) and of the calming pancreas (Path B).

Paths a and b.—Along these two paths indicate the active influences by which the functions of the controlling organs can be increased or diminished. Along Path *a* pass the nervous impulses. It is along this path that the piqûre of Claude Bernard exerts its effect, and psychical disturbances obtain their influence over the sugar production of diabetes. There may also exist other paths which influence the production of adrenalin, and consequently that of sugar also. I refer to the over-activity of the suprarenals and the hypertension developed in chronic nephritis. But there is so much uncertainty surrounding this and other questions, that I have only suggested in the dia-

gram the possibility of other paths than that of the sympathetic.

Path b indicates the certain relationship between the thyroid and the pancreas. As you see, the indicator on this path carries a negative sign to show that the internal secretion of the pancreas is not increased but inhibited by the thyroid. A path from the parathyroids to the pancreas (b^1) is also shown on the diagram. The indicator carries a positive sign. Up to the present the probability of the existence of this path is only supported by certain experimental facts. There is no clinical evidence for it in diabetes. It is, however, only of subordinate importance. The impulses passing to the pancreas from the hypophysis cerebri appear to be more far-reaching. I may refer to the extraordinary frequency of diabetes in acromegaly compared with the astonishing tolerance of carbohydrates shown in cases of fatty degeneration of the so-called dystrophia adiposo-genitalis (Hypophysäre Fettsucht). The influence of the pituitary gland is identical with that of the thyroid.

Paths a and b are secondary. When the functions of the two principal organs (pancreas and suprarenals) are normal, the extent of the stimuli they originate is of no great or immediate importance. When, however, there is any morbid predisposition (such as anatomical changes, functional debility, or diminished excitability of the pancreas, or increased excitability of the suprarenals) the more distant organs can exert a distinct influence on sugar production.

C. The Diabetic Hyperirritation of the Sugar-Forming Apparatus

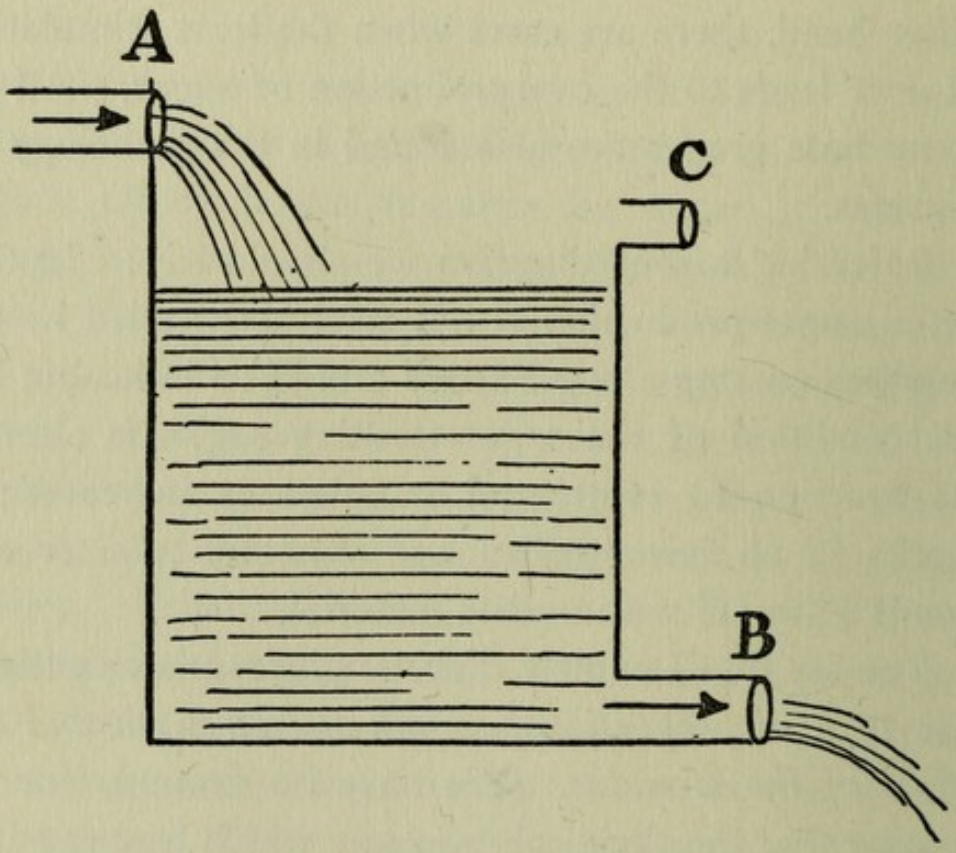
We must look for the immediate cause of the overproduction of sugar in diabetes in the morbid overexcitability of the sugar factory in the liver. Under normal conditions of excitability, overproduction never occurs, although the demands on sugar production change enormously from hour to hour. The two guards placed over the sugar factory, the pancreas and the suprarenals ensure an accurate regulation under normal conditions. It is otherwise, however, when the inhibitory power of the pancreas falls into abeyance, or when a wave of adrenalin stimulates the sugar factory. What must now happen is obvious. Every stimulus which under such circumstances acts on the sugar factory, and excites it to sugar-production, produces abnormally large oscillation in the regulatory mechanism. The amount of sugar formed and passed on into the blood stream is now not merely that which is required by the tissues and can be oxidized by them, but an excessive amount is produced by the uncontrolled mechanism which the tissues cannot take up immediately. This excess remains in the blood and is the source of glycosuria. Owing to the overexcitability of the sugar factory the due proportion between the strength of the stimulus and its effect is not maintained. The disproportion between these two values — the stimulus and the effect — also determines the severity of the diabetes. Thus great differences in

degree occur. There are cases in which the sugar factory when only slightly charged, works in quite a normal manner, and the control only breaks down when the sugar factory is greatly overcharged. On the other hand, there are cases when the least stimulation at once leads to the overproduction of sugar. All intermediate grades are also found in the pathology of diabetes.

Referring to our diagram we should say: In diabetes, sugar-production is not solely controlled by the impulses passing along Paths I and II as in health, but the condition of the sugar-forming organ is altered. Its reaction to centripetal impulses is increased; it works in an uncontrolled and wasteful manner and floods Path III with useless material.

You see that I explain diabetic glycosuria as entirely due to a *disproportion between the strength and the effect of the stimulus.* We have no grounds for assuming that the chemical processes which lead to sugar formation in the liver, or the materials from which sugar is produced are qualitatively otherwise than normal. Quantitatively, however, the chemical processes are considerably above the required limit. This theory leaves us no room for the assumption that there is diminished oxidation of sugar in the tissues, and that other materials are used by the tissues in diabetics in place of sugar, which streams to them by the blood in large or excessive amounts. I must here point out that *over-production* of sugar and *failure to oxidize* sugar are two quite different things.

This will be clearly shown by means of a little diagram.



Imagine an open vessel, filled nearly to the brim with water. It has an escape pipe B, through which the water constantly flows out, while an equal quantity flows in at the supply pipe A. Thus the surface of the water always remains at the same height. If the conditions are altered and the vessel overflows, this may be due to several things.

Either the escape pipe has got blocked so that the proper amount of water cannot flow away, or the water flows in more rapidly, owing, perhaps, to increased

pressure in the supply. Thus two quite different causes may produce the same result, namely the overflow of the vessel.

Our diagram, of course, does not take into account the details of the biological control.

EXPLANATION OF THE DIAGRAM

The vessel	—	the blood.
The water	—	the sugar in the blood.
The supply A	—	the sugar production in the liver.
The escape B	—	the consumption of sugar by the tissues.
The escape C	—	the escape of the excess of sugar by the kidneys.

Of course theoretically it is also possible that the sugar production A may be increased and at the same time its consumption B be diminished. If this is assumed to occur in diabetes, we must be quite clear in our minds that we are assuming the co-existence of two entirely different functional disturbances. The seat and character of the two chemical processes are quite different. In diabetes we can only be certain of the disturbance of function A; all the experiments designed to find positive evidence for the disturbance of function B have failed. I allude to the theories of R. Lépine and O. Cohnheim, which have long since been abandoned. On the other hand, in the observations on respiration, after the portal circulation has been cut off, we have positive evidence that the muscles can oxidize sugar perfectly well even when the pancreas has been extirpated. We must recognize that in order to maintain, at the present time, the existence of

defective oxidation of sugar in diabetes, entirely new and positive evidence must be produced.

D. Is Diabetes a Single Morbid Entity?

We now come to the question as to whether we are right in regarding diabetes as a single morbid entity. Under the imposing impression of the discovery of the " pancreatic diabetes " most clinicians and pathologists trend to the view that diabetes is caused by the diminution or absence of the internal secretion of the pancreas, to the exclusion of other concomitant factors. If we once more glance at our first diagram we shall see the theoretical objections to this unitarian doctrine. For it is clear that the impulses coming from various parts of the body may have the eventual or immediate effect of increasing the excitability of the sugar factory.

According to the primary anatomical or functional disturbances we have to distinguish

Pancreas diabetes	—	pancreatic group.
Thyroid diabetes	—	
Hypophysis diabetes	—	
Suprarenal diabetes	—	suprarenal group.
Neurogenous diabetes	—	

To a great extent the answers to these questions must be left to the future. But I think we can certainly say that most, if not all, cases of really chronic diabetes must be referred to pancreatic insufficiency.

Every year, more delicate histological investigations bring new evidence for this view. This was first of all shown in cases of severe diabetes; for exact histological observations on the pancreas are for the present very scarce in those extremely frequent cases in which some final complications ended a long period of slight glycosuria. In spite of the extraordinary variety of the course of the disease and of the intensity of the glycosuria, all cases of diabetes have one point in common. Including the very slight and the quite severe, which really correspond in their principal symptoms, the general unity of type in all is much more conspicuous than any of the points of divergence. Some authors, especially the French, are continually seeking to introduce new schemes of classification in diabetes. How artificial and far-fetched these clinical schemes of classification seem! The divisions are purely arbitary. The separation of such forms as diàbète maigre, diabète obèse, diabète arthritique, diabète nerveux, diabète constitutionel, diabète artériosclérotique, etc., has only ætiological, prognostic or therapeutic interest. But really these differentiations do not shake the essential unity of the metabolic disturbance in diabetes in the very least. I think I shall be voicing the opinion of all pathologists when I say, that every individual, who has a diminished tolerance for carbohydrates, either permanently, or extending at least over a considerable period, and thus exhibits the most important clinical symptom of diabetes, must be considered as a subject of pancreatic in-

sufficiency. We need not always expect to find perceptible anatomical evidence, for there may be functional impairment where no macroscopic or microscopic pathological appearances can be discovered.

The usual share taken by the pancreas in exciting the metabolic disturbances of diabetes is in full agreement with our theory. For it assumes, that a healthy and functionally active pancreas is, under all conditions, powerful enough to make its inhibitory action felt on the sugar factory. Much overfeeding with sugar, considerable stimulation of the sympathetic nervous system, acute toxic conditions which mobilize the adrenalin, etc., may *temporarily* exert so powerful an exciting influence as to overcome the inhibitory action of the pancreas. Then *transitory, non-diabetic glycosuria occurs.* But when, in any particular case, alimentary, nervous or toxic stimuli which would not set up glycosuria in average individuals, always produce fresh attacks of glycosuria, we must assume that somehow the inhibitory action of the pancreas is insufficient. It is quite wrong and unscientific to adopt the intensity of the glycosuria as a standard whereby to determine whether or not the pancreas is involved. We may learn this from the course of those cases which, light in the beginning, in their later stages manifest all the most severe and ominous characteristics of pancreatic diabetes. I allude to those cases of diabetes in children which every doctor regards as pancreatic. All who have seen the beginnings of these cases know that in the early months they appear to be of the

slightest degree imaginable. Very careful investigations show the presence of a little sugar on one or two occasions only. Many controlled tests show it to be completely absent, it is even difficult in many cases to produce sugar excretion even by unusually large amounts of starchy foods. Thus from the clinical standpoint we have to do with merely a very slight transitory glycosuria, and yet anyone who knows anything of diabetes is aware that the chances are that at least ninety per cent. of such cases will in another year have developed into hopelessly severe diabetes. In children, diabetes is nearly always progressive, and all that treatment can do, is to delay the advance of the disease. In the diabetes of children there is most usually an idiopathic, progressive atrophy of the islands of Langerhans. In adults, other inflammatory and degenerative changes in the parenchyma and interstitial tissues are far more common. Often the process remains stationary at an early stage of its development, or retrogress; or the disappearance of some groups of islands is compensated by the hypertrophy of others, as Weichselbaum recently showed. Accordingly in adults we very often meet with cases which permanently assume a very slight and harmless character; this appears when judicious treatment protects the diseased and weakened organ from becoming overtaxed. But there is no reason for doubting that in these cases also the permanent tendency of glycosuria is closely connected with pancreatic insufficiency.

The more completely I find myself in agreement with

the views of Minkowski and all the other exponents of experimental pathology who hold that in all cases of chronic diabetic disturbance of metabolism, pancreatic insufficiency must be assumed to exist, the more I feel bound to insist that in such cases all the other factors, which can exert a direct or indirect influence on sugar-production, must have an easier part to play. The most potent inhibitory power is weakened, or in the most severe cases entirely removed, and so the other factors, which are essentially excitant, have free access to the sugar factory. Thus in diabetes besides the alimentary factor, the other exciting impulses from the suprarenals, the nervous system, the thyroids, etc., make their effects far more easily felt. Whether this occurs, and to what extent, depends on the individual's constitution and the presence of complications. The most varied clinical pictures occur, which also vary from the point of view of treatment and prognosis. I allude to cases complicated by neurasthenia, Graves's disease, acromegaly, melancholia, etc. The resulting clinical pictures are easily explained by a reference to our diagram.

The analysis of the endogenous factors which are able to influence sugar-production do not by any means destroy the essential unity of diabetes in man. It enables us, however, to understand more clearly the manifold symptoms, and to estimate more exactly the influences which so often dominate the increase or diminution of diabetic glycosuria. The essential unity is maintained by our constant assumption of pancreatic insufficiency.

IV. THE THERAPY OF DIABETES

I do not propose to mention here all the questions connected with the therapy of diabetes mellitus. I will limit myself chiefly to some of the important standpoints which arise from the considerations already advanced, and only more fully deal with certain questions. As for the rest, I must refer you in part to my earlier lectures in New York,* and in part to the sixth edition of my monograph on diabetes, which has recently been published (Berlin. A. Hirschwald, Publisher).

A. Introduction

The treatment of diabetes has been restricted to certain definite lines since the days of Rollo, and this limitation is but now being extended. Rollo was the first to discover that urinary sugar decreased or disappeared from the urine when sugar and mealstuffs were excluded from the dietary; he found also that the general condition of the patients then got better. In those days the chemical constitution of foodstuffs was quite unknown, and many decades passed before the various articles of diet were analyzed. To-day we have a more precise knowledge of the composition of foods. But we cannot say that certain foodstuffs are suitable for diabetics simply because of their chemical composition. Such hard and fast chemical figures

* "Diabetes Mellitus, Its Pathological Chemistry and Treatment," New York, E. B. Treat & Co., 1905.

would mislead us. Further investigations on the influence of the individual foodstuffs revealed new and special peculiarities and it has not been possible to explain them satisfactorily either from our knowledge of their chemistry, or our experience of their digestion and assimilation. There was also the remarkable fact, that diabetics could often assimilate a food well when it is given singly, but badly when it is mixed with others. We have still at present to gain much more from empiricism and clinical experience than was thought to be possible at the time when the subject of food chemistry first made its triumphant entry.

B. What is the Object of Carbohydrate Restriction?

In spite of such special considerations the general direction that the intake of carbohydrates should be restricted or excluded, stands to-day in the foreground of diabetic therapy, just as it did in the previous century. It is perhaps more emphasized than heretofore. What is the object of this treatment?

a. Avoidance of Loss of Energy

The exclusion of carbohydrates avoids first of all loss of sugar and through the substitution of fat we give the diabetic patient a material which, owing to the special character of his diseased functions, he cannot squander so easily. Only in the most severe cases does a sugar loss accompany such a diet, and then only

to a slight degree. The patient recovers himself; he gains strength, for he now receives a diet, which he can dispose of physiologically, whilst at an earlier date under conditions of excessive sugar production he dissipated and lost the greater part of its nutritional value.

From the standpoint of general nutrition we could confine ourselves upon diminishing the intake of carbohydrates as far as to prevent large loss of sugar and we could fill up the gap by a quantity of fat, sufficient to cover the energy loss and to satisfy the total calorific requirements. The patient then remains in a good state of nutrition or even increases his body weight. To this the practitioner's method of treatment is limited in the great majority of cases, namely, to a diminution of the glycosuria to a low value and a care for the general nutrition. The physician most frequently advises his patient that it is better to have some tenths per cent. of sugar in the urine, with a daily loss of a few grams of sugar, than to decrease further the carbohydrate intake. I do not know if this is an average medical opinion in your country. In my sphere of action I have found it to be generally so. The basis of this practice is mostly the fear of acetonuria. A fear of acetonuria is, however, quite needless in the majority of cases. I will return to this point later. Partly a certain degree of laziness leads to that method of diabetic treatment; for it requires a great deal of care and trouble to induce the disappearance of the last trace of sugar from the urine. I believe that one would take much more trouble to attain this as soon as

one appreciates clearly the advantages that would accrue to the diabetic patient by making the urine absolutely sugar-free.

b. Prevention of Complications

Diabetes is a disease which is especially prone to complications. There is scarcely another chronic condition which is associated with so many forms of complications, or which is such a hindrance to the favorable issue of occasional complications; yet there is not another one which admits of being influenced so favorably in this regard as does diabetes mellitus. It is an old and yet ever new experience that the danger of complications may be remarkably minimized if it is found possible to keep the urine free from sugar. Of course, it is not the final small loss of sugar which concerns us, but the reduction of the hyperglycæmia. All pathologists agree about this. Recently this view has received additional confirmation. We have always learned that the hyperglycæmia persists so long as the urine contains sugar. Newer and more delicate methods of blood analysis have made this more certain; there are only two or three cases in which this has not been obtained, and we cannot explain at present what other factors are at work. We have learned also, however, that as a rule the hyperglycæmia persists much longer than the glycosuria. After the urine has been freed from the last traces of sugar, often several weeks elapse before the blood sugar returns to its normal level. If one does not ensure that the urine is per-

fectly sugar free, but allows that on occasional days or even from time to time during a few hours only, sugar is demonstrable in the urine, then we may be sure that the hyperglycæmia has not disappeared and may furnish the cause of the complications.

If we turn to our clinical experience for an indication of the types of diabetes in which complications most frequently occur, we are reminded that it is by no means the severest and most malignant cases which are so attacked. The worst cases of diabetes progress rapidly and death occurs before complications have time to develop. Emaciation, loss of energy, and diabetic auto-intoxication are the most prominent. Much more frequent are complications as furunculosis, neuralgia, carious teeth, optic neuritis, etc., in the light and even very light cases. The glycosuria has continued for some long time, and the patients had satisfied themselves that the sugar has not at any time been more than ½-1 per cent. and sometimes was completely absent. If in these slight cases, which upon a fairly liberal diet remains apparently sugar free, we examine the urine several times each day and not only a 24 hours' mixed sample, we shall find that the number of absolutely sugar-free cases is considerably diminished, and we shall learn that at certain times sugar reappears in the urine. The same patient may pass urine half-an-hour later which again is quite sugar-free. I have analyzed the blood in many cases of this kind. Hyperglycæmia was present in all of them.

One may perhaps wonder how it is that in spite of

the hyperglycæmia, the glycosuria is inconsistent. This depends upon special renal conditions, a fact which I called attention to some seven years ago; the kidney becomes less permeable to sugar as time goes on. While at the beginning of the disease, glycosuria appears when the sugar content of the blood is 1 per mille, later on the urine may be free from sugar, although the blood control has reached 1.5 per mille.

I consider this as a compensatory mechanism of the organism in order to avoid the loss of sugar. This fact has been since then confirmed by many observers. It has been shown also that the relations existing between hyperglycæmia and glycosuria are controlled by other factors, but an explanation is as yet not available. For instance, hyperglycæmia is present in febrile conditions, yet glycosuria is rare. One can only suppose that here the cause is some change in the renal filter.

Let us return now to a consideration of the complications of diabetes. I have taken an active interest in the forms of neuritis; they seem to be a direct heritage of diabetes; in no other complication is it so easily possible to trace the absolute dependence of the condition upon the course of the underlying disease. Diabetic neuritis exhibits numerous manifestations. Frequently it is only a slight pain which moves about, now in the arms, shoulders, muscles of the breast, back or gluteal region, bones, now in large joints, such as shoulders or knees. Very often there is pain in the calves that later becomes a definite cramp at night. A favorite seat of marked sensibility and slight pain is

the external cutaneous femoral nerve which manifests paresthesia and neuralgia. If we examine diabetics carefully from this standpoint, we shall find that 50 per cent. at least of all diabetics show hypo- or hyperesthesia of this region. As I have said, these sensory changes are often "wandering" in type. We may call them "dolores vagi." At other times the area affected is more definitely related to certain nerve tissues and we meet with a definite, although not very severe, form of neuralgia (sciatica, lumbago, intercostal neuralgia, brachial neuralgia, etc.). This diabetic neuritis exhibits an elective character in that it picks out the sensory fibers. I place the feelings of pains by fatigue in the same category. Somewhat rarely the motor fibers are also attacked; the nerve more frequently involved is the crural nerve; then comes the axillary and the oculomotor nerves. Of the sensory nerves, the optic nerve is the most often affected. This is often not noticed. If we, however, examine regularly the visual fields of our diabetic patients we shall be surprised to find how often there is a certain contraction of the visual field, in some cases for all colors, in others for individual colors. The ophthalmoscope may not reveal the slightest changes. These are characteristic features of a retrobulbar optic neuritis.

I ought here to point out that these above-mentioned sensory disturbances have sometimes led to inaccurate diagnosis. For months or years the patients had been treated for rheumatism or gout with restriction of

meat food, and the application of electricity, massage, baths of various sorts, and more recently with radium emanations. A certain improvement had resulted, but there had not followed any permanent healing and prevention of recurrences. Occasionally the urine had been tested for sugar; none had been found, or only traces, and these had disappeared before the next analysis. Therefore one had rejected the diagnosis of diabetes, but this was wrong. One had rather to deal with a pure diabetic neuritis. I have seen many hundreds of such cases, and am able to state that in every one of them surprising results have followed a well-directed use of anti-diabetic dietaries. I may emphasize the fact that complete healing of the troublesome symptoms will only take place when the urine is quite freed from sugar; it is not sufficient simply to obtain a diminution. It is also necessary to remember that unless the hyperglycæmia is removed the troubles will not cease. This is the same in all diabetic complications. In diabetic gangrene it is especially important to attack the hyperglycæmic condition. We are often surprised that the process heals so slowly in spite of the fact that the urine is free from sugar; if the blood is analyzed, however, the explanation will be quite clear; the hyperglycæmia has not disappeared and very energetic treatment will be found necessary to effect its removal. Once this is effected, the healing will progress more rapidly.

You see, therefore, that the carbohydrate restriction and the substitution of other nutritive material are not

alone aimed at the cessation of the diabetic glycosuria, but the same measures tend secondly to avoid possible complications and to terminate them when they occur.

c. Treatment of the Hyperirritation of the Sugar-Forming Apparatus

1. *Disadvantages of Carbohydrates.*—Still more important is another consequence of the carbohydrate restriction. We have seen that in diabetes the sugar factory is in such a high state of excitability, that every stimulus calls forth an unduly intense reaction, or, to put the matter in other words, an excessive formation of sugar is induced. The indications are to obtain rest for the overstimulated organ, to decrease the overweighting of the regulating factors to a minimum and to spare the sugar producing organs as much as possible. We utilize the same principles in all acute and chronic diseases. When a leg is injured, we put the patient to bed; in cardiac diseases we forbid bodily overstrain or undue excitement; in anatomical or functional changes in the stomach we select a form of diet which will give the organ the smallest possible amount of work; in renal disease, food is chosen which contains a minimum quantity of material which may damage the renal cells during elimination, or cause extra work to be thrown on the kidney. We consider that by such systematic sparing of the organs we are putting them into the best circumstances for their recovery and return to normal vigor. Then when we recognize the signs of a reappearing health and activity, we endeavor

by the aid of carefully graduated work to accustom the organ to its usual functions and to prepare it for the average amount of doing. This all appeals to us as being self-evident, and of course, we ought equally to apply the same principles in our diabetic therapy. As a rule, however, this conception does not obtain, and where it does it is usually carried out in a half-hearted measure only. This arises from the nature of the disease. With affections of the joints, muscles, heart, stomach, etc., therapeutic errors, neglect or too rapid return to work of the damaged organ, are at once evident; they admonish us at once to renewed care and vigilance. In diabetes, however, the chief difficulty lies in the fact that the danger is one of the future. This is the insidious peculiarity of diabetes. We do not at all disturb for the present the general well-being of the diabetic if we treat him badly and overweight his weakened functions; yes, we may even improve by psychical influence his momentary well being if we permit a more liberal diet. We are, however, playing a dangerous game. We are thinking only of the present and forgetting the future, the fortunes of which depend upon the vigilance of the practitioner. If we allow the patient suffering from renal disease as much meat and sodium chloride as a healthy individual can take each day without hurt, the damaged kidney is stimulated to do more work; we injure it further, and delay the recovery of the portions which can yet be healed. When we allow the diabetic to take whatever quantity of carbohydrate he likes, we commit the same fault; we overweight the compensa-

tory powers and hinder the recovery of the organs concerned. Carbohydrates act upon the sugar forming processes more intensely than any other irritant. When the carbohydrates enter the liver they set the glycogen-forming and glycogen-destroying processes in full swing. We see that carbohydrates also overweight the functions concerned with the regulation of the processes. This overloading brings about an immediate result, namely, an overflowing of the carbohydrates into the blood and its excretion by the urine. But it does not stop at that. It is quite easy to show that this is not the only harm which follows too great an intake of carbohydrate. We learn this from a case in which we determined a diet for a diabetic patient which allowed him to remain sugar free and then we exceeded the bounds of tolerance. It may be two or three days, or even a longer time, before the damage becomes really apparent. I append a table:

Day	Diet			Sugar in urine
1	Restricted	+ 20 gr.	Bread	0
2	"	"	"	0
3	"	"	"	0
4	"	50	"	0
5	"	"	"	0
6	"	"	"	5.2 gr.
7	"	"	"	12.7 "
8	"	20	"	11.3 "
9	"	"	"	8.2 "
10	"	"	"	7.1 "
11	"	"	"	4.9 "
12	"	"	"	6.4 "
13	"	0–	"–	0
14	"	20	Bread	0
15	"	"	"	0

The patient remained sugar-free so long as the daily intake of carbohydrates did not exceed 20 grams of bread. In order to see if he could be allowed more bread the amount was increased to 50 grams daily.

On the first two days, the patient took the 50 grams of bread wonderfully well; there was not a trace of sugar in the urine. The third day's urine contained a small amount, the fourth day's a marked glycosuria. We returned to the earlier diet at once. If it had been only the excess of 30 grams of bread, the organism was not quite ready for, then the urine upon the first, or at latest, the second day of the earlier diet would have been again free from sugar; the small quantity of carbohydrates present in the slight excess of bread is naturally rapidly consumed. But here we have a glycosuria which lasted five days longer and the urine only became free from sugar when we left away all carbohydrates one day long. But then the urine attained the same freedom from sugar as at the commencement of the experiment. The example is a typical one. It shows something that we can see every day; I could bring forward hundreds of similar instances. What ought we to learn from this? We may learn that we saddled the liver with more carbohydrate than it could deal with, and also brought about upon that hypersensitive organ an irritant action, which outlasted the primary effect and only disappeared when we allowed the irritated organ complete rest. We may perhaps sum up the matter in the following sentence: Overworking of the sugar

manufactories in diabetes not only leads to an immediate abnormal increase in the production of sugar, it also leaves behind an increased excitability.

2. *Disadvantages of Large Intakes of Albumin.*—As in the case of carbohydrates, so in that of large albumin intakes there follows an increased excitability of the sugar forming process, although much depends upon the type of the albumin. The extent of the irritation is less than that of the carbohydrate. This has been pointed out previously. The influence of the albumin is not the same in every case, however; a certain stage of the disease is necessary for the influence to attain any importance. This was so in the following example: The patient's urine remained free from sugar so long as the intake did not exceed 70 grams of albumin and as long as large amounts of green vegetables and fat were given. To this diet there was added 200 grams of beefsteak (raw weight) on two successive days. Already on the first day, sugar appeared in the urine; there was more on the second day; although through an immediate return to the first diet the sugar was reduced, the glycosuria failed to disappear for four days. Here also there was a

Day	Diet	Sugar in the urine
1	Meat, eggs, green vegetables, butter—containing 70 gr. of proteids	0
2	"	0
3	"	0
4	the same and 200 gr beefsteak	5.2 gr.
5	"	13.8 "

Day	Diet	Sugar in the urine
6	the same as on the I to III day	6.7 gr.
7	"	4.8 "
8	"	3.2 "
9	"	1.8 "
10	"	0

long drawnout effect of the transitory irritant. You cannot show in every case so clearly that forced work leaves such effects. The first need is naturally a proper arrangement of the dietary, and a careful watch over the patient. Secondly, it may happen in many cases, especially those of slight diabetes, that the effects appear more slowly than in the instance we have quoted. Sometimes, two or three weeks may be necessary before we clearly see that we overstrained the power of the sugar factory. This peculiarity of the slighter cases makes the determination of the tolerance factors very difficult, and may lead the inexperienced worker into error.

3. *Recovery of the Sugar-Forming Apparatus.*— When, on the one hand, we see that the overworking of the sugar factories becomes evident, in one instance quickly and in another more slowly, but that in all there is a definite progress to greater excitation of the organs and disorder of the regulating functions, we are bound to observe, on the other hand, that the principles of the calming therapy (Schonungs-therapie) are the only ones upon which the best and most satisfactory results may be based. Good results are often obtained within a short time. Sometimes weeks and months are necessary before a satisfactory effect follows. We must not forget, however, that in many

other cases our efforts may be futile, for we are face to face with a chronic disease and as in cardiac conditions and other chronic diseases we cannot expect too much.

An immediate improvement, however, can be obtained in every case of diabetes — light or severe — as a result of the calming treatment, and this may be demonstrated quite easily. I append an example of this.

The patient was on a fixed diet which contained 75 grams of bread in addition to albumin, fat and green vegetables; you will see that there was an average sugar output of 15 grams daily. Bread was then withdrawn and the patient put on a carbohydrate free diet for three weeks. The sugar soon disappeared. We then added bread gradually, and every third day we substituted a restricted diet. In this way we continued until we reached an intake of 80 grams of bread without a trace of sugar appearing in the urine. Through this form of calming treatment (Schonungscur) the tolerance of the patient was improved markedly in a very short time.

Day	Diet	Sugar in the urine
1	Restricted diet and 75 gr. bread	15.8 gr.
2	" "	12.2
3	" "	16.9
4	" "	14.1
5	" without bread	7.2
6	" "	2.1
7	" "	traces
8-27	" "	0

Day	Diet	Sugar in the urine
28	Restricted diet and 25 gr. bread	0
29	" "	0
30	" without bread	0
31	" and 35 gr. bread	0
32	" "	0
33	" without bread	0
34	" and 50 gr. bread	0
35	" "	0
36	" without bread	0
37	" and 65 gr. bread	0
38	" "	0
39	" without bread	0
40	" and 80 gr. bread	0
41	" "	0
42	" without bread	0
43	" and 80 gr. bread	0
44	" "	0

We decided further that the patient should take 60 grams of bread daily, but that once each week there should be a "vegetable" day on which not only the carbohydrate should be cut off, but the albumin reduced to a minimum. The first observation dates 15 years ago. Year by year the tolerance of the patient has improved and we have now got so far that sugar appears only when the amount of bread consumed exceeds 300 grams. That is a quantity which is more than the average intake of normal men. From the practical standpoint, therefore, we may consider the patient as cured; this is the more remarkable as the patient was 25 years old when the malady first appeared — an age pregnant with danger for a diabetic patient.

I could bring forward many similar examples, but I think that I have said sufficient to make clear the

principle underlying this form of treatment. I have treated personally a large number of diabetics and I know, in the majority of cases, the terminations of the condition. The wider my experience got, the more I learned to appreciate the enormous importance of the benefits attained by the institution and carrying out of well defined restricted dieting. It has been under these conditions alone that I have obtained real and permanent improvement.

C. Principles of Treatment in Slight Cases

One must not assume that every case of diabetes necessarily goes to the bad. There are some cases which do not show any progressive tendencies and only become worse when they are neglected or when there is allowed an always repeated excessive excitation of the sugar factory. The majority of these cases are among those just over 50 years of age. It is well known that the prognosis of diabetes in general is the more disastrous, the earlier in life the disease commences. Still, there are many diabetics of middle or early middle life in which a favorable prognosis is permissible and decades of life may be predicted provided that one avoids all that may give the disease a bad turn.

Of course, the earlier the case can be taken in hand the better it will yield to our treatment. We must profit by the period, when the glycosuria is still slight and disappears altogether under diminution or exclusion of carbohydrate food. One must ensure that

this be a permanent disappearance and that even transitory reappearance of the glycosuria will not occur. As I have said before, I think that this aim mostly is not fully attained and that not enough weight is laid upon the attainment, because one is more immediately concerned with the avoidance of large sugar excretion, and does not remember that even the slightest trace of urinary sugar shows that the sugar regulating functions are overburdened and over-irritated and that the sugar-excitation of an already defective function must lead to further deficiences. This is the more to be deplored, since it requires but slight restrictions and only a careful regulation of the dietary to keep the urine quite free from sugar. We may perhaps alter a French proverb to fit the case and say "Ce n'est que le dernier pas qui coute."

As regards the question of diet, the all-important point is the regulation of the carbohydrate and protein supplies. The degree to which the carbohydrate group in general or individual members of this group in particular should be reduced, must vary naturally in every case; and the same is true for the reduction of the protein group and its individual members as an auxiliary measure. I may say that out of 100 diabetics no two should be given the same dietetic prescriptions. As a general rule, the slighter the case and the greater the hope, that by avoiding unnecessary irritation the controlling factors may be brought back to health and strength, the more strict should be our regulations. This may be carried out with more con-

fidence, inasmuch as the danger of acidosis may be entirely excluded in these slight cases. Transient acetonuria may easily be set up if the diet is rapidly changed, but dangerous degrees of acetonuria need not be feared. When finally, after a considerable period, a threatening degree of acidosis occurs, it will be found that the glycosuria is also markedly worse. Then the acidosis does not appear as a result of the diminution of the carbohydrates, but because the whole disease is becoming worse in spite of the precautions taken against it. In many cases this is the inevitable course of events.

D. The Principles of Treatment in Transitional Cases

Contrariwise to my practice in slight cases, I am much more liberal in the severer ones; more liberal perhaps than the majority of physicians. In every case, I do indeed at first try to render the urine free from sugar by cutting out the carbohydrates and at the same time reducing the proteins, and very often by employing the so-called oatmeal cure as an additional measure, concerning which more will be said later. When this plan is carried out with necessary care and attention to detail, and when it is pursued for a sufficient length of time, it is surprising how often the severe form of glycosuria can be converted into a slighter form. To succeed in doing this, is to confer a great benefit on the patient. It is no light task,

and I should never undertake the risks of carrying out the necessary dietetic measures except in a sanatorium for dieting. There are rocks ahead in the shape of acetonuria which, though undoubtedly dangerous, may be avoided if foresight is used in directing the treatment.

E. Principles of Treatment in Severe Cases

When it is definitely impossible to convert a severe diabetes into a slight one, use what pains and care as to detail we may, the time has come for the employment of milder measures. The condition is one of permanent, irremediable over-stimulation of the sugar factory, and it makes little difference whether the patient excretes 20 or 30 grams of sugar under the very strict diet, and while suffering the greatest privations, or whether he excretes 50 to 60 grams under a careful but easily tolerated regimen. In the latter case, it is easier to secure the supply of a sufficient total of calories, as large quantities of fat can be supplied with the prescribed allowance of carbohydrates. On the other hand, I consider that it is most helpful to make an occasional break in the liberal dietary by interposing days in which the claims on the sugar factory are reduced to the smallest imaginable dimensions. These are days of recuperation for the sugar factory; indeed they are the Sundays interposed among working days. They shall do for the sugar factory what Sundays do for the body and soul, coming in, as they do, between the working days of the week.

Three degrees of these days of abstaining may be distinguished:

(a) Days of simply strict diet — that is, when carbohydrates are excluded.

(b) Days of vegetable diet, when only bacon, butter and a few eggs are taken besides green vegetables.

(c) Fast days, in which only weak tea, lemon squash, or whisky and soda are allowed. On such days, I am in the habit of ordering also rest in bed to reduce the total production of calories, and thereby the claims made on the sugar factory, to the smallest amount imaginable. There are but few diabetics who do not become sugar-free on these days, and you will at the time notice an enormous fall in the acetonuria. Fast days, combined with bed rest, are excellently borne. I never find that the patient's strength is unduly diminished by them. An important result is regularly attained in the immediate and well marked rise of tolerance which follows.

Of course it is only by taking into consideration the special conditions of each case, that one can settle how these days of abstaining are to be distributed, and whether we can confine ourselves to the milder varieties or whether we must occasionally call to our aid the most rigid kind — namely, the single days of fasting. Without going further into details, I will now give some examples:

I. Example:

6 days' restricted diet + 80 gr. bread (or equivalents).
1 day restricted diet alone.

5 days' restricted diet + 80 gr. bread.
1 day vegetable-egg-day.
The same scheme begins anew.

II. Example:
5 days' restricted diet + 60 gr. bread.
1 day restricted diet alone.
1 day vegetable-egg-day.
5 days' restricted diet + 60 gr. bread.
2 days' vegetable-egg-days.
The same scheme begins anew.

III. Example:
5 days' restricted diet + 60 gr. bread.
2 days' vegetable-egg-days.
5 days' restricted diet and 60 gr. bread.
1 day vegetable-egg-day.
1 day fasting day.
The same scheme begins anew.

IV. Example:
6 days' restricted diet + 80 gr. bread.
1 day vegetable-egg-day.
6 days' restricted diet + 80 gr. bread.
1 day vegetable-egg-day.
5 days' restricted diet alone.
1 day vegetable-egg-day.
1 day fasting day.
The same begins anew.

Many other combinations are possible and useful under certain circumstances. As increasing experience will show you, that in the severer cases the tolerance for carbohydrates will be improved in proportion as the protein supply is diminished, and that meat especially must be reduced, whereas the other proteins need not be diminished to the same extent. The patient must also be advised to take large quantities of fat, and it is necessary to give detailed study to the form and amounts in which the fats are consumed, in order to avoid damage to the digestive organs.

F. Tolerance Determination

If you do not wish, as it were, to serve a ready-made treatment to all, but consider it important that each patient should be ordered the mode of life and form of diet which is most suitable to his individual case, you will have to undertake very minute investigations. This is true of the slight as well as of the severe cases. I might even say that it is of more importance in the slighter cases than in the more serious, as in the former there is more to be gained by correct dietetic rules and more to be lost by wrong ones.

These tests I have called the "estimation of tolerance." They were first made by R. Kuelz in Marburg, and served him as the basis of an individualistic treatment of diabetes. I have further extended his methods, and adapted them to the modern scientific conceptions of dietetics. The whole of modern diabetic therapy is, however, based on the principles for which Kuelz contended. Before then there was only a hard and fast, superficial treatment, which took no account of the variety of clinical pictures seen in the disease. Kuelz took the diabetic into his private clinic, and tested him until he had found the method of dieting which gave the best results in that particular case. Many control tests were made, at least once in twelve months. Kuelz has now been dead for seventeen years. The greater number of his patients came under my care later on, and it is a brilliant proof of the fruitfulness of his methods, that I now have many

patients still under observation who were treated by Kuelz seventeen years ago and more, and who are still in excellent health.

In the meantime, Kuelz's original method has required much modification and extension. At first it was thought sufficient to determine the amount of carbohydrate which could be given to the patient, while ensuring a minimal excretion of sugar on the one hand and of acetone on the other. This is a relatively easy problem but its solution does not satisfy us at the present time. We now know that there are no diabetics who show a constant degree of tolerance for carbohydrates. It varies with the kind of carbohydrate, and with the intervals at which the carbohydrate is given. Many will stand the same total of carbohydrate much better when the whole amount is given at once; others must be given small portions frequently during the day. Many stand carbohydrates best in the morning, others in the afternoon or evening. Some patients show a much higher degree of tolerance when they take muscular exercise immediately after the carbohydrate food (especially the slight cases); others have to rest after carbohydrate food (especially the severe cases). Many patients do better on one kind of carbohydrate every day, such as bread alone or potato alone, or fruit alone; others can be given any change of carbohydrate they desire. Often it makes the greatest difference with what other kind of food the carbohydrate is mixed. It has frequently been noted that it is here

especially that the amount and kind of protein is important. I append a very convincing example from a man aged 38.

Day	Diet	Sugar in the urine
1	250 g. Oatmeal, 300 g. butter, 10 eggs (= 52 g. proteids)	0
2	"	0
3	"	0
4	"	0
5	250 g. Oatmeal, 300 g. butter, 250 g. beefsteak (= 52 g. proteids)	0
6	"	5.1 g.
7	"	12.3
8	"	22.0
9	"	27.4
10	green vegetables, eggs, butter	5.0 day-time 0 night-time
11	250 g. oatmeal, 300 g. butter, 10 eggs	0
12	"	0
13	"	0

Thus we cannot simply say the patient tolerated 25 grams of oatmeal, but we must add that this amount was only borne when combined with eggs and not when combined with meat.

The following is also an interesting example: A young diabetic girl of 20, who had a short time before had slight haematemesis, for two weeks took 2 litres of milk and 300 grams of cream, and 10 lightly boiled eggs (52 grams of protein) daily.

Day	Diet	Sugar in the urine
1-14	2000 g. milk, 300 g. cream, 10 eggs (= 52 gr. proteids)	0 to 5 gramm

Day	Diet	Sugar in the urine
15	2000 g. milk, 300 g. cream, ca. 150 g. curds (=52 gr. casein)	7.2 gr.
16	"	12.8
17	"	17.2
18	"	22.6
19	2000 g. milk, 300 g. cream, 10 eggs (=52 proteids)	14.8
20	"	11.7
21	"	9.3
22	"	8.1
23-28	"	0-6 g.

The daily excretion of sugar in the urine varied from 0 to 5 grams. In place of the eggs I then gave her for one week freshly precipitated washed and pressed casein, which she took mixed with cream. The nitrogen content of the casein was determined daily, and the patient took the same quantity of casein as she had previously taken of egg albumin. I thought that the patient would bear casein better than eggs, as it was the same protein as that which she had been taking in considerable quantities in her milk, and had been accustomed to take well. But the result was exactly the opposite; increasing amounts of sugar appeared in the urine, and then again fell to nothing, or a mere trace, as soon as she returned to the diet of milk and eggs. I could add many similar examples.

Besides the influence exerted by diet, its quantities and the way in which it is mixed, there are many other factors to be considered, some of which influence the glycosuria and the acetonuria, and some of which are of importance as regards the general health

of the patient. Such, for instance, is the amount which the patient drinks, the influence of alcohol, of baths and other hydrotherapeutic measures, of sleep, etc. I have treated this subject in another place ("Neurogenous Diabetes," *Medizin. Klinik,* Heft 1, 1912), and have shown that in many patients the amount of glycosuria is increased by want of sleep, and pointed out how these patients may be improved by treating the sleeplessness. It is true that often the matter is reversed; in many patients the sleeplessness depends on the diabetes, that is on the injurious influence of the hyperglycæmia on the nervous system. The best and most reliable method of improving the sleep is then an energetic régime. These are the commonest cases. The others in which sleeplessness induces or increases glycosuria are much more rare. In these it is apparently a stimulation of the sympathetic nervous system of central origin which is communicated to the suprarenals. There are then mostly other symptoms of sympathetic stimulation. The cases are usually ones with slight glycosuria, and marvelous results are obtained by combining the diabetic treatment with bromides or codeine, or by hydrotherapy or residence in a mountainous country.

You will see therefore that, for us, every case of diabetes bristles with questions; we need all our powers of observation and experience, and in addition to chemical investigations and a measured dietary we need also a minute investigation of all the physical and psychical conditions in order to obtain a clear

insight into the case, a full mead of success for the present measures, and a favorable outlook for the future. In place of the old-fashioned single test of tolerance, a very complicated procedure has arisen, which takes into consideration the extraordinary variations met with in cases of diabetes; and it is clear that work like this can be more readily carried out in a suitable nursing home than by observations and treatment undertaken in the patient's own dwelling. It is not my intention to enter in detail into the treatment of diabetes, but there are some important questions which must not be left aside.

G. Carbohydrates or Oatmeal Cures

You all know that twelve years ago I made the discovery that under certain circumstances large quantities of oatmeal can be tolerated; and from this discovery the so-called "oatmeal cures" have gradually been evolved, concerning which by this time a considerable amount of literature has appeared. For the first five years I was opposed by nearly all authors who wrote on the treatment of diabetes with oatmeal; they had not sufficiently observed the clear directions which I had given for carrying out the oatmeal cure, and consequently they got bad results. For the last five years things have been different. My observations have been fully confirmed by many well-known authors, and I now have to complain that the oatmeal cure has been much over-valued. Partly in its original form and partly in numerous modifications it has been much

more frequently and exclusively employed than is advisable in the interest of diabetes. I have myself from time to time warned people most emphatically that the oatmeal cure was not to be regarded as a panacea for diabetes; this warning has not been sufficiently taken to heart. The most important points are illustrated by the following example, taken from the case of a fellow-countryman of your own, aged 48, whom I treated some time ago for a number of years.

Day	Diet	Sugar	Nitrogen	NH_3	Aceton.
1	Restricted and 75 g. bread	70.8 g.	18.2 g.	2.2 g.	2.6 g.
2	" "	58.2	19.5	2.8	2.7
3	" "	65.8	20.7	2.3	2.5
4	" ; no carbohydrates	43.3	23.8	3.2	3.9
5	" "	34.7	19.5	2.1	2.3
6	" "	35.2	19.7	2.0	2.8
7	" "	33.7	18.9	2.2	3.1
8	" "	38.9	20.1	2.9	3.8
9	" and 25 g. oatmeal	42.9	17.6	2.0	1.8
10	" "	53.8	18.9	2.4	1.7
11	" ; no carbohydrates	39.1	20.6	1.8	2.2
12	" "	32.0	17.5	2.2	2.7
13	" "	29.7	19.5	1.6	2.1
14	" "	28.3	18.6	1.7	1.6
15	Green vegetables, butter, 5 eggs	14.1	15.8	1.2	1.4
16	" "	6.4	9.9	1.1	1.2
17	" "	traces	10.3	1.5	1.7
18	" "	0	11.8	1.3	1.2
19	250 gr. oatmeal, 300 g. butter, 100 g. glidin. (veget. prot.)	0	9.8	0.9	0.6
20	" "	0	12.1	0.7	0.3
21	" "	0	8.8	0.7	0.1

Day	Diet	Sugar	Nitrogen	NH_3	Aceton.
22	Green vegetables, butter 5 eggs	0	7.9	0.8	0.25
23	" "	0	8.3	0.8	0.3
24	Restricted; no carbohydrates	0	13.7	0.9	0.2
25	" "	0	16.1	0.9	0.15
26	" "	0	15.6	1.1	0.2
27	" "	0	18.1	1.3	0.3
28	" and 25 g. oatmeal	0	16.2	0.9	0.1
29	" "	0	15.4	0.7	0.2
30	" "	0	17.2	1.0	0.35
31	" "	2.8	16.7	1.1	0.4
32	"; no carbohydrates	0	17.2	1.3	0.3
33	" "	0	16.1	0.8	0.2
34	" "	0	19.3	0.9	0.15
35	" "	0	16.4	0.7	0.08
36	" "	0	17.8	0.9	0.09

Analysis of the Table.—As you see, the case was one of severe diabetes with marked acetonuria. Carbohydrates were excluded on the fourth day, but the patient did not cease to excrete sugar. The glycosuria decreased considerably, and finally remained at about 30 grams per day (twelfth to fourteenth day). The ammonia and acetone increased in the beginning which is usual when bread is excluded, but the gradual spontaneous fall in these figures gave a favorable outlook for the future. Then on the 9th and 10th days, 25 grams of oatmeal were added, with very bad results, as you see. I then cut off meat, and considerably diminished the total amounts of protein, as can be seen from the figures of nitrogen excretion. By means of this more severe régime, I succeeded in diminishing the glycosuria considerably, and on the fourth vegetable-day it had entirely disappeared.

Then for three days the patient was subjected to a typical oatmeal diet, with the addition of a considerable quantity of vegetable protein. We gave Klopfer's glidin, as it is far the best among the vegetable protein-preparates. No sugar was excreted and the acetone fell enormously. No wonder that the 22nd and 23rd day (vegetable diet) produced no sugar. But you will see that from the 24th day onwards the patient was able to bear the ordinary diabetic diet rich in proteids, which had formerly (days 8 to 11 and 11 to 14) resulted in the output of large quantities of sugar. Thus in the interval his tolerance had been considerably raised. From the 28th to the 31st day I interposed an experiment with 25 grams of oatmeal (just as formerly on the 9th and 10th day). The result was not quite satisfactory; it is very characteristic that the small amount of 25 grams of oatmeal was not well borne when combined with meat diet, whereas formerly ten times as much had been exceedingly well tolerated.

The most important point brought out by this table is, that a system of diet was discovered which enabled a large amount of carbohydrate to be absorbed and assimilated without producing glycosuria, even in a severe case (days 19 to 21). Although we must not suppose that such a diet could be carried out for long, and although I drew attention in my first publications to the fact that a long continuance of such a régime destroys its efficacy, yet the intermediate result is of the greatest importance for the whole treatment of

diabetes. It makes all the difference to the chemical processes of the body, that we can now employ a method by means of which, from time to time, we can fight the harms which may spring from long periods of restricted diet. You will see from the table the remarkable effect on the acetonuria which the oatmeal can produce. The acetone at once fell, and thenceforth remained at a low level not only for a few days or weeks, but as I must say for many years. The immediate and permanent results are not always so favorable as in this example; but cases are exceedingly numerous in which the oatmeal cure will avert the sudden danger of severe acidosis, and allow us time to bring the sugar production gradually into correspondence with the sugar consumption.

In order to obtain a good result from the oatmeal cure, an important preliminary is to reduce the glycosuria as much as possible by previously diminishing the intake of food to a marked extent. A few vegetable days are often sufficient, as in our example; but often it is necessary to let a single fast day precede the oatmeal cure. I never order more than three oatmeal days in succession; on the other hand, it is often useful to let a vegetable day or a fast day follow immediately on the oatmeal days, and then to begin the oatmeal period anew. By this means, the object may be often attained which the first oatmeal period failed to accomplish.

At first we tried to explain the peculiar action of the oatmeal cures by the special properties of oatmeal

starch, or by the presence of special chemical substances in the grain. Further researches, undertaken by myself and others, have, however, shown that similar results can be obtained with other meals, provided that strict adherence is given to the rules I have laid down, that is, to render the urine free from sugar beforehand, and so give no meat with the carbohydrates. I have myself experimented with barley meal, banana meal, linseed meal, peas meal, potatoes and apples; others have tried wheat meal and grape sugar.

These new experiences by widening the original oatmeal cure, no doubt mark a great practical and theoretical advance and we have now a larger choice, when we determine to institute a carbohydrate cure. However, it has become increasingly apparent that it was a peculiarly lucky chance that I first chose oatmeal for these investigations; for the different kinds of meal have not by any means the same value. In most cases in which comparative observations were made, oatmeal showed itself to be much the best. We do not yet know why the oatmeal cure sometimes does good and sometimes harm, and why in some cases one carbohydrate and in others another, gives better results. Much work is yet to be done with regard to this, which will no doubt yield great results in the treatment of severe diabetes.

Almost all the authors who have studied the effects of large quantities of oatmeal and other carbohydrates on diabetic glycosuria, agree in stating that only temporary use must be made of such methods of cure.

They should be inserted between periods of stricter diet, especially in the case of patients who can only as a rule be allowed very small quantities of carbohydrate, if any. In the slighter forms where from 80 to 100 grams of bread can be borne without glycosuria, such cures are at least useless, and the general impression is that they do more harm than good. Clearer indications cannot at present be laid down, and a very considerable amount of personal experience is necessary before one can predict whether this method of treatment will have good or bad results.

There is also another form of "carbohydrate cure" to mention, namely that proposed by R. Kolisch and G. Rosenfeld, and other workers. They base their ideas upon the type of nutrition which will allow the relatively largest amount of carbohydrates to be used — "Greatest oxidation conditions of carbohydrates" as Rosenfeld calls it. The following shows an example of the method:

Day	Diet			Sugar in the urine	Sugar average	Sugar assimilated (average)
	Proteids	Fat	Carbohydr.			
1	112 g.	160 g.	36 g.	20.4 g.		
2	"	"	"	18.2	21.0	15.0
3	"	"	"	24.5		
4	"	"	83 g.	36.9		
5	"	"	"	47.1		
6	"	"	"	42.8	47.5	35.5 g.
7	"	"	"	51.3		
8	"	"	"	59.4		
9	81	"	"	56.2		
10	"	"	"	42.8		
11	"	"	"	37.4	39.8	43.2
12	"	"	"	32.9		
13	"	"	"	29.7		

Day	Diet			Sugar in the urine	Sugar average	Sugar assimilated (average)
	Proteids	Fat	Carbohydr.			
14	81	160 g.	83 g.	35.2		
15	"	"	"	42.3		
16	"	"	"	41.8	43.5	39.5
17	"	"	"	48.3		
18	"	"	"	49.8		
19	81	"	0	20.2		
20	"	"	0	8.2		
21	"	"	0	1.6		
22	46	"	0	0		
23-28	81	"	"	0		
29	81	"	20	0		
30	"	"	"	0		
31	"	"	"	0		
32	"	"	"	0		
33	"	"	"	1.7 g		
34	"	"	0	0		
35	112	"	0	0		
36	46	"	0	0		
37	81	"	30	0		
38	"	"	"	0		
39	"	"	"	2.6		
40	46	"	0	0		
41	81	"	30	0		
42	112	"	"	0		
43	"	"	0	0		

This is an instance of a slight case. In four days after the considerable quantity of 83 grams of carbohydrate was withdrawn, the urine became sugar-free (on the twenty-second day) and it remained so on carbohydrate-free diet. On the three first days, out of 36 grams of carbohydrate the patient assimilated 15.0 grams only; when the intake was raised to 83 grams, he did not excrete the whole difference (47 grams), but the glycosuria rose from 16.5 grams to 47.5 grams, and the assimilation was represented by

43.2 grams. The assimilation improved further, when the proteids were decreased, but the betterment was limited practically to the first five days (9-13); while during the following five days the glycosuria rose and the assimilation was less complete. In the terminology of Rosenfeld and Kolisch we may say: "the best oxidation conditions" occurred with 83 grams of carbohydrate and a simultaneous strong decrease of protein; these authors would consider rightly that this is the ideal dietary for this case. You will at once see, however, that there are two chief drawbacks:

(1) The assimilation improves at the commencement only; later it decreases as the tissues come under the influence of the continued large quantities of carbohydrates. If we put the observation in the form of a curve we shall obtain similar curves in almost every case; and I am of the opinion that the authors, who recommended this form of dieting, did not continue it long enough; otherwise the results would have been less favorable.

(2) By this method, a freedom from glycosuria is never attained. I need only refer you to my earlier statement as to the great advantages of such a freedom.

The second part of the table (from 19 day onwards) shows the result of the methods I employ, and which are followed by nearly all recent workers. So soon as the carbohydrate was entirely withdrawn the urine became free from sugar. Then we added a

small quantity of carbohydrate and intercalated from time to time some days of restricted diet; with this, as you see, the general result was much more encouraging. On the 31st day, we were able to obtain the assimilation of as much carbohydrate as under the "best oxidation conditions" (14-18 day). The difference was only 9 grams and we had the additional advantage, that the urine remained practically free from sugar. The result would have been more favorable had it been possible to keep the patient longer upon a strict diet. However, we had lost so much time during the early period of the experiment that we could only allow 10 days for the strict diet.

I think, speaking generally, that this method of the so-called "best oxidation conditions for carbohydrates" is not to be recommended in cases, in which definite decrease of carbohydrate or long continued withdrawal makes the urine perfectly sugar free. The method certainly provides a convenient form of treatment for these patients; but its advantages relate to the present condition only — it does not provide for the future. I regard it as retrogressive in character.

It is another matter if we cannot obtain a sugar free urine by the removal of carbohydrates and the danger of acidosis threatens in the distance. For such cases the method is not new. In my contribution to the "Twentieth Century Practice of Medicine" made some seventeen years ago, you will find that I suggested a daily intake of 50-80 grams of carbohydrates

for such cases, proposing also that short periods of restricted diet should be interposed. This is the standpoint of the majority of physicians to-day.

H. Therapy of Acidosis *

I must not close this section on the dietetic treatment of diabetes without making some remarks upon the prophylaxis and treatment of acidosis. I shall refer, however, only to the more important points. I can rely upon the experience gained from thousands of cases of diabetes which I have treated during the last years in hospitals and sanatoriums for weeks and months, and have daily records of the acetone and oxybutyric acid outputs. In the majority of these cases, the observations have been repeated and controlled over periods of many years — some of them over twenty years.

They fall into two main groups:

(1) Those cases in which by systematic partial or complete restriction of carbohydrates or by changes from strict to liberal diets, a sugar free or almost sugar free urine is obtained. Of course, one of the primary objects is to maintain the general nutrition at a high level; this is naturally the first care. We find, almost without exception, that the acetonuria is practically undemonstrable, or that it sinks to a danger free level. At the commencement, while the patient is getting accustomed to the dietary, we may have to

* A more complete description of the treatment in acidosis is to be found in the last chapter of this book — page 126.

deal with an increased acetonuria; the ferric chloride reaction may be strongly positive and oxybutyric acid may appear in the urine. This is the reason why so many physicians consider that the withdrawal of carbohydrates is dangerous; they relinquish the scheme of restricted diet as soon as these phenomena appear. I believe that, if they have not a wide experience, they act rightly in such instances. For all problems of this transitory period are very difficult, and only an extended personal experience and the most careful daily control and daily estimations of acetone enable a safe steering of the ship past these dangerous rocks. Everyone meets with disastrous experiences at the onset, and also I have not been able to escape them. In the first time, when as a result of closer investigation upon diabetes, partly from theoretical considerations and partly because of the astonishingly good results of Kuelz and Stockvis, I became a follower of the restricted diet method. I often was frightened by the acetonuria and I had to ask myself if this was really the best way after all. The time required to accustom a patient, *without danger,* to a diet which ensures sugar free urine, varies considerably. Sometimes it is a matter of days only; sometimes it requires weeks. During this period the tissues learn only by degrees to utilize fatty acids without carbohydrates. When this dangerous transitory period is however once safely passed, there follows a long interval in which, in spite of a restricted diet, acetonuria need not be feared. We have, it is true,

often to reckon with a few centigrammes, or even 1 or 2 decigrammes, of acetone in the total daily urine, because we cannot make the chemical changes in the fatty acid cleavage entirely independent of the carbohydrate intakes. But we would find a similar quantity of acetone in the urines of healthy individuals subjected to a similar dietary. This is therefore an alimentary acetonuria and not one arising from the diabetes and leading to dangerous results. It is advisable that this slight physiological acetonuria should be tolerated rather than an attempt made to overcome it by increasing the carbohydrate intake — a project which in the end would most certainly make the diabetic condition worse. Every fear that the small amount of acetonuria could increase to a dangerous height must disappear in view of the experience founded on fact. Of those of my patients, who upon suitable dietaries permanently kept free from glycosuria, or almost so, many of course have died. I have taken the trouble to ascertain the cause of death in these instances. In 82 cases there was not a single one who succumbed to diabetic coma; the immediate causes were quite otherwise: — pneumonia, influenza, typhoid fever, tuberculosis, cerebral hemorrhage, arteriosclerosis, carcinoma, etc.

Naturally, we cannot obtain the best results in every case; many continue their diabetic career unchecked, in consequence of progressive pancreatic lesions. Here the tolerance gets lower, the glycosuria cannot be stopped, and the acetone and sugar outputs

increase, not because of continued restricted diet, but in spite of these wise prescriptions.

(2) This leads us on to other cases in which it is impossible to render the urine sugar free even after restricted diet. To obtain sugar free urine it would be necessary to apply more rigorous regulations and to introduce vegetable and oatcure days. As I have already shown, it is useful to interpose such days from time to time, so as to lessen the excessive rise in the sugar output. At one time, when the oatcure and its counterfeits were not known and when for these abstaining periods there was only the choice between an ordinary restricted and a vegetable diet, the patient ran each time a fresh danger of acidosis. Now that we have learned to combine these days of restricted diet with days of oatcure etc., the conditions are quite opposite. We gain if we rightly advance facts — just during these periods, an increased tolerance for carbohydrates and a diminished acetonuria. Such vegetable and oatcure periods must however not be used too freely — four to six times per year is quite sufficient.

In the long intervening periods we must give the patient with severe glycosuria a relatively large amount of carbohydrates. He will naturally excrete much sugar, but it makes no great prognostic difference, whether the output reaches 40 or 60 grams per day or more. Single vegetable or hunger days now and then must curb the increasing glycosuria. We must proceed in this way, because experience has shown that

by these means the acetonuria is kept down to the lowest level. The extent of acetonuria varies in different cases, and it is common knowledge that there is in severe diabetes a tendency to a gradual augmenting of the acetone excretion; for the majority of cases of diabetes with marked glycosuria tend to persistent progression. These are the cases in which, according to old custom and the newer proposals of Rosenfeld and Kolisch, we try to point out that form of diet which warrants the largest quantity of carbohydrate to be assimilated, whilst we lay not too much stress upon the amount of sugar in the urine. When we endeavor to obtain this information, we find that it is not only difficult but requires much time, as each case must be investigated as an entity; it is important to follow it through for long periods. Hard and fast rules do more harm than good.

I may bring forward here an observation made in 1902. It concerns a patient, aged 52, with a glycosuria of ten years standing, and a definite acetonuria. However, the patient was able to work for another eight years. He then died from an attack of apoplexy.

Day	Diet	Sugar	Nitrogen	Aceton
1	Restricted diet and 100 g. bread	80.2 g.	20.4 g.	2.3 g.
2	" "	92.3	23.6	2.8
3	" "	79.4	22.8	2.6
4	" without bread	62.8	25.3	3.6
5	" "	58.1	23.8	3.9
6	" "	54.2	24.1	3.2
7	" "	53.8	19.3	3.5
8	Vegetable-egg-day	38.2	14.8	2.6
9	"	21.1	11.2	1.9

Day	Diet	Sugar	Nitrogen	Aceton
10	Vegetable-egg-day	18.7	10.7	1.8
11	Oatmeal 250 gr., butter 300 g.	23.4	6.8	2.1
12	" "	13.4	5.9	1.1
13	" "	12.7	8.1	0.7
14	Vegetable-egg-day	2.8	11.6	0.8
15	"	0	10.8	1.3
16	"	0	12.9	1.6
17	Oatmeal 250 g., butter 300 g.	0	7.9	0.7
18	" "	0	6.2	0.3
19	" "	0	6.9	0.4
20	Vegetable-egg-day	0	10.3	0.8
21	"	0	12.4	0.9
22	Vegetable-egg-day and 200 g. fish	6.9	14.2	0.8
23	" "	11.2	15.8	1.3
24	Restricted diet; once meat, once fish	20.4	18.2	1.9
25	" " "	17.3	18.1	1.4
26	Restricted diet and 60 g. bread	29.1	17.1	1.1
27	" "	35.4	16.8	1.5
28	" "	33.9	18.2	1.9
29	" 100 g. bread	49.9	15.4	1.3
30	" "	55.0	14.7	0.8
31	" "	62.7	16.9	0.6
32	" "	59.3	15.3	0.9
33	Vegetable-egg-day	18.6	10.1	0.9
34	Restricted diet and 120 g. bread	48.8	14.7	0.7
35	" "	64.3	15.2	1.3
36	" "	78.6	14.6	1.6
37	" "	85.2	16.7	1.8
38	Vegetable-egg-day	22.3	11.7	1.3
39	Restricted diet and 80 g. bread	29.8	16.8	1.1
40	" "	38.2	18.1	0.8
41	" "	40.1	15.2	0.7
42	" "	35.3	14.2	0.5
43	" "	34.9	14.7	0.6

Day	Diet	Sugar	Nitrogen	Aceton
44	Vegetable-egg-day	12.7	9.2	0.5
45	Restricted diet without bread	16.9	13.7	0.6
46	" "	20.3	14.9	0.9
47	" "	20.7	16.1	0.9
48	" " and 80 g. bread	31.6	15.4	0.6
49	" " "	34.2	14.3	0.7
50	" " "	38.1	14.9	0.5
51	" " "	36.7	16.2	0.6
52	" " "	35.8	14.7	0.5

From this observation we learn that (1) in a case of severe glycosuria, by a simple restriction of carbohydrate it was not possible to stop the glycosuria (days 4-10; 22-25; 44-47).

(2) The marked influence of the interposed vegetable and oatcure days upon the raising of the tolerance and still more upon the diminution of the acetonuria. The good effect was not only temporary; it persisted. Also during succeeding months and years the acetone output varied from 0.5-1 gram. These are not dangerous quantities; one had to be satisfied with them, for except in the times when the oatcure was given we could not obtain any lower figures.

(3) 80 grams of bread as an addition to the restricted diet was the amount which was best borne. With 100-120 grams of bread glycosuria increased too much and the acetone output was higher. With 60 grams of bread glycosuria appeared nearly to an equal extent as with 80 grams, but the acetonuria was much more marked.

The deductions made were as follows: The patient should be given a limited amount of albumin and 80

grams of bread daily; every fifth day a vegetable-egg-day should be ordered and every second month a period of vegetable-oat days prescribed. The results justified the prescription; for many years the patient exhibited remarkable energy and remained free from complications. Of course it was necessary to repeat the observations from time to time in order to see if the amount of bread should be changed; for instance, I found that in the following year the lowest acetone output with 60 grams of bread; this indicated improvement in the diabetic process, while three years later it was preferable to raise the bread to 100 grams, because this was the quantity which produced the smallest excretion of acetone bodies. As to the necessity of prescribing alkalies to all patients who are in danger of acidosis I need not refer. It is already well known.

I. Drugs

a. Salicylates, Antipyrin, Nervina, etc.

I must give a few words only to the treatment of diabetes by drugs. We know of certain drugs which tend to decrease the glycosuria, namely salicylates, antipyrin, calomel, jambul. However, we must bear in mind that carefully conducted investigations show that the powers of these medicaments are somewhat limited. The positive results are so slight that we really ought to consider whether we are right in subjecting the patients to the action of such strong drugs. Salicylic acid is by far the most valuable. At one

time I recommended aspirin, but I have had three cases of diabetes lately in which an acute nephritis followed the use of aspirin; I am now naturally a little less inclined to prescribe it.

Perhaps the most useful drug is nervina and among them the bromides, veronal and opiates. Of the last, I prefer the new Pantopon to the older and much used extractum opii and codein. If we reflect as to the type of case in which nervina is valuable, we are bound to conclude that the benefit is much more marked in nervous patients, particularly those suffering from insomnia. You will often find that after a bad night, the glycosuria is more obvious than after a good night. I can bring to mind cases which during a sleepless period and a restricted diet excreted large amounts of sugar, while in times in which good sleep was obtained by the use of veronal or bromides, 40 to 50 grams of bread could be taken without any onset of glycosuria (see *Med. Klinik,* No. 1, 1912. "Neurogenous Diabetes"). It seems most probable that the nervina lower the stimuli which are sent from the central nervous system to the liver by way of the chromaffin system, or cut them out; that they exert an influence upon the internal secretion of the pancreas is not known and is rather improbable. We know, however, that the neurogenous elements in glycosuria vary considerably in different individuals and so it is easy to understand how it is that nervina in one case produce good results while in others they are unsatisfactory or ineffective.

Of course it is not necessary to treat all the nervous manifestations of diabetes with narcotics. There are other methods, such as hydrotherapy, etc. I need not go into this aspect of the question just now. The use of narcotics can only be temporary; in the end they lead to more disadvantages; that goes without saying. If we ask ourselves whether these drugs possess the power to produce a marked and permanent influence upon the metabolism of a diabetic, we are compelled to give regretfully a negative reply. They are only aids with a limited application.

b. Mineral Waters

What I have said about drugs must also be stated about mineral waters (Carlsbad, Neuenahr, Vichy, etc.). No one believes to-day that Carlsbad and the other waters possess the power of curing diabetes. Yet we hear about satisfactory results from this cure. Its value lies in the fact that at least for a month the diabetic at Carlsbad lives carefully, and that in connection with the drinking of the waters, there are certain dietary restrictions which he does not undergo in his own house. It is thus quite natural for the glycosuria to decrease and the tolerance to rise; in some cases the improved tolerance may last for some time, although the advance is soon lost when the patient returns to the irregular dietaries of home life. In addition, in the health resort places there is an absence of unrest and worry and business cares, and this tends to diminish the general nervous tension and to

weaken the harmful nervous stimuli. In slight diabetes there is also the regular muscular exercise practiced at spas which in itself influences the glycosuria favorably. In other patients, there are the complicating disturbances of the stomach, intestine, liver and kidney which lower the general well being of the body, and which are improved by a " drink-cure." So it is that the majority of diabetics look back upon their " drink-cure " with content and gratitude.

These drink-cures at Carlsbad, Neuenahr, etc., however, are only of real use for the future if the patient, when he returns home, has learned to order his life and especially his nutrition according to the needs of the case. But in the spas it is difficult or rather impossible to attain this aim; for the control that is a necessary basis for the individual dietetic prescriptions, is not at hand in the spas. This can be done much better in sanatoria and clinics. By these remarks I will not disparage the value of the " drink-cures." The sanatorium treatment of diabetes is a necessary help and not a substitute for the " drink-cures." It is the well tried basis for the *home-treatment.* What in the sanatorium has been pointed out as the best form of his diet, that the patient shall continue at home. Remember, not the one month " drink-cure " governs his future, but the way he lives the remaining eleven months of the year, decides his life.

If on the other side the therapeutic extent of the mineral water cure be exaggerated, it constitutes a

source of danger for the diabetic, who is liable to imagine that he has done all that is necessary for his health and so does not put a curb on his diet or on his general condition of existence.

c. Specialties, Secret Medicines

I must not draw to a close without considering the mischief caused by the secret remedies and patent medicines which are constantly being advocated. Most of them contain much stuff that is quite worthless; they also contain some drugs which do cause a slight diminution in the glycosuria, namely, salicylic acid, jambul preparations and others. In others, arsenic or alkaloids have been found; these are drugs which the physician prescribes in definite doses under a guarantee of their chemical purity; this guarantee is not available for these secret remedies. It would be interesting to follow out an inquiry into the why and the wherefore of the demand for these patent remedies. The manufacturer and retailer insists, either in print or by word of mouth, that during the course of medicine the dietary shall be free from carbohydrates, or practically so. The urinary sugar then of course sinks. The real cause is the well-recognized dietary limitations and the restriction of carbohydrates. Later the carbohydrates are gradually increased just as they are in scientific treatment, for the instructions issued from the manufacturer of patent medicines and specialties are copied from medical works.

The scientifically trained physician, who adds certain drugs to his dietetic treatment, now for this reason, now for that one, knows that the drugs play only a subordinate part. The vendor of patent medicines, on the other hand, labels his compound as the peculiarly combative and specific factor in the treatment and lays claim to a new discovery in the therapy of the disease. We must not go so far as to say that the whole matter always is a deliberate fraud; most frequently, it is an error of judgment arising from the fact that the vendors of these specialties have not had a training sufficiently scientific to enable them to discriminate between cause and effect.[1]

[1] As an example of these defective statements I may mention L. Bauer's Antidiabeticum, because it is also much sold widely in this country. The vendor claims that this preparation exerts a favorable influence upon diabetes. The compound is a mixture of a number of various indifferent extracts and contains, in addition, some salicylic acid, jambul extract, and kola extract. The *Deutsches Kaiserliche Gesundheitsamt,* that is the Imperial German office for public health, came to the conclusion that the claims made for this preparation could not be substantiated, and that the favorable results depended upon the observance of the directions as to food. Investigations conducted in scientific institutions have confirmed this statement; in view of the continually renewed assertions of the vendor, the "Kaiserliche Gesundheitsamt" again carefully went into the matter, and once more issued its destructive verdict. The vendor continued to make anew certain outrageous claims for his preparations, so Antidiabeticum was placed upon the black list of patent medicines and its announcements were forbidden in Germany under a penalty. In spite of this verdict of the highest recognized authority in the empire, the vendor would not acknowledge his error, but elected to accuse those who did not agree with him of a grudge against his great discovery. The cause of his error lies near to hand; the manufacturer of Antidiabeticum is a layman as re-

They exhibit unbounded faith in their statements, and their enthusiasm converts to their own faulty standpoint, not only the laity but also some physicians. If the physician falls into such a trap it is always because he does not understand the dietetic treatment of diabetes or has not taken the trouble to learn it. It often happens that he hears of one of his patients undergoing one of the much advertised treatments; the dietetic instructions sent with the remedy happen to be correct ones, and the doctor is astonished at the result. A deficiency in judgment and personal criticism allows the doctor to assume that he has come across something which is unknown in medicial science.

He is right in so far that he cannot personally explain the result, but he occupies a false position when he identifies his own capabilities with that of the medical scientist. An apology for his standpoint can only be based upon the fact that the therapy of dietetics in general, and of diabetes in particular, demands an acquaintance with a large mass of special knowledge and that in the earlier days clinical studies in this direction were very limited, while even now in many clinics there is much to be desired in this regard.

J. Concluding Remarks

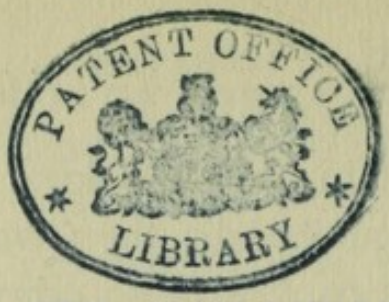
We hope that this will undergo a change for the

gards scientific and medical things. It is easy from the human standpoint to understand that he has committed the logical fault of considering an old and well recognized method (restrictions in diet) as a new one, after having colored it with an insignificant corollary (the drug).

better in time. Each year brings further knowledge and shows that with dietetic therapy successes can be obtained which are unequaled by any other form of treatment in the diseases of internal medicine. We must certainly neither forget nor neglect to give an adequate attention to the wonderful aids yielded by bacteriology, serology and opotherapy; all these, methods, however, are limited in their applications; dietetics, on the other hand, play a part in all forms of disease and extends into every aspect of internal medicine. Modern dietetics may be regarded as an offshoot from researches upon metabolism; both are intimately connected. I am proud as one who has made many contributions on this subject, to realize that dietetics is now recognized as a fruitful branch of scientific medicine, although at one time it was a little known and neglected step-child which the practicing physician, but not the scientific worker, cared for.

The cradle of scientific dietetics is certainly in Germany, but to-day all countries are taking their share in the work. Most valuable are the stimuli and advances which this country has contributed to the study of dietetics as a science. Your Department of Agriculture and your physiologists, Atwater, Benedict, Chittenden, Lusk, Mendel and others, working upon a broadly conceived and bold plan of action, have made fundamental additions to the laws of nutrition which show the high standard of knowledge and intense scientific capacity which, to its imperishable honor, modern America has attained.

Every subject in the physiology and pathology of metabolism is enriched by the advances made in the science of nutrition, but in no other disease have the results of experimental investigations been of greater importance than that upon which I had the honor to address you, namely diabetes mellitus.



ACETONURIA: ITS INFLUENCE ON THE TREATMENT OF DIABETES MELLITUS *

One of the most difficult problems in the treatment of diabetes is how to regulate the diet of glycosurics who are excreting acetone bodies. The observation that diabetic coma is coincident with the excretion of large quantities of acetone bodies has led us to consider the acetone bodies as the most dangerous enemies of the diabetic, and no doubt rightly, in a certain sense. Thus, both in practice and in the literature, we frequently find it stated that acetonuria must be avoided under all circumstances, and that it is better to suffer from a large output of sugar than from even a small output of acetone. This is not quite a correct view, and if adhered to will often turn the treatment of diabetes off the right path. The risk of acetonuria must certainly not be underestimated, neither must it be exaggerated. Diabetics may exhibit an acetonuria of a perfectly harmless nature, which must be regarded as physiological.

Before describing the circumstances and direction in which the occurrence of acetonuria should influence the course of treatment in diabetes, I must say a few words on the origin of the acetone bodies. This will make it

* This lecture was read before the St. Louis Medical Society, September 30th, 1912. It goes more fully into the very important questions on acetonuria, than was possible in the previous lectures.

easier for us to understand what follows. We have, it is true, no complete knowledge of the chemical process which gives rise to the production of acetone bodies, nor of the factors which control this process quantitatively; but our knowledge is sufficient to form an important basis in practice.

The primary acetone bodies are B-oxybutyric acid and aceto-acetic acid, from which acetone is probably derived as a secondary product. They are formed in the liver; generally speaking, the other organs take only a small share in the process. By far the most important sources of acetone bodies are the lower fatty acids in which the carbon atoms are arranged in straight chains, and certain amido-fatty acids. This has been clearly explained by G. Embden's researches. It also decides the old question as to whether proteins share in the formation of acetone bodies. This is quite possible, as the amido-fatty acids are components of all protein molecules. Both theory and practical experience show, however, that only small amounts are derived from this source, and that the pure fatty acids are by far the most important bodies in this connection.

The daily metabolism of fatty acids is enormous. We must recognize the possibility (which amounts almost to a probability) that the acetone bodies are normal intermediate products in the decomposition of fatty acids. How then does it come about that no acetone bodies, or only traces of them, appear in the blood and urine under normal conditions of nutrition and metabolism? Although suggested by a few earlier researches,

it was first clearly proved by the remarkable work of F. Hirschfeld that the production of acetone bodies in larger or smaller amounts depends entirely on the non-co-operation of the carbohydrates. The correctness of this view can be easily shown by suddenly depriving a healthy person of carbohydrate food. One of my former assistants carried out the following investigation upon himself:

Day	Diet	Calories of the food	Oxybutyric-acid
1	mixed	2200	0
2	200 g. meat, 200 g. fat	2130	0.84 g.
3	200 g. " 200 g. "	2130	1.91
4	250 g. " 300 g. "	3228	8.73
5	250 g. " 250 g. "	2658	20.00
6	250 g. " 250 g. " , 150 g. Reis	3180	2.21

For the sake of clearness, the total acetone bodies are reckoned as oxybutyric acid. You see that acetone bodies appear at once when the carbohydrates are withdrawn from the diet, and that they continue to increase considerably till the fourth day, when they again immediately decrease as soon as 150 grams of rice are added to the food. This is an alimentary acetonuria; it is normal and physiological in origin.

Relying on this and other similar examples, the following statement has often been enunciated: when a sufficiently large amount of carbohydrate is burnt up in the body, the fatty acids are involved in the process and are oxidized to carbon dioxide and water. G. Rosenfeld, in a somewhat different connection, coined the expression that " the fats are burnt, as it were, in

the fire of the carbohydrates." But when no carbohydrates are present, the decomposition of the fatty acids proceeds differently; by oxidation and decomposition one part is converted into acetone bodies, which being difficult to oxidize, pass over into the blood, and subsequently into the urine with acids substances (oxybutyric acid and aceto-acetic acid).

The quintessence of this observation, namely the fact that the normal course of carbohydrate metabolism hinders acetonuria, is well established; the view, however, that the principal factor is the *oxidation* of the carbohydrates must be thrown overboard, especially as the liver is known to be the principal seat of the formation of acetone bodies. The amount of carbohydrate oxidized in the liver is quite insignificant compared to that in other organs, and more particularly in the muscles. Moreover, it is not allowed to apply to diabetes mellitus (which is the disease always quoted as an example); for in this disease the oxidation of carbohydrates is not at all diminished.

We are drawn more and more to the conclusion that it is the *special carbohydrate metabolism* in the liver which in some way prevents acetonuria; on the one hand we have the perpetual formation and decomposition of glycogen, and on the other, its presence in the liver cells. The grape sugar in the blood cannot prevent the formation of acetone bodies; for it is present under the conditions which are specially favorable to their formation. In diabetes and also in pyrexia, the entire blood is rich in sugar. But all the conditions in

which we meet with acetonuria have this in common, namely, that they give rise to a diminution in the amount of glycogen; and if we take into consideration all the theoretical conclusions and practical observations we can now quite definitely assert that it is the presence of glycogen in the liver cells which assures the normal decomposition of the fatty acids. Deficiency of glycogen in the liver cells, on the contrary, favors the formation of acetone bodies. We do not know whether the glycogen itself is utilized in the normal decomposition of the fatty acids, or whether it is at times combined with the fatty acids or the products of their decomposition, or whether it only plays the part of a catalyzer.

It is a most remarkable fact and of the highest importance in the treatment of diabetes that forms of diet which at first lead to acetonuria, after a time cease to do so. For example, acetonuria is markedly decreased after *extended fasting* or a lengthy diet of protein and fat. As an example, I will quote a case of fermentative dyspepsia in which I ordered a diet consisting solely of meat, eggs, bacon, butter, drained sour milk cheese, and various kinds of over-ripe cream cheese during a period of three weeks, for therapeutic purposes. This was practically a carbohydrate-free diet. The daily excretion of acetone bodies calculated as oxybutyric acid was:

in	the	first	week.....	average:	12.8	gramm
"	"	second	"	"	8.3	"
"	"	third	"	"	2.2	"

Judging by our experience, a further continuance of the same diet would have led to still greater reduction of these figures, which would ultimately have reached zero.

A sort of tolerance, therefore, occurs, probably depending on the fact that the liver in time forms glycogen (and stores it up in large quantities) from substances which it does not use for this purpose under the normal conditions of nutrition. For instance, it may perhaps use the amido acids of the proteins, or the fatty acids — the latter in the same way in which grape sugar is formed from fatty acids and afterwards decomposed into lactic acid in the blood or muscles. Lactic acid, however, to a certain extent, inhibits the formation of acetone.

Nature herself shows us that a diet of protein and fat is not necessarily followed by acetonuria. The inhabitants of the Polar regions consume very little, if any, carbohydrate; and in the same way, carnivorous animals consume none at all. But they excrete no acetone bodies. Thus we learn that omnivorous man can continue in perfect health without carbohydrates, just as can a carnivorous animal.

What then is the position of the diabetic with regard to this matter? The diabetic is at a disadvantage compared with the healthy individual as regards the regular decomposition of fatty acids. The disturbance of metabolism which he suffers consists in a heightened tendency to sugar formation in the liver. All forms of stimulation which act on the liver and excite it to sugar

production, result in the formation of an abnormally large amount. First it is the glycogen which falls a victim to the morbid increase in sugar formation. The glycogen disappears from the cells as fast as it is formed. This, at any rate, is what happens in the most severe cases. In the slighter cases, no doubt, a certain amount of glycogen can be retained in the cells, as is shown by experiment and by chemical analysis of the liver post-mortem. Generally speaking, the exaggerated stimulus to sugar formation makes the retention of glycogen impossible, and thus in diabetics the biochemical essentials for acetonuria are produced. We must therefore determine the significance of diabetic acetonuria, both as regards prognosis and treatment, from this point of view.

The course of an acetonuria, as met with in diabetics, varies very greatly. On theoretical and empirical grounds we must distinguish absolutely between the slight and severe types of glycosuria; and also in these two principal groups there are differences which are both remarkable in themselves, and of great practical importance.

A. Slight Glycosuria

This group includes those cases in which the urine is rendered free from sugar when carbohydrates are much reduced, or entirely excluded from the diet. Total exclusion of carbohydrates is only practiced at the beginning of the treatment; after a short time small quantities are again introduced, and later somewhat larger

amounts; due caution being exercised in making each increase. On practical grounds we must cease to reckon among the slight forms those cases in which the urine only remains free from sugar when all carbohydrates are excluded for a lengthy period.

a. Cases in which Carbohydrates had been Freely Used

Patients who have hitherto taken a mixed diet fairly rich in carbohydrates are discovered to have sugar in their urine. Three or four per cent., perhaps, is found, or even more. Subsequent search for acetone bodies shows that they are absent.

The treatment of the metabolic disturbance is at once taken in hand; the carbohydrates are decreased every day, till after about a week they are completely excluded. This is done in order to abolish the most powerful of all the factors which stimulate the manufacture of sugar in the liver; and to spare those organs whose functions preside over sugar formation as a whole; and by this means to give them time and opportunity for recovery. This protective treatment, or in other words, the period of strict diet, is calculated to last for about two or three weeks, before carbohydrates are again very cautiously added to the diet.

The sugar in the urine diminishes and reaches zero after a few days of strict diet. But about two or three days after we have excluded the carbohydrates, we are horrified at finding a strongly positive reaction with chloride of iron; a quantitative estimation gives about one gram of acetone and 2 to 5 grams of oxy-

butyric acid, or perhaps considerably more. Unless the rationale of the formation of acetone is well understood, the "strict diet" will usually at once be abandoned. The doctor, fearing the development of coma, will order carbohydrate food perhaps in lavish quantities and with precipitant haste. But he is wrong. By this he throws away all his chances of practically influencing the morbid processes peculiar to diabetes. This acetonuria is entirely physiological; healthy individuals would have behaved in exactly the same manner, if put upon the same diet. It is an alimentary, and not a diabetic, acetonuria. I refer to the example given above — namely the research made up upon himself by one of my assistants. If, undeterred, we continue the strict diet, the acetonuria will again disappear in about eight or fourteen days, and the normal formation of acetone will again be established. In the many thousand cases which I have treated in the course of years, I have never seen one mishap due to the continuance of strict diet under these circumstances. Example from a man of 48 years treated in 1897:

Day	Diet	Sugar	Ferri-chlorid Reaction	Aceton
1	Mixed, rich in carbohydrates	60.8 g.	0	0
2	" "	69.2	0	0
3	Severe and 100 g. Bread	52.4	0	0
4	" " "	48.3	0	0
5	" 50 "	43.8	0	0.03
6	" " "	38.1	0	0.2
7	" without carbohydrates	19.4	0	0.43
8	" " "	4.3	+	0.7
9	" " "	0	+	1.3
10	" " "	0	++	1.8
11	" " "	0	++	1.1

Day	Diet	Sugar	Ferri-chlorid Reaction	Aceton
12	Severe without carbohydrates	0	+	0.8
13	" " "	0	+	0.52
14	" " "	0	traces	0.43
15	" " "	0	0	0.32
16	" " "	0	0	0.33
17	" " "	0	0	0.19
18	" " "	0	0	0.07
19	" " "	0	0	0.07
20	" " "	0	0	0.05
21	" " "	0	0	0.03
22	" and 20 g. Bread	0	0	0.05
23	" " "	0	0	0.03
24	" no carbohydrates	0	0	0.02
25	" and 30 g. Bread	0	0	0.02
26	" " 40 "	0	0	0.02
27	" no carbohydrates	0	0	traces
28	" and 50 g. Bread	0	0	"
29	" " "	0	0	"
30	" no carbohydrates	0	0	"

I have chosen this instance from among many others, because from observations on this case during a period of fifteen years I know that acetone bodies have never been present again in amounts large enough for quantitative estimation, although the patient restricts himself to the amount of only 50 to 80 grams of bread, and frequently for a time observes a stricter diet. A higher maximum could never be attained; as soon as the daily intake of bread or its equivalents reached 100 grams, sugar reappeared in a few days, if not immediately — a sign that the diabetic tendency was still active. The general condition of the patient who is now 60 years of age has all the time been excellent.

b. Cases in which Carbohydrates had been Disused

Here we have to do with a patient who has known for some months or years that he is suffering from diabetes, and throughout this period has confined himself to a diet very poor in carbohydrates. However, he has taken more carbohydrate than he could tolerate, and he excretes a certain amount of sugar either continuously or at least after the meals. You rightly suppose that a rather stricter regulation of the diet is all that is necessary to stop the glycosuria altogether, and you consider this desirable in order to arrest the continued hyperglycæmia and the complications which it entails. As in the case previously described, we at once enjoin a strict diet, and test continuously for acetonuria. We have found none before the beginning of the treatment, and to our delight we see that it does not occur during the period of strict dieting. The reaction with perchloride of iron continues negative, and the qualitative test for acetone shows at most only a trace. Why is this? This patient was so completely accustomed to a diet poor in carbohydrates, that their further total removal does not appreciably disturb the carbohydrate (that is, the glycogen) economy of the liver cells. Without any hesitation the practitioner will carry on the strict diet in these cases as long as he considers it advantageous for these or any other reasons.

When you have, for some years, placed diabetics on strict dietetic systems again and again — which, in

practice, is a very valuable and approved procedure — you will see that it is only during the first period of severe dieting, which the patient starts after a mixed diet rich with carbohydrates, that large amounts of acetone are found. When, in the intervals, the patient has confined himself within the limit laid down for him, in later periods of strict diet there is no further appearance of acetonuria — provided, of course, that the case still belongs to the category of slight glycosurics.

Year	Diet	Sugar	Aceton
1904	(a) mixed, rich in carbohydrates	40-50 gr.	0
	(b) 14 days severe diet; no carbohydrates	0	maxim: 1.4 gr. minim: 0.2 gr.
	(c) 11 months severe diet and 50-60 gr. bread	0	traces.
1905	(a) 14 days severe diet; no carbohydrates	0	traces; maximum 0.05 gr.
	(b) 11 months severe diet and 70 gr. bread	0	0 or traces
1906	One week severe diet; no carbohydrates	0	0 or traces

To curb the disease for length of time, to this degree, it is not always possible; for many cases, originally slight, carry in them the seeds of progressive deterioration, and we cannot check their course even by the most careful treatment, although we may be able to prolong it. From what I have already said concerning acetonuria in slight cases of glycosuria it follows that it requires no special attention from the therapeutic point of view. Of course, a sharp look-out must be kept. When the

patient is under careful control during the strict dieting — and this is the only period which can lead to acetonuria — the risks are so small that for a long time now I have even ceased to order alkalies when patients suffering from obviously slight glycosuria have to undergo periods of strict diet.

I must not leave this subject without mentioning that there are many cases of obviously slight glycosuria in which a few decigrams of acetone remain in the urine and the reaction with perchloride of iron never entirely disappears; not only during the entire period of strict dieting, but even when a considerable amount of bread is added, and completely assimilated (about 60 to 70 grams of bread or its equivalent).

Some of these cases are harmless, namely those in which the symptom occurs in persons of late middle age. No great importance need be attached to it, moreover, when it is observed in pregnant women with slight diabetes. Pregnancy of itself predisposes to acetonuria, and it is a fact well established by experience, that at other times also the amount of acetone bodies formed is very much under the influence of the personal equation. Not only diabetics but also healthy persons show great variations in acetone formation under precisely the same conditions of diet. In healthy persons, kept under identical experimental conditions, the acetone values may show a difference of 300 to 400 per cent. When a man with a family predisposition towards a large formation of acetone gets diabetes, acetone values may easily be obtained

which cause anxiety to the doctor; and it often requires a long and detailed study before one can be sure that it is a case of harmless, though unusually large physiological acetone formation, and not a dangerous pathological condition. The distinction is often very difficult to determine.

Continued acetone excretion of about one decigram or more when occurring in young diabetics must, however, be regarded with the greatest mistrust — even in obviously slight glycosuria. In this stage of the disease, the patients will tolerate a certain amount of carbohydrate, namely about 80 to 100 grams, provided that it is distributed in small portions throughout the day. The urine will then remain free from sugar, but will give a positive acetone reaction. We must take this as a sign that the capacity for glycogen storage in the liver has already been considerably damaged. In some of these cases I have estimated the sugar in the blood, and as was to be expected, have found considerable hyperglycæmia. With our present knowledge we cannot be surprised that, in spite of this, no sugar appeared in the urine; for we know that in many diabetics the kidneys become very impervious to sugar, even in the absence of nephritis, which never occurs early in such cases. The prognosis in these cases is very unfavorable. I have never seen any which did not assume a severe form in a year or two.

In spite of the persistent acetonuria, I would recommend you in these cases to stick to a diet which allows no sugar to pass into the urine, and to make the diet

as strict as the patient can bear. It is the only method by which the inevitable turn for the worse can possibly be postponed for long. A certain amount of alkalies must however also be prescribed, in order to ensure the removal of the acid products of metabolism. These, moreover, are just the cases which are specially suitable for the occasional application of an oatmeal-cure.

B. Severe Forms of Glycosuria

The matter becomes more serious when we have to deal with the cases of so-called "severe glycosuria," that is, those cases in which the withdrawal of carbohydrates alone does not free the urine from sugar, and in which to accomplish this we have also to effect a decrease in the protein constituents of the diet. If this measure is successful in rendering the urine free from sugar, the case may well be regarded as an intermediate form, and called "semi-severe." Such cases mostly develop from cases of slight glycosuria which have been neglected, and their place in the classification is entitled, because as a result of patient and well-directed treatment they can be brought again to their original slight type. In the genuinely severe cases, however, it is only very exceptionally that we can succeed in freeing the urine from sugar, and then only for a short time, however much we restrict the protein intake. We must consider separately the semi-severe cases in which some improvement is possible, and the severe ones; for with regard to acetonuria

these two types require an entirely different dietetic treatment.

a. Semi-Severe Cases

As a rule, the patient has been a diabetic for a considerable time. He has adopted the anti-diabetic requirements which, as usually ordered by medical practitioners, contains on an average about 80 to 100 grams of carbohydrate. The urine contains some percentage of sugar, but gives no marked reaction with chloride of iron; quantitative estimations, however, show that 1 or 2 decigrams of acetone can be obtained from the urine during twenty-four hours. The general condition is, on the whole, good, and the nutrition quite satisfactory. Closer investigation, however, shows that in most cases one or other of the complications of diabetes is developing or already present — such as the tendency to furunculosis, disturbances of vision, neuralgic or neuritic pains, which are often very incorrectly diagnosed as "gouty" or "rheumatic," and so treated. The patient has often been sent on previous occasions to spas, and there under the influence of a stricter regulation of diet and a careful ordering of his whole manner of life, has ceased to pass sugar and remained in this state for some time. Later on, however, these "cures" have failed, or produced only a quite inappreciable result.

We now make up our minds to try to convert the semi-severe type of glycosuria to the slight form from which it originated. It is not anxiety about the loss

of sugar which makes us do this, but the danger of prolonged hyperglycæmia, and also the always reappearing observation that it is just these cases that exhibit a further tendency to get worse when once they have begun to be progressive. The only practicable method is the dietetic; at times this not only involves very severe dietetic measures, but at the same time exposes the patient to the risk of acetonuria. It is obvious that here we must make free use of alkalies, but a mere allusion to this fact is all that is necessary here; I shall deal with the therapeutic use of alkalies in detail later on.

In accordance with our scheme of treatment we slowly reduce the input of carbohydrates to zero; the glycosuria diminishes, but does not disappear. At the same time, the amount of acetone bodies in the urine rises considerably; the reaction with chloride of iron becomes strongly positive, and we find 1 to 2 grams of acetone in twenty-four hours' urine. Nevertheless we persevere with the restricted diet, and the amount of acetone continues to rise, or at least remains very high. No doubt by this we are exposing the patient to a certain amount of risk, but this can be reduced to some extent by administering about 10 to 15 grams of bicarbonate of soda. We also keep a sharp lookout on the patient, and as soon as we discover any symptoms pointing to impending diabetic auto-intoxication — such as headache, excitement, hyperaesthesia of the stomach, etc.— we shall add carbohydrates to the diet. We have been advancing too rapidly, and must wait

a little while, and then begin again to try and eliminate the carbohydrates.

It is just in these cases that we get brilliant results by interposing from time to time periods of diet composed exclusively of oatmeal or some similar food, accompanied and followed by two or three days of green vegetable food and eggs. By following out this dietetic plan quite systematically we shall find that in time — perhaps after three or four weeks or longer — the glycosuria will diminish and ultimately disappear. Although the patient is on a diet absolutely free from carbohydrates, except on the days when he takes oatmeal, the amount of acetone bodies in the urine is diminished, and the reaction with chloride of iron disappears. Encouraged by this pleasing result, we leave the patient on absolutely strict diet not only for a few weeks, but during many months. He improves splendidly and puts on weight. Later on, when we add some carbohydrates to the diet, we find that small quantities can now be borne without causing sugar to be excreted. We have achieved our aim — the originally obstinate case of "severe glycosuria" has been converted into a "slight" type.

Example. This case was published by myself some years ago; the desired result was attained in a relatively short time. It shows at the same time both the relative and absolute advantages of the oatmeal cure.[1]

[1] The first part of this table is published in von Noorden, "Diabetes Mellitus, its Pathological Chemistry and Treatment," p. 191, New York, E. B. Treat & Co., 1905. The second part of the table has not been published before.

Day	Diet	Sugar gramm	Aceton gramm	Ferri-chlorid-Reaction	NH_3 gramm
1	Severe + 100 g. Bread	89.2	0.30	0	1.2
2	" " "	84.9	0.28	0	1.3
3	" 50 "	78.3	0.32	0	1.5
4	" " "	77.1	0.58	+	1.7
5	Severe Diet	50.4	2.1	++	3.2
6	" "	48.3	2.4	++	3.8
7	" "	58.9	3.1	++	4.3
8	Vegetable-egg-day	28.2	2.1	++	2.9
9	" " "	20.3	1.9	++	2.8
10	250 g. oat, 300 g. Butter	38.3	1.9	++	2.4
11	" " " "	40.3	1.3	+	1.6
12	" " " "	30.0	0.9	+	1.5
13	" " " "	20.1	0.6	+	1.1
14	Vegetable-egg-day	8.0	0.8	+	1.3
15	" " "	2.3	1.2	+	1.8
16	250 g. oat, 300 g. Butter	18.3	0.5	0	0.9
17	" " " "	5.6	0.1	0	0.9
18	" " " "	0	0.05	0	1.0
19	Vegetable-egg-day	0	0.1	0	0.8
20	" " "	0	0.1	0	0.8
21	Severe Diet with meat	0	0.15	0	0.7
22	" " " "	0	0.18	0	1.0
23	Severe Diet and 20 g. Bread	0	0.12	0	0.9
24	" " " " "	0	0.13	0	0.8
25	Severe Diet; no carbohydrates	0	0.14	0	0.9
	The Severe Diet is continued during three months. Then:				
1	Severe Diet	0	0.07	0	1.0
2	"+ " and 20 g. Bread	0	traces	0	0.9
3	" " " 40 "	0	"	0	1.1
4	" " " 50 "	0	"	0	—
5	" " " 50 "	traces	"	0	—
6	" " " no carbohydrates	0	"	0	—

The next table shows the effect of a long continued restricted diet.

Day	Food	Sugar	Aceton
1	Severe + 75 gr. Bread	73.4 gr.	2.0 gr.
2	Fast-day	day: 9.8	
		night: 0	0.4
3	150 g. Oats, 180 g. Butter	0.9	1.5
4	240 g. " 300 "	9.5	1.5
5	180 g. " 200 "	1.7	1.0
6	Vegetable-egg-day	0.6	0.6
7	Severe Diet; no carbohydrate	10.2	1.3
8	" " " "	16.1	2.2
9	" " " "	20.9	2.3
10	" " " "	26.4	1.8

Now followed several months of severe diet with a daily maximum of 20 g. carbohydrates after a year:

1	Severe + 35 g. Bread	0	—
2	" 45 "	0	—
3	" 55 "	0	—
4	" 65 "	traces	—

I beg to take notice of:

1. The marked decrease in the output of the sugar and acetone which after 12 hours had fallen from 73 grams to 9.8 grams, and at the end of twenty-four hours to practically nil.

2. The extraordinary effect of the three days "oat-cure." During this short period at least 350 grams of carbohydrate were assimilated.

3. The unfavorable influence of the albumin-rich but carbohydrate-free diet (7th to 10th day) compared with the "oat-diet" period (3rd to 5th day). During yonder period the acetonuria attained a great height.

From the good result the fast days and especially the oat days offered, I concluded that it would be possible to reduce this case to a slight form of glycosuria. Thus I was justified in prolonging the period of strict diet. You see that after a year, the tolerance is distinctly increased and that upon a diet which a year previously resulted in the appearance of 73 grams of sugar and 2 grams of acetone there is now only a trace of sugar and acetone.

What has taken place between the commencement and the close of the treatment? We will later discuss the reason why the patient had only slight ketonuria in the beginning, as long as he took a plenty supply of carbohydrates. When all carbohydrates were withdrawn, the ketonuria ought to have increased since the diastatic function of the liver was being carried on at an enormous height and the small amount of glycogen formed from albumins was rapidly carried off from the cells. Without the influence of the glycogen, the cleavage of fatty acids followed the wrong course. In the meantime, however, we have methodically and intentionally spared the glycogenic functions of the liver and this calming treatment (Schonungs therapie) has resulted in a decrease of the irritant of the sugar forming function. The cells have in part regained their activities to utilize glycogen and at this moment the acetone bodies begin to decrease. We benefited the patient a great deal. His general condition improved, the

tendency to ketonuria has disappeared and the sugar production returned to its normal level — a level, however, which is maintained only so long as the sugar manufacturing is not too much overburdened. If we were to give carbohydrates again either in too great an amount or too rapidly, then the old conditions at once would return.

What would have happened if we had been frightened by the intense acetonuria and had returned at once to the original quantity of carbohydrate or even increased it? The ketonuria would also have disappeared — perhaps not forever, but still for a length of time. This is remarkable, and is not easily explained by certain theories of ketonuria. It is not difficult to show that the ketonuria disappears, although the consumed carbohydrates are not at all utilized, namely, although the quantity of sugar in the urine exceeds that of the total carbohydrates of the food.

I may mention a case which occurred when I was still an assistant in Gerhardt's Clinic. I was then of the opinion that in every case of acetonuria — even when of transitory form only — a restricted diet were not admissible.

In the following table the carbohydrates present in the restricted diet are calculated as 20 grams. In this the preformed carbohydrate groups of the proteins are included. The assumed amount of 20 grams is rather too high than too low, as the food was very carefully selected.

Day	Food	Acetone	Carbohydrate in food	Carbohydrate in urine	Difference
1	Severe + 100 g. Bread	0.11 g.	80 g.	72.8 g.	+7.2 g.
2	" " "	0.18	80	79.3	+0.7
3	" " "	0.23	80	71.4	+8.6
4	" " "	0.22	80	80.6	−0.6
5	Severe without additions	0.61	20	59.3	−39.3
6	" " "	1.7	20	59.2	−30.2
7	" " "	2.1	20	54.3	−34.3
8	Severe + 120 g. Bread	1.9	92	66.3	+25.7
9	" " "	1.4	92	78.4	+13.6
10	" " "	0.8	92	82.5	+ 9.5
11	" " "	0.4	92	90.1	+ 0.9
12	" " "	0.2	92	99.3	− 7.3
13	" " "	0.3	92	92.8	− 0.8
14	" " "	0.18	92	102.6	−10.6

We see that the large amount of 120 grams of bread is associated with a decrease of the acetonuria and we see its return to the quantity present at the beginning of the experiment, although the tolerance for carbohydrates is altered for the worse. Just when not the smallest amount of the consumed carbohydrates was assimilated, we met with the lowest output of acetone.

In such instances it is only possible to explain the decreased acetonuria by assuming that the carbohydrate streaming in from the intestine to the liver, even in severe diabetes, does not simply pass through the liver, but is taken up by the cells and remains there as glycogen for a short time before it falls a victim to the increasing wave of diastatic action. When it happens that the period of retention is not too short, the contact action of the glycogen upon the fatty

acids suffices for their return to their normal course of cleavage.

We thus see that the ketonuria may yield both to carbohydrate starvation and carbohydrate abundance. The practitioner may perhaps regard the latter way as the least dangerous, but this is not so. Although for the moment it may be easier, it is not consonant with the duty of the physician in his care for the future. Such an apparently agreeable allowance of carbohydrate leads with unfailing regularity to a disorder of the sugar factory and increases the tendency to unbridled production of sugar — in one case slowly and another rapidly — and exposes the patient to all the dangers associated with permanent hyperglycæmia — dangers which we fear as the complications of diabetes. It is certainly true that it is not every diabetic who shows this tendency to get worse. Many cases remain in the same condition for years, or decades, or even improve in spite of neglect from the dietetic standpoint; but in the transitional type of case — between the slight and severe glycosurias — which we are now discussing, it is the rule that every lack of dietetic observance means a step backwards for the patient.

In cases therefore in which there is the possibility of return of slight glycosuria, I hold that it is not permissible to make such a draft upon the future for the sake of the momentary comfort. I must advance the view that in every case of severe or medium glycosuria the hyperglycæmia and glycosuria must be reduced to

the smallest possible amount, in spite of an unavoidable period of increased and perhaps dangerous acetone formation, and that the tendency to ketonuria must be treated not through the allowance of carbohydrate but by a systematic calming of the sugar forming processes. I am not alone in this view. Minkowski, Naunyn and Luethje are of the same opinion, and Luethje (*Therapeut. Monatshefte,* 1910, No. 8) has recently published a remarkable paper upon the dietetic treatment in which he comes to the same conclusions. I may also add that my experience goes to show that the diabetics who have been most benefited by my treatment are those in which a severe glycosuria resulting from neglected dieting has been curbed by a long period of strict carbohydrate free food.

b. The Really Severe Forms of Glycosuria

There are cases, however, which cannot be brought within these limits. In spite of all the dodges and tricks of an extended experience, the ketonuria progresses to an intolerable height, so soon as we cut off or only decrease the carbohydrate and it remains at this height so long as we continue this régime. We have to expect in these cases that even a carbohydrate rich diet will not lead to a disappearance of the ketonuria; it only moderates the output. These are the worst type of cases — the end stage of severe glycosuria — which for months or years, however, are compatible with the continuation of life. As a rule they tend to

one end and are regarded as hopeless. One must not, however, lay down one's arms straight away; a number of them yield to patience and resourcefulness and return to a milder type. It is not easy to say when this will occur and why it is. In some cases of severe diabetes, spontaneous improvement now and then sets in; on the other side there are many cases of slight diabetes in which dangerous symptoms temporarily appear, so that we fear we must give up hope. We see this specially in acute infections, among which staphylococcal, streptococcal, and influenza are the most important. I remember several cases of furunculosis and staphylococcal sepsis, in which within a week a slight diabetes progressed to a severe glycosuria with marked acetonuria. When the infection terminated the diabetes assumed again the milder form.

There remain, however, as we have indicated, certain cases of severe diabetes which do not return to the slighter types. We meet with them at all ages, but most frequently in children and young adults. On a liberal diet the ketonuria is ameliorated; on a restricted diet it progresses continuously. Here the restriction of carbohydrates is not allowed. We then must remember that the intestinal carbohydrates streaming to the liver, to some extent control the amount of ketonaemia; and we must concern ourselves with the immediate dangers of the condition without giving too much thought to the future.

According to our hypothesis, in such cases the carbohydrate of the food entering the liver by the portal

vein remains in the hepatic cells for a short time as glycogen and so exerts a very slight but necessary influence on the cleavage of the fatty acids; the glycogen formation, however, is far too small to inhibit completely the abnormal cleavage of fatty acids. In these cases we have to content ourselves to curb the excess of the sugar output by prescribing three or four fast days each month. Experience shows that the withdrawal of carbohydrates in this manner does not cause an increased ketonuria; there is rather a lowering of the output, just contrary as we find in the healthy when starvation or carbohydrate restriction is practiced. I formerly ordered that every eighth or tenth day shall be a vegetable-egg-fat-day. I even now go further and, following Naunyn, advise a hunger day, when only tea, weak bouillon and large amounts of brandy and soda are permitted; the patient on this day remains in bed so that the sugar forming organs may be spared to the utmost. As a result the urine often becomes sugar free and the ketonuria shows a distinct decrease, even in the most severe cases. We need have no fears that the hunger day will damage seriously the general nutrition. Of course the body weight falls on the fast day, but the loss is rapidly made up and by this combined method, which the table demonstrates we often obtain considerable increases in weight.

Day	Food	Sugar in the urine	NH_3	Aceton in the urine
1-7	Mixed, with 100 gr. carbohydrates	80-110 gr.	2-3 gr.	2.1-3.0 gr.

Day	Food	Sugar in the urine	NH_3	Aceton in the urine
8	hunger-bed-day	day: 10.5 night: trace.	0-7	0.8
9-16	Mixed, with 100 gr. carbohydrates	60-85	2.0-2.5	1.8-2.8
17	hunger-bed-day	day: 8.4 night: 0	0.7	0.9

In the more advanced stages of the diabetic process the diastatic action is so disturbed that the formation of glycogen is without any beneficial effect. The extent of the ketonuria remains almost unaffected by the administration or withdrawal of carbohydrates. Hence one does not select to cause the patient unnecessary and useless restriction. This stage is rarely associated with a return to milder forms; it progresses unhindered towards coma.

I have only indicated the more important types of ketonuria and mentioned examples which best illustrate them. There are, of course, transitional and intermediate classes, but these are easy to orientiate, once one is able to define the chief forms of the condition.

C. Special Indications

We may now consider the use and importance of certain therapeutic measures in the prevention and the treatment of acetonaemia.

a. Alkaline Therapy

This is based chiefly on the views of the school of Schmiedeberg and Naunyn that in the diabetic autointoxication abnormal acids appear in the blood stream.

Whether or not the matter is one of poisoning by acids, namely the action of acid ions upon tissues and of loss of the fixed alkalies required for the neutralization of the acids, is still an unsettled question. Such views appear to me not quite right, for there is most probably a *specific* toxic action of certain acids, which increase the acid influence of the aceto-acetic and oxybutyric acids. We must not, however, dip further into this interesting theoretical question just now. At all events, we hold that when large quantities of acids appear in the tissues, we must administer a full mead of alkalies. It is a widely spread though false view that alkalies diminish or hinder the formation of acetone bodies. In this regard their influence is of the slightest. The favorable results are due to the fact that the alkalies combine with the acids and so hasten their excretion. The acids are removed from the blood and tissues; the dangerous ketonaemia is combatted while the ketonuria — namely, the elimination of the acid products from the blood — is increased. At least, this is what happens at the commencement of the alkali therapy. Later the output sinks to a lower level, dependent upon the nutritional intake and upon the general extent of the specific diabetic process. The alkali determines the output of the ketone bodies, much as large quantities of water affect the urinary output of the products of the metabolism of albumin.

The amounts of alkali required vary within broad limits, from case to case. When the urine does not give the ferric chloride reaction, alkalies are not

specially indicated. In the definite slight cases in which the reaction appears when restricted diet is taken, alkalies are not really necessary, although we are accustomed to give 5 to 6 grams daily. That this quantity is sufficient is shown by the alkalinity of the urine. It is only in the medium cases of glycosuria, however, that the administration of alkalies is of importance. As long as there the ferric chloride reaction turns positive alkalies should not be foregone. For these cases, and for all cases where long periods of alkali therapy are prescribed, I do not recommend more than 15 to 20 grams per day. There are some who advise the use of large doses and give 40 to 60 grams sodium bicarbonate daily for many weeks or months. When not a high grade of acid intoxication threatens, these quantities are not necessary; I cannot rid myself of the impression that such doses in the long run injure the various functions of the stomach and so ultimately disturb the entire general nutrition. One frequently finds that patients who have taken large quantities of alkalies for long periods, suffer from symptoms of hyperacidity. I have given test meals to such diabetic patients and found the total hydrochloric acid values reach up to 0.4 per cent. The high alkali intake thus induces a compensatory hyperacidity which, on the one hand, opposes the object of the alkali therapy, and, on the other hand, causes discomfort and dislocation of the total energy exchange.

If the amount is limited to 15 grams daily, it is well

to give 5 grams first thing in the morning and 5 grams just before sleeping in a small glass of plain or aërated water; the remainder dissolved in a bottle of mineral water may be administered during the day as the patient likes best, but on no account should it be given at meal times. Sometimes it is very useful to give sodium citrate instead of the bicarbonate citrate. The citrate is slightly laxative and this is welcome. The alkali values of the two sets is about equal. Among the other fixed alkalies, there come also magnesium and calcium in consideration. Although they are absorbed only incompletely, they are useful strings to our bow; the magnesium when there is a tendency to constipation, the carbonate of calcium when diarrhœa occurs. One of the best preparations of magnesia is the magnesium perhydrol of Merck; it is suitable for long continued use also.

The really large doses of alkali are first called for when the ketonaemia reaches a height which is dangerous to life and when we have to face the possibility of coma. This condition, of course, often occurs suddenly; but in other instances it often happens that for several weeks it is impossible to be sure whether coma will or will not set in. Sometimes we have a long time to battle with a comatoid stage in which it is difficult to prognose safely from hour to hour. Together with general prostration, however, there is in such cases one symptom which is of prime importance, namely, a constipation due to intestinal paralysis. Many years ago, the late Dr. Schmitz of Neuenahr, who made so

many important observations upon diabetes, showed that in those cases of severe ketonaemia, it was important to evacuate the intestinal contents. I must acknowledge the correctness of his contention, although a theoretical explanation is not available. I remember a case in which the acetonuria reached the extraordinary height of 7 grams per day, and in which I uneasily awaited the onset of coma. The rectum was distended with hard faeces; enemata failed to dislodge them. Digital removal was attempted and ½ milligram of physostigmin injected. An enormous stool resulted, and on the next day the acetonuria decreased to a fourth of its previous amount. In our treatment of acidosis we must therefore take measures for dealing also with the constipation.

With regard to the administration of alkalies, there are several means at our disposal. Via the stomach hardly 60 grams a day can be given. This is not sufficient, as Magnus Levy has calculated and experience has taught to neutralize the excessive and dangerous grades of acidosis. If the colon is cleared out it is possible to utilize alkaline enemata with good results; the only useful form is the so-called "drop enema" composed of 3 per cent. solution of sodium bicarbonate; this will be almost entirely absorbed, while large enemata irritate the intestine so much, that a second enema will be scarcely retained or absorbed; with the "drop enema" 40 to 50 grams sodium bicarbonate may be introduced and absorbed without producing the slightest harm or irritation.

In some cases it is necessary to resort to intravenous injections. Then it is best to use 3½ to 4 per cent. sodium carbonate solution, which contains double the amount of sodium present in the same amount of the bicarbonate. The technique is the same as that for the injection of salvarsan. Subcutaneous injections should be avoided, as local necrosis frequently follows. The blood is much more tolerant of the strong soda solutions. The result is sometimes astounding. Patients who have been completely unconscious often after the first 300 to 400 c. c. of the soda solution recover from the coma, and after the surmounting of the momentary danger remain well for a relatively long period. Of course, these are the rarer cases; as a rule, the fatal issue is postponed for a short time only.

b. Feeding (Lævulose, Oaten, Fasting-Day)

The question of nutriment during incipient coma is an important one. It is a rule that carbohydrates should liberally be given and this is mostly right. At all events, I mean that one cannot expect much from carbohydrates administration during the danger stages. Lævulose has been a favorite at these times, because it is associated with a greater tendency to glycogen formation than the other varieties of sugar. It is not difficult to give 100 grams or more in the form of lemonade. I have not found the practical results equal to theoretical expectations. There is little doubt that lævulose cannot be relied upon in the treatment of

diabetes to the extent its supporters have claimed. Although the glycosuria is less increased by a single dose of lævulose than by such of other sugars, in the end lævulose is not less harmful than glucose or saccharose, etc.

Besides lævulose, milk and oat preparations are of use in the late stages of acidosis. Formerly I employed milk in 200-250 gram doses every two hours. But oat food proved to be still better, and I believe that I am right in saying that many cases in which coma threatened have been tided over the crisis by an exclusive diet of oaten preparations. Whichever form of nutrition one chooses later, it seems to me advisable at first to take another way of dietetic therapy — a way, which at first might cause hesitation, but practically gave the best results. We give the patient no food at all and only administer large quantities of whiskey well diluted. About 100-150 grams (3-5 ozs) per day is generally reached. It is astonishing how much alcohol these patients will take without the slightest after-results, even when it has not been their custom to take alcohol. On such alcohol days the ketonuria decreases to a remarkable degree and the general condition of the patient is an agreeable surprise. This is the more remarkable when one considers that other narcotic poisons, such as chloroform and ether, increases the acidosis. When, after one or two days of alcohol dietary an improvement appears and the momentary danger is over, the time has come for the use of milk and oatmeal soups and a very

gradual and careful return to the diet usually indicated for diabetics. Of course the outlook, sadly enough, is still cloudy. Once or twice we may succeed to snatch from the coma its victim. But as a rule, it is a matter of weeks or, at the most, months, before a further attack brings about the end.

As a rule, it must be considered that the treatment of the comatose and pre-comatose states is a very ungrateful one; hence so much the more weight ought to be laid upon the precept that in the early days of the diabetic process the end should be sighted and by the sparing of the sugar forming apparatus the tissues should be enabled to retain the diastatic activities and restrain the production of ketone bodies. I mean, this is a thankful piece of work. The carrying out of the matter is rather difficult, for the diabetic who is not the subject of ketonuria or other complications and finds himself feeling in good form is a difficult subject to convince that certain dietetic restrictions, ordered by the physician who looks beyond the present into the future, are really necessary. We cannot hope, even if we ensure the practical applications of our advice in the early stages, to put an end to diabetic autointoxication in the world, for there are many cases which progress persistently, no matter what therapeutic measures we take. On the other hand, however, there are numerous other cases in which success is attained and we are able to hinder, or avoid, the onset of the complications of coma.

THE END