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DISEASES OF METABOLISM AND NUTRITION

VON NOORDEN

No. VII.

DIABETES MELLITUS

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DISEASES OF METABOLISM AND NUTRITION.

A SERIES OF MONOGRAPHS

By Prof. Dr. CARL von NOORDEN,
Phys.-in-Chief to the City Hosp., Frankfort-on-Main.

Authorized American Edition.
Edited by Boardman Reed, M.D., Philadelphia.

I.—Obesity: the Indications for Reduction Cures
II.—Nephritis
III.—Colitis: or Membranous Catarrh of the Intestines (*Colica Mucosa*)
IV.—The Acid Autointoxications
V.—Saline Therapy
VI.—Drink Restriction (*Thirst Cures*)
VII.—Diabetes Mellitus

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DIABETES MELLITUS:

ITS PATHOLOGICAL CHEMISTRY AND TREATMENT:

BEING PART VII OF SEVERAL

CLINICAL TREATISES

ON THE PATHOLOGY AND THERAPY OF

DISORDERS OF METABOLISM AND NUTRITION.

BY

PROFESSOR DR. CARL VON NOORDEN,

Physician-in-Chief to the City Hospital, Frankfort-on-Main.

TRANSLATED BY FLORENCE BUCHANAN, D.Sc., AND I. WALKER HALL, M.D.

UNDER THE DIRECTION OF BOARDMAN REED, M.D., LATE PROFESSOR OF DISEASES OF THE GASTRO-INTESTINAL TRACT, ETC., TEMPLE COLLEGE, PHILADELPHIA.

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1907.

NOTE BY THE AMERICAN EDITOR.

The medical profession has again been placed under deep obligations to Professor Carl von Noorden. The addition of this thorough-going treatise on diabetes to his series of monographs will prove a boon to a large class of patients, and should be welcomed by the physicians of all lands. Those who read English are to be congratulated upon the publication of this new and original work in the English language.

The old-fashioned routine treatment of diabetes by merely restricting according to a fixed formula, the carbohydrates of the diet, or attempting (usually unsuccessfully) to exclude them altogether, leaving the patient to make up the deficiency by eating mainly of proteids *ad libitum,* was most crude, insufficient and unsatisfactory. The administration of opium or other active drugs and the giving of alkalies or alkaline waters without a frequent and thorough examination of the urine for much more than a determination of the amounts of sugar and albumin present, have brought equally unfortunate results in most cases.

Von Noorden, uniting in himself, as only a few others do, a thorough knowledge of physiology, physiologic chemistry and pathology with a remarkable genius for

organizing and energetically carrying out original investigations, especially in the most interesting field of diseases involving disturbances of metabolism, and an enormous clinical experience gained among patients studied in public and private hospitals and sanitariums under conditions of scientific exactness rarely attained, is preeminently qualified to acquaint us with the latest discoveries and conclusions concerning the origin, complications and dangers of diabetes, as well as to tell us the most successful methods of avoiding and combating them, and of curing the disease when a cure is possible.

A perusal not only of this monograph, but also of the previous volumes of the series, must awaken in the mind of the thoughtful practitioner a feeling of satisfaction that the chasm between pathology and clinical medicine, between the workers in the laboratory and those at the bedside, is being bridged, and the practice of medicine being more and more established upon a solid scientific basis.

The lectures on diabetes recently delivered in this country by Professor von Noorden could be heard by a few only of the many physicians who would gladly have benefited by them; but this publication will doubtless assure a study of them by most of the progressive practitioners of the English-speaking world.

BOARDMAN REED.

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INTRODUCTORY NOTE

GENTLEMEN:—It is with great pleasure that I avail myself of the honour you have conferred upon me in asking me, through your President, to deliver a series of lectures upon the disorders of metabolism. With the permission of your President I have chosen the subject of diabetes mellitus. This disease has been investigated more fully than the other results of faulty metabolism, and our knowledge of it is accordingly more extensive. It also possesses a great interest for us because of the extraordinary number of old and new problems with which it is intimately connected.

I propose in these lectures to deal chiefly with the pathological chemistry and the treatment of diabetes, only referring to the symptomatology, the course, and the complications of the disease in so far as it is necessary to make clear the points in question.

I. DEFINITION

Until we know more about the nature of the diabetic process than we do at present, we must content ourselves with defining diabetes mellitus as *a chronic disease in which glucose is excreted in the urine,* thus associating it with its most important clinical symptom, as generations before us have also done. We must, however, make certain reservations in accepting this definition, and postulate:

1. That we are concerned only with such quantities of glucose as are demonstrable by ordinary clinical methods, leaving for the moment the question as to whether normal urine contains traces of grape sugar recognisable only by the most delicate tests.

2. That the tendency to glycosuria is a chronic condition, extending over a few weeks or months at least. There are various morbid states in which there is a transitory tendency to glycosuria, but such are not spoken of as diabetes mellitus, although much may be said in favour of their having a common pathological basis.

3. That the sugar appears in the urine when the diet does not contain more carbohydrates than usual; for on a diet abnormally rich in any of the different kinds of carbohydrates even a healthy man excretes them to some extent. The latter cases are spoken of as ali-

mentary glycosuria in contradistinction to diabetic glycosuria.

We shall have occasion to refer later both to spontaneous and alimentary non-diabetic glycosuria.

There are other sugars besides grape-sugar which frequently appear in the urine, namely milk sugar or lactose, pentoses, glycuronic acid, and fruit sugar, or lævulose. The excretion of lactose is a physiological process which only occurs in women during the period of lactation, when more sugar is being formed in the mammary glands than is taken from them. In such cases part of the lactose formed is taken up by the blood and excreted by the kidneys. The other mentioned sugars are only excreted under pathological conditions; these, however, must be sharply distinguished from diabetes mellitus, those cases in which pentoses or glycuronic acid are present in the urine being certainly distinct from it, although it is by no means so certain that lævulosuria is not a process very closely allied to true diabetes.

II. THE PATHOGENESIS OF GLYCOSURIA

The blood contains normally about one in a thousand parts of sugar, most of which is in the form of grape-sugar. The traces of isomaltose and dextrin which may occur have no bearing on the present subject. It used to be thought that the sugar circulating in the blood existed either in a free state or in solution, but this view must probably now be withdrawn in favour of the hypothesis that the greater part, if not the whole, of the sugar exists in a loose combination with other substances. Some have designated albuminates, others lecithin, as its carrier. We do not really know at present with what substance it is combined, but its existence in the form of a compound appears to have an important physiological significance, serving to prevent such a readily diffusible substance as sugar from passing through the renal filter. The healthy kidneys are, at any rate, impermeable to the amount of sugar normally present in the blood.

A. CONDITIONS OF GLYCOSURIA

Glycosuria may occur

1. When the sugar exists in an abnormally loose combination in the blood.

2. When the kidneys for some reason or other lose the ability of being impermeable to sugar.

3. When the blood from any cause becomes abnormally rich in sugar. This condition is known as hyperglycæmia, and ever since the fundamental researches of Claude Bernard it has commonly been accepted as the real and proximate cause of diabetic glycosuria.

We have, then, to discuss these three possibilities. The two first I can deal with briefly, since they are of much less importance than the third.

1. *The sugar exists in an abnormally loose combination in the blood.* As I have already said, sugar in the organs and in the blood is probably not present in a free molecular state, but is loosely bound to some as yet unidentified substance. E. Drechsel discovered a combination of grape-sugar with lecithin, to which he gave the name of *jecorin.* On the strength of this R. Kolisch advanced the hypothesis that the kidneys are permeable to free glucose while impermeable to jecorin; that jecorin is the normal sugar of the blood, and that in diabetes the formation of jecorin is, for some unknown reason, disturbed, thus leaving an abnormal amount of free glucose to circulate in the blood and to be excreted by the kidneys. Hence, according to this hypothesis, glycosuria depends upon a morbid and insufficient fixation of the sugar in the blood, and not on hyperglycæmia properly so-called. A good deal of attention was for a time rightly bestowed on this ingenious theory, and it was tested in many ways, the

result, however, shewing that the methods used by Kolisch were not sufficiently accurate for the purpose in view. After the short reign of one year the hypothesis was abandoned. I do not believe, however, that it has yet received its death-blow. It is true that we require more knowledge as to the combinations in which sugar normally exists in the blood, but when this is known the next step will be to ascertain whether in diabetes there occur any variations from the normal relations of sugar to the other constituents of the blood, and it is possible that then the hypothesis of Kolisch may be revived in another form.

2. *The kidneys lose their impermeability to sugar.* There is one particular form of glycosuria which is undoubtedly caused by the permeability of the kidneys to sugar. This is the phloridzin-glycosuria discovered by v. Mering. Both man and many of the lower animals excrete sugar when fed on, or better, subcutaneously injected with, a sufficient quantity of phloridzin. Glycosuria continues so long as the phloridzin is administered, and a chronic glycosuria may thus be produced. The animals subsequently succumb in consequence of the great loss of sugar, and the symptoms they exhibit in so doing are similar to those of true diabetes mellitus. There are, however, important differences. While, for instance, the amount of sugar in the blood of a man with diabetes has been shown to be above the normal, the amount in phloridzin-diabetes is almost always below it. Although a few quite opposite statements have been made, they are not

such as will carry much weight. In experiments made in my own laboratory a considerable diminution of the amount of sugar in the blood always took place after the administration of large doses of phloridzin. It is evident that glycosuria is produced in this case by the kidneys being enabled, under the influence of phloridzin, to extract the sugar from the blood. The greater the physiological capability of the kidneys the more intense is this action. Diseased kidneys react much less and much more slowly to phloridzin poisoning, a well-known fact which has been made use of in the diagnosis of renal disorders. It is not so reliable a method as was at first supposed, but in conjunction with catheterisation of the ureters it gives good results when it is necessary to ascertain whether only one or both kidneys are diseased. In the latter case the secreted urine of the diseased kidney yields a smaller quantity of sugar, and at a later period after the injection of the phloridzin, than that of the healthy kidney. It must for the present remain undecided whether phloridzin-glycosuria is due merely to a greater permeability of the kidneys and is a passive process, or whether, as is more probable, the renal epithelium plays an active part in the production of the results observed.

Other poisons, such as diuretin and caffein, whose administration may be followed by glycosuria, have been also said to act on the kidneys. The effect produced by them is, however, different from that which results from the use of phloridzin, as, instead of

producing glycosuria with certainty, they only cause its appearance in small animals under especially favourable circumstances, that is to say, only when the animal is being fed on a fat diet especially rich in carbohydrates.

In man, glycosuria due to the action of diuretin or caffein is exceedingly rare. It is still uncertain whether the process quite corresponds to that which takes place in phloridzin poisoning. Recent, observations make it more probable that hyperglycæmia is first produced, in contrast to its absence in phloridzin poisoning, and that it is this which necessarily gives rise to glycosuria. We must, therefore, for the present consider phloridzin poisoning as the only certain means of producing a glycosuria in which the kidney epithelia play a distinctive part.

Of late an attempt has been made to distinguish a clinical form of diabetes which corresponds to phloridzin diabetes, *i.e.*, a condition dependent upon increased permeability of the kidneys. For this condition the name of "diabete rénale" proposed by the French authors has been accepted. The following three symptoms are considered to be characteristic of it:

1. The presence of kidney disease (nephritis).

2. Slight glycosuria which is but little influenced by the nature of the food.

3. Diminution of the amount of sugar in the blood.

Much that has been published on the subject will not, however, stand the test of careful criticism. I cannot enter upon the question here, as I should have to

analyse each case separately and in detail in order to show you that it does not really sustain what it is supposed to prove. I consider that up to the present time no case of diabetes mellitus has been described which indisputably shows that glycosuria arises from the increased permeability of the kidneys. The doctrine of renal diabetes remains in the region of hypothesis.

Much more certain is the reverse observation. If, namely, in a case of chronic glycosuria the kidneys become diseased, the intensity of the glycosuria usually diminishes. Clinicians have for long been struck by this phenomenon. Stocvis, in his time, deliberately stated that a case of diabetes mellitus might be fully cured by the onset of a granular atrophy of the kidneys.

The fact is true, although it seldom occurs. I do not, however, agree with Stocvis that such an outcome of the disease is either favourable or desirable. The contracted granular kidney is a much greater danger than the diabetes.

Experimental observations have also been made showing that the glycosuria produced after either extirpation of the pancreas or poisoning by adrenalin may be diminished by inducing a nephritis in the animal. These observations, both clinical and experimental, are most important and interesting. There is not, however, as yet, sufficient accumulation of material to explain them.

3. *Glycosuria produced by hyperglycæmia.* As I have already remarked, it has been generally recognised since the time of Claude Bernard's classical researches on the subject, that hyperglycæmia is the real cause of the outflow of sugar from the kidneys in diabetes. The kidney is only impermeable to sugar when its percentage in the blood is not above a certain limit. When is this limit attained? Claude Bernard, and others working with obsolete and inexact methods, certainly overestimated the sugar contents of normal blood when they place it at 2 or 3, or even 4, per thousand. According to more recent and more accurate observations the normal limit is much lower and barely exceeds 1 per thousand in man. In diabetes the proportion is almost always much greater in man, 3 or 4 per thousand being common, and values of 7 to 10 per thousand are occasionally obtained. The same is true in animals in which glycosuria has been artificially produced by extirpation of the pancreas, injury of the medulla oblongata (piqûre) or of other parts of the nervous system, by different kinds of poisoning, by adrenalin, or by overfeeding with carbohydrates. In fact, hyperglycæmia occurs in all cases of natural, spontaneous, and experimental glycosuria, with the exception of phloridzin-diabetes, so that one can hardly doubt its having some general significance in the production of glycosuria.

Investigations have, of course, been made in order to determine whether the degrees of hyperglycæmia

are directly proportional to those of glycosuria. Pavy gives the following table for diabetes in man:

	Urine.	*Blood.*
Sugar per 1000 parts.....	109.9	5.763
" " " "	94.1	5.545
" " " "	93.4	4.970
" " " "	61.3	2.625
" " " "	48.1	1.848
" " " "	45.5	2.789
" " " "	31.7	1.543

The results obtained both by J. Seegen and by B. Naunyn, and also in my own laboratory, differ from these, and shew that such a table cannot be universally applied. Cases have been described on the one hand in which the percentage of sugar in the blood was only slightly above the normal in spite of marked glycosuria, and on the other hand, cases in which the percentage in the blood was much higher than one would have expected from the smallness of the amount of sugar in the urine. It is clear, however, that the limit of sugar in the blood which cannot be exceeded without the danger of its passage through the renal epithelium is a very sharply defined one. When once it is exceeded, there may be very considerable glycosuria although the hyperglycæmia cannot be recognised by ordinary artificial methods. It seems to me that this is what usually takes place at the beginning of diabetes, and as time goes on the kidneys adapt themselves to the altered circumstances and acquire greater impermeability to sugar. One may regard this as a compensatory or protective arrangement. The consequence

is, that in the late stages of diabetes the hyperglycæmia is much more readily identified than it is during the earlier stages of the disease.

B. THE CAUSES OF NON-DIABETIC HYPERGLYCÆMIA

Having once established the fact that hyperglycæmia is the usual cause of glycosuria, the conditions which determine the excess of sugar in the blood must next be ascertained. I will put aside for the moment the question of the sources from which the sugar of the blood is derived, reminding you only that it is not the carbohydrates of the food alone, but certainly also the proteid molecule, and probably also the fat, that must be taken into account. I shall have to return to this subject later. It is the mechanism of hyperglycæmia that I propose now to consider.

1. *The Hepatogenous Forms of Glycosuria*

(*a*) *Experimental Part.*—All discussions and researches are based upon the famous "piqûre" experiment of Cl. Bernard. This distinguished observer shewed that puncture at the tip of the calamus scriptorius in the fourth ventricle of animals is followed by a glycosuria which persists for several hours. At the end of this period the liver is found to be free from glycogen. The glycogen of the muscles does not usually wholly disappear although it is much reduced in amount. If before making the puncture the liver has been freed from glycogen by starving or by chasing the animal, or by careful strychnine poisoning, by

inducing fever, by ligaturing the bile ducts, glycosuria is not produced. The significance of these experiments, namely, that from the excited spot in the brain a stimulus is conveyed to the liver which causes it to yield up its store of glycogen, has not been seriously disputed. According to some authors it is the vasomotor nerves that are primarily affected, others assume that the nerves excited act directly upon the liver cells, and again others regard the primary excitation as directly acting upon the pancreas, the effect on the liver being a secondary one. We may here put all these questions on one side since they are only of theoretical interest and no conclusive answer can yet be given to them.

The most important point for our purpose is the sudden removal of glycogen from the liver. The glycogen leaves the liver as glucose, hyperglycæmia results and is followed in turn by glycosuria. There is thus but little difficulty in understanding why the "piqûre" is ineffectual in animals whose glycogen store is low, and moreover why the glycosuria only lasts for a limited time—only so long as the glycogen, accumulated sometimes in large, sometimes in small, quantities, continues to be given off, and until the excess of sugar thrown into the blood has been eliminated by the kidneys or used up by the tissues.

Later investigations have shown that the typical "piqûre" is not the only operation which causes the liver to expel its glycogen. It has been shown that numerous other injuries to the nervous system produce

the same effect in animals, but none of them give rise to glycosuria with so much certainty as the "piqûre." Many poisons, especially several narcotics, and also preparations of theobromine and caffein, may be mentioned as producing the effect. Although there can be no doubt that all these traumatically and toxically produced cases of glycosuria are of hepatic origin, *i.e.*, are due to the expulsion of the glycogen from the liver, the question may yet be raised with regard to some of them—especially those produced by toxins—as to whether it is not the pancreas rather than the nervous system or the liver that is primarily affected by the poison.

(*b*) *Clinical Part.*—It is probable that some of the above-mentioned experiments on animals have a bearing on certain forms of glycosuria which have been observed in man. I refer especially to the transitory glycosuria produced by strong psychical excitement after injury or shock to the central nervous system, by painful colic, by poisoning with morphin, with hydrocyanic acid, with nitrobenzol, with phosphorus, with sulphuric acid, etc. Numerous cases of this kind are known. It has often been objected that people who exhibit glycosuria from such causes as these are masked diabetics, and that any one of these particular forms of injury acts only as it were as "agent provocateur," the yet dormant disease becoming active later and developing in the usual manner. This may frequently be the case, but it in no wise alters our conception of what occurs. It only shows that a healthy man

is not naturally inclined to hepatogenous glycosuria, and that special additional circumstances are necessary in order to produce phenomena similar to those so often observed in experiments upon animals.

Much more to the point is the question whether not only transitory glycosuria, but also certain true diabetic diseases, are neuro-hepatogenous in origin, and thus due to certain pathological processes which occasion periodical or constant stimulation of Claude Bernard's centre and thus affect the liver. Although many clinicians would answer this question in the affirmative, I cannot yet bring myself to agree with them. In my opinion, one must either explain *every* case of diabetes as of neurogenous origin or else none of them. Whoever would grant to neurogenous diabetes a special position in pathology, must produce evidence first of all that it differs in some essential points from ordinary diabetes. This was attempted many years ago by J. A. Hoffman. The result was a failure and has now no more than an historical interest. There are certainly great differences in the form in which diabetes manifests itself clinically—it may be benign or malignant, chronic or acute, just as tuberculosis of the lungs may be. But the differences are of a quantitative, not of a qualitative kind. The course of the disease is influenced by peculiarities of general constitution, by anatomical processes which occur in the pancreas, by complicating diseases, by modes of life and treatment. Nervous factors also exert an influence on its course, both on the symptoms and on the prognosis, being more

marked in the early stages and in slight cases than in later and in severe cases. But all these different clinical manifestations are insufficient for the recognition, or even the suspicion of a difference in the nature of the disease. My opinion is that we must definitely acknowledge that acute neuro-hepatogenous glycosuria occurs in human pathology, and also that true diabetes glycosuria may be increased or diminished by nervous influences. At the same time it is at least doubtful whether actual chronic diabetes is or could be brought about solely by any nervous influences which are at all analogous to Claude Bernard's "piqûre."

2. *Alimentary Glycosuria*

Physiological alimentary glycosuria is in certain respects also of hepatogenous origin, but it is still a moot point whether the *pathological* reduction of the sugar-assimilating power may be assigned to hepatic causes, or is brought about by other factors. We must, therefore, discuss the alimentary glycosuria in the healthy and in the diseased body separately.

(*a*) *Alimentary Glycosuria in the Healthy Body.*— We may speak of *physiological alimentary glycosuria* when the excretion of sugar is produced by excessive accumulation of carbohydrates. Normally, the carbohydrates of the food, after being split up by the ferments of the intestine and of the intestinal wall into simple compounds, are conveyed to the liver by the portal vein. By far the greater part of them—

especially those carbohydrates most frequently present in our food besides glucose itself, namely, starch, cane-sugar, invert-sugar, milk-sugar—are changed into glucose before they enter the circulation. Only lævulose, small quantities of dextrin, maltose and galactose may also pass as such to the liver. They represent the remnants which have escaped the fermentation activity of the intestine, and their further fate is similar to that of the grape-sugar. For the flow of sugar brought to it by the portal vein the liver serves as a large and capacious reservoir. Almost all sugar is in the first instance retained here and deposited as glycogen in the liver cells. By this means the entire vascular system beyond the liver is protected from an excess of sugar. It is only very slowly and gradually that the sugar passes on from the liver, and it does so exclusively in the form of glucose. The process is so slow that even after a heavy meal of carbohydrate food the amount of sugar is not appreciably increased in the arteries and veins of the body. The sugar which leaves the liver by such an even flow is partly used immediately for the nourishment and work of the body-tissues; partly accumulates in the muscles and glands in the form of glycogen, ready for later use, and may partly be transformed into fat. This, however, only occurs when the total demands of the body for energy-forming substances are fully satisfied. Until lately, it was thought that the formation of fat from carbohydrates also took place exclusively in the liver, that organ endowed with so many wonderful functions.

But recently, a considerable amount of evidence has been brought forward to show that this power of forming fat is shared by other organs, especially by the cells of the connective-tissues. Some twelve years ago I drew attention to the probability of this being the case, in my text-book on Metabolism. The formation of fat from carbohydrates may take place to an enormous extent on a rich diet, but the process requires a certain length of time. Thus when an immoderate amount of carbohydrate is present in the food, and the flow of carbohydrates to the liver exceeds the amount of accommodation available for it at the moment, in either the liver or other glycogen-storing organs, there is not sufficient time for its transformation to fat, so that a certain amount of sugar then flows through the liver cells, gives rise to hyperglycæmia of the arterial blood and subsequently to glycosuria.

The limits up to which the healthy body can dispose of or make use of the carbohydrates of the food varies according to the nature of the carbohydrate. For *starch* no limit is known: even if 400 or 500 grammes of starch are consumed in a few hours, alimentary glycosuria does not occur. The splitting up of starch by ferments in the intestine and its later absorption evidently takes place so slowly and gradually that the assimilative power of the liver and other organs are always able to keep pace with it. Of the sugars themselves, *glucose* has the highest limit (150 to 200 grammes, in one dose). If this assimilation limit is gradually exceeded during successive experiments on

the same person, the whole excess is not excreted in its entirety; always only a few percentage of the embodied sugar appears in the urine, a sign that the body puts forth its regulative powers the more strongly, the more this is required of it. I found, *e.g.*, in one person:

After an intake of		100	gms.	glucose,	0.0	gms.	sugar	in the	urine.
"	"	150	"	"	0.15	"	"	"	"
"	"	200	"	"	0.26	"	"	"	"
"	"	250	"	"	0.52	"	"	"	"

These numbers do not admit of universal application, they are higher in some people, lower in others.

The assimilation-limit for *lævulose* is very little lower than that for grape-sugar. It varies from 140 to 160 grammes in a single dose. It was at one time taught that it was the same sugar that was ingested in excess which again appeared in the urine. As far as lævulose is concerned I must demur to this statement, as I have met with several cases in which after administration of lævulose it was exclusively, or to a very large extent, glucose that was found in the urine. This fact is scarcely surprising when we remember how easily grape-sugar and fruit-sugar may be converted the one into the other.

Cane-sugar has also a high assimilation limit, namely from 150 to 200 grammes, while that of *milk-sugar* is much lower, being only about 120 grammes. There are, indeed, many people who cannot take even 60 to 80 grammes of milk-sugar at one time without excreting it. The condition of things with these two types

of sugar (disacharides: cane-sugar = grape-sugar + fruit-sugar; milk-sugar = grape-sugar + gelactose) is somewhat different from that which obtains with the hexoses we have just been considering. With them any part that is not split up in the intestine and which reaches the blood unaltered, must necessarily be excreted with the urine, for neither the liver nor any other organ has the power of appropriating or assimilating the cane-sugar and the milk-sugar. Their appearance in the urine is, therefore, no proof that there is a superabundant amount of glycogen in the liver, but rather that the ferment-producing-power of the intestine is insufficient. A superabundance in the liver can only be inferred if glucose also occurs in the urine. Contrary to what has long been held, I find such cases to be by no means rare when large quantities of cane-sugar or of milk-sugar are ingested.

Of the other kinds of sugar, I will here only refer to *maltose*. The normal intestine splits this disacharide, and by far the greatest amount of it passes in the form of glucose into the blood and hence to the liver. If the splitting has not been completed in the intestine it may be continued in the blood, as this also contains a ferment which will act upon it. Now it happens that there are a few otherwise healthy individuals who can tolerate all other kinds of carbohydrate except maltose, for which they possess a particularly low assimilation limit. Amongst our foodstuffs, beer is the only one which contains large quantities of maltose. I have often had patients in my

consulting room who came to me in great consternation because they have been told that sugar is present in their urine. It has only required a little further investigation to show that it only appeared after drinking beer. Often half a litre of beer is sufficient to give rise to sugar in the urine, while cane-sugar or even very large quantities of starch occasion no such symptom. One must infer that in these people the maltose-splitting ferment is not present in sufficient amount in the blood. This striking fact is one which should be widely known in order that the danger may be avoided of confusing a serious disease with what is really quite a harmless symptom.

I have, unfortunately, not yet succeeded in determining whether it is grape-sugar or unaltered maltose which appears in the urine.

Finally, I should like in this connection to mention the *pentoses,* although it is uncertain whether alimentary pentosuria should be placed in the same category as the other forms of alimentary glycosuria. Carbohydrates with only five atoms of carbon are common enough in nature, especially in the vegetable kingdom. They must also occur in the animal body since they may be split off in large quantities from nucleoproteids. The animal body probably does not obtain them from the vegetable kingdom, but forms them independently. The pentoses of the food and those which become free when the nucleoproteids disintegrate are usually fully destroyed or made use of by the body. The way in which they are made use of is

at present somewhat obscure. When the pentoses are administered as such in the food they are associated with a far lower assimilation limit than the hexatomic carbohydrates. After the ingestion of even so small a quantity as 30 to 50 grammes almost the half reappears in the urine. Much more rare than this peculiarity is the fact that a few people regularly excrete pentoses even when their food contains neither pentoses nor their precursors (the so-called pentosanes). Pentose taken in as food by these individuals is partially transformed to the urine in them also, but not to a greater extent than obtains in other individuals. In these cases of so-called *spontaneous pentosuria* it is evidently a question of some peculiar anomaly of metabolism, not of real disease; for the individuals were otherwise in a perfectly healthy condition. It frequently occurs as a family peculiarity. Of its biological significance nothing certain is known. Its practical significance lies in the readiness with which it may be confused with true glycosuria and diabetes mellitus, for the ordinary sugar tests apply equally to the pentoses and the hexoses. Many cases are known in which people have been put on a limited diet, much to their annoyance, simply because, from a superficial examination of the urine, they have been erroneously thought to be diabetics. The danger of making such a mistake could be so easily avoided if in every doubtful case, in addition to applying the usual tests for sugar, it were seen whether the urine also gave the Orcin reaction characteristic of the pentoses.

(*b*) *Pathological Alimentary Glycosuria.* — For many decades the attention of the profession has been directed towards the question as to whether alimentary glycosuria occurs more readily in the presence of certain diseased conditions than in normal individuals. To solve this problem the method usually employed has been to prescribe a single dose of 100 grammes of sugar in ¼ litre water or tea to be taken either in the morning fasting, or two hours after breakfast. In a healthy individual no sugar appears in the urine as the result of this treatment. Many investigators have made use of common cane-sugar for the purpose. This has been the case especially in France, but is not to be recommended, since, as I have already said, the transference of sugar into the urine after the administration of cane-sugar may depend quite as much upon anomalies in the fermentation and absorption processes in the intestine as upon abnormalities in the formation of glycogen. The results are more simple and more easy to interpret if the hexatomic carbohydrates—grape-sugar or fruit-sugar—are employed.

The investigations made on alimentary glycosuria in disease were originally intended to elucidate the nature and the conditions of diabetic glycosuria. They did not fulfil this expectation, but they brought to light many other points of interest. In modern times, under the influence of the French school, the term "insuffisience hepatique" is always used when the sample of urine, obtained after a dose of 100 grammes of sugar, gives a positive result. It is, however, very unlikely

that the phenomenon is to be explained from one and the same point of view in all the different types of cases in which such a condition may occur.

We may distinguish first of all a group of diseases in which *nervous* factors evidently play an important part. Alimentary glycosuria is frequently met with in cases of neurasthenia, of traumatic neuroses, in acute diseases of the brain and in meningitis, in many forms of mental debility, especially in mania and paralysis. One can hardly help supposing that in all these cases the centres of the medulla oblongata are in a state of increased excitability and that the alimentary glycosuria is induced through the same nerve channels as in the piqûre experiment of Claude Bernard. The condition of the liver cells is so altered as a result of the stimulation of the nerves that they can no longer store up glycogen in any large quantity especially when the flow of sugar to them from the portal vein is a very sudden one.

In a second group we may place those cases in which we suspect the *function of the pancreas* to be slightly sub-normal. We shall have to consider the relations of the pancreas to diabetes in greater detail at a later stage; it will be enough to mention here that disturbances in the function of the pancreas markedly diminish the glycogen-storing capacity of the liver. This is one of the cardinal phenomena of true diabetes mellitus. When we find alimentary glycosuria occurring in severe and acute cases of febrile diseases, or in acute and chronic cases of alcoholic intoxication, as we fre-

quently do, we may at once suspect that toxic disturbances of the pancreas are present. At one time parenchymatous disturbances of the liver were alone held responsible for these cases of alimentary glycosuria; but the glycosuria of acute infectious diseases and of alcoholism differ in several essential points from the glycosuria of liver diseases:

1. The glycosuria is much more marked:

After 100 grammes of grape-sugar, as much as 10 to 20 grammes of glucose may be excreted, while in all other forms of alimentary glycosuria the quantity excreted is not greater than 2 to 5 grammes.

2. In liver diseases the organism, as a rule, reacts more strongly to lævulose than to glucose. In fever and in alcoholic intoxications, the influence of glucose considerably exceeds that of lævulose. The same is true in diabetes mellitus.

3. Both in fever and alcoholic intoxication, glycosuria can be produced not only by the accumulation of grape-sugar but also by excessive storing of starch, as was first discovered in my clinic four years ago (J. Strauss). I believe that in fever and alcoholic intoxication one has to do with real though transitory disturbances of the pancreas; disturbances, however, which present the same characters as those which occur in true diabetes mellitus, although they differ in being of a much slighter nature and permitting of complete recovery.

We must not, however, forget that true chronic and progressive diabetes mellitus is frequently asso-

ciated with infectious diseases of different kinds and that it is a common experience to find that true diabetes is made temporarily or permanently worse by the supervention of acute infection. The alimentary glycosuria of Graves' disease should, perhaps, be placed in this category. It is true that attention has recently been drawn to the reciprocal relations between the thyroid gland and the pancreas in Graves' disease, but on the other hand it must not be left out of account that it is one followed by so many nervous disturbances that the glycosuria may well be of neurogenous origin.

To a third group belong the *liver diseases*. In all the older writings you will find it stated that it is extremely easy to produce alimentary glycosuria by the administration of grape-sugar in cases of atrophic or hyperthropic cirrhosis of the liver, in acute atrophy of the liver and in obstructions to the flow of bile. I have already insisted, in my text-book on Metabolism, on the erroneousness of this statement, and all the newer authors are in accordance with me. It has, however, recently been ascertained (H. Strauss) that lævulose passes comparatively easily into the urine in all diseases of the liver. The quantity found there present after a single dose of 100 grammes of lævulose varies from 1 to 20 grammes. Alimentary lævulosuria is now regarded as a certain sign of "insufficience hépatique," and it is an occurrence which is the exact opposite of that which takes place in diabetes mellitus; for diabetics possess, without exception, a much better

power of assimilation for lævulose than for grape-sugar.

C. DIABETIC HYPERGLYCÆMIA AND GLYCOSURIA

1. *Diminution in the Amount of Sugar Destruction*

(*a*) *Poverty of Glycogen in the Organs.*—In following out the behaviour of the carbohydrates in the body of a diabetic we are at once struck not only by the already mentioned hyperglycæmia, but also by the fundamental fact of the extraordinary poverty of the organs in glycogen. These observations were first made on the post-mortem tissues of diabetics. The puncture of the liver of the living diabetic has confirmed them. Later, the experimental results of pancreas extirpation pointed to the same condition. Every time a marked diabetes was induced in an animal by successful total extirpation of the pancreas, the liver and the muscles were found to be almost entirely free from glycogen, even when glucose or starch had been administered to the animals shortly before death. New observations made in my laboratory on the liver and muscles removed from the body immediately after death have fully confirmed these experimental results. E. Pflüger has lately attempted to criticise and to depreciate the observations hitherto made by bringing forward a few cases in which the liver contained large quantities of glycogen after death. These were evidently cases of not very severe diabetes; though the patients died, it was more as the result of complications

than of the diabetes itself. It is known from experiments on pancreas extirpation that it is only in severe pancreas diabetes that the organs really become free from glycogen. The slight glycosuria occasioned in animals by incomplete extirpation of the pancreas is accompanied by a diminution in the amount of glycogen stored, but not by complete failure to store it.

While the typical glycogen depots, however, do not store it, other cells, especially the white blood-corpuscles and the epithelia of the kidneys assume the functions. The quantities there accumulated are, however, infinitely small as compared with those which *fail* to be accumulated in the liver and muscles.

With regard to the reasons which prevent the liver and muscles from storing glycogen I shall have something to say later. The question is one of extreme importance, for it is in the answer to it, as it seems to me, that the secret of diabetes lies.

(*b*) *Defective Glycogen Formation as the Cause of the Hyperglycæmia.*—The incapacity of the organs to form glycogen explains almost all the peculiarities of diabetic glycosuria. It explains, first of all, the hyperglycæmia which we have been led to regard as the most proximate and immediate cause of the glycosuria. The carbohydrates coming from the intestine or originating from the proteids, and possibly from the fats and other substances of the tissues, can find no proper resting place. In as far as they cannot at once be utilised by the tissues at the same rate as they reach the blood, they remain in the blood, increase its sugar contents,

and are in danger of being caught and excreted by the kidneys. The glycosuria is therefore always most intense when the absorption of carbohydrates is at its greatest height. We find, *e.g.*, many diabetics with 2 to 3 per cent. sugar in the urine during the first five hours after feeding on 100 grammes of bread. If they then take no more carbohydrates for the rest of the day, the urine is gradually freed from sugar and after a further six hours it may not contain even a trace. This is, indeed, the rule in all early slight cases of diabetes, and it is a reason for the non-recognition of many cases of early diabetes, for with many it is customary to bring or to take for analysis only that urine that was passed in the early morning, and this is often free from sugar while that passed during the day after food contains a considerable amount.

(*c*) *Defective Glycogen Formation as the Cause of Deficient Oxidation of Sugar.*—It is evident that the prevention of the accumulation of glycogen must lead to hyperglycæmia and glycosuria. There are, however, probably other pathological processes intimately connected with it. If it were only the accumulation of glycogen in the liver and in the glycogen depots that were disturbed, it ought to be quite easy to diminish the glycosuria by increasing the muscular work. This muscular work is maintained during health almost exclusively at the expense of carbohydrates, but the muscle, in case of need, is always free to draw on other materials, especially fats and proteids. Let us take the case of a diabetic fed on a diet free from carbo-

hydrates and in spite of this excreting 50 grammes of sugar a day while he is going about his usual occupations. Let him now ascend a mountain 600 metres high. For this work (ascent and descent) the expenditure of 80 to 100 grammes of carbohydrate, according to the body weight of the patient, is necessary. We should expect, therefore, that the glycosuria would be greatly reduced or that it would quite disappear, since we have given the sugar, that could not be deposited in the glycogen depots and that would otherwise be excreted with the urine, an opportunity of proving itself useful and serving for combustion in the muscles. But we find to our surprise that the glycosuria is hardly if at all reduced. The muscles disdain to use up those carbohydrates which under normal conditions are exclusively utilised for such muscular work. I have at my command the details of many observations upon diabetics in which the sugar in the urine was diminished only by a few grammes, although 80 to 100 grammes would be an average amount required by a normal adult for the work that was done. I must here interpose a clinical observation: You will find it stated in all text-books that one should urge diabetics to take as much exercise as possible in order to burn up more of the sugar formed in the body. But this is a correct procedure for slight cases of diabetes only. We have already seen that in slight cases the capacity of the organs to fix the glycogen is not abolished but only reduced. We may now make the statement that in those cases in which the

power of fixing glycogen is to some extent retained, muscular work may lead to increased sugar transformation and hence to diminution of the glycosuria. But even here, in so far as my experience goes, the reduction of the glycosuria is not proportional to the amount of work done. In severe cases of diabetes the text-book dictum certainly does not hold true. You may often find that the glycosuria even increases when you put a diabetic to hard muscular work. We may, therefore, formulate the further statement that in cases where the organs have completely, or almost completely, lost their capacity for storing glycogen the combustion of sugar is not increased by muscular work to any appreciable extent. What does this mean? The fact is in full accordance with modern ideas regarding the elaboration of the food-stuffs in the cells. The food-stuffs, whether carbohydrates, fats, or proteids, are not assimilated as loosely-combined or as free molecules, but must first enter into some firm chemical combination with the protoplasm of the cell before they can be utilised. So far as the carbohydrates are concerned, our experience with diabetics leads us to assume that the protoplasm is not able to assimilate the free hexatomic sugar in the blood and in the cells, but that the assimilation and further elaboration of the carbohydrates into protoplasm can only take place when by polymerisation glycogen has been formed from the hexose. Granting this hypothesis, it is easy to understand why in a severe case of diabetes the muscles are not able to consume more sugar when at

work than when at rest, in spite of being permeated by a fluid overladen with sugar. The connecting link, namely, the fixation of glycogen, is wanting.

Besides this comparison of the effects produced by rest and work on the excretion of sugar, we have other evidence that sugar is either not utilised at all, or at least only with much greater difficulty by the tissues of a diabetic. This is given by the behaviour of the respiratory quotient. If carbohydrates alone are available for combustion in the body, the ratio between the expired CO_2 and the inspired O is 1 ; if fats alone, the quotient falls to 0.7. On a mixed diet in which oxidation extends simultaneously to carbohydrates, fats and proteids, values between 0.75 and 0.90 are obtained. In cases of severe diabetes the respiratory quotient is either at its lowest normal limit or even below it.

This is due to the carbohydrates, which normally tending to raise the respiratory quotient, here play no part in metabolic activities. The respiratory quotient is not raised, or only very inconsiderably raised by giving such a patient large quantities of carbohydrate food, and it makes no difference whether he is made to take exercise or not. The carbohydrates pass unused through his muscles. In a healthy subject, on the other hand, feeding on carbohydrates immediately raises the respiratory quotient and every kind of muscular work produces the same effect, to begin with, at any rate, since healthy muscle first attacks its own glycogen and later, when this is

exhausted, it brings that of the liver into play, and only at a later stage, when the glycogen of the body has been more or less used up, does the respiratory quotient again sink, because the muscle is now compelled to draw upon fats and proteids. The methods of investigating the respiratory exchanges have now become so refined and exact that the results may be placed by the side of such as are obtained in exact chemical analysis and equally trustworthy conclusions may be drawn from them. It may be asserted with perfect confidence that the diabetic—in a degree corresponding to the severity of his disease—has lost the power of utilising carbohydrates.

(*d*) *Comparison of the Arterial and Venous Blood.*—It was at one time attempted to show this in another way. Arterial and venous blood taken from the limbs of diabetic dogs were analysed. A few authors found that the muscles of such an animal took less sugar from the blood than the muscles of a healthy animal, but this could not be confirmed by other observers. That different results were obtained is hardly to be wondered at, considering the many technical and analytical difficulties involved in the methods employed, the sources of error being greater than the differences to be expected between arterial and venous blood. Nevertheless, we may hope and even expect that this experimental method will eventually be made sufficiently delicate to yield definite and reliable results.

(*e*) *Behaviour of Lævulose in Diabetes.*—Of special importance for all questions appertaining to

the appearance of hyperglycæmia and the non-consumption of sugar are the results obtained with lævulose. I have said that the tissues, and especially the muscles, of diabetics cannot utilise the carbohydrates because the sugar has not been transformed into glycogen. Now in lævulose we have a carbohydrate which is much more easily appropriated by diabetics than are grape-sugar and starch. This fact was discovered independently by Bouchardat and by E. Kutz. Then followed the experiments with pancreas diabetes on animals. The discoverers of this, v. Mering and Minkowski, themselves established the fact that animals in which the pancreas had been extirpated retained the capacity for forming glycogen out of lævulose while they had entirely, or almost entirely, lost it for forming glycogen out of grape-sugar or starch. Pointing in the same direction are a few experiments on the respiratory quotient of diabetics obtained after feeding on lævulose. They were first made in my clinic, and have as yet only been partially published. It was found that the respiratory quotient rose after feeding on lævulose. We have already seen that it does not do so after feeding on grape-sugar. These three things: diminished sugar excretion after lævulose, storing of glycogen after lævulose and a rise of respiratory quotient after lævulose, have evidently some intimate connection with one another.

We may summarise what has so far been said in the following terms:

The most important peculiarity of the diabetic con-

dition consists in the loss of the capacity, by those organs whose normal function it is, namely, liver, muscles, and perhaps with certain restrictions, glands—to perform the function of taking from the blood the therein circulating glucose,—largely derived from the ordinary carbohydrates of the food,—and of storing it up as glycogen. To comparatively the same extent as they have lost this faculty so have they also lost that of burning off the carbohydrates. For the natural fuel of the cells is not glucose, but glycogen. As a consequence the sugar which enters the blood, derived either from the food substances or from other sources, remains in the blood stream in the first instance and thus gives rise to hyperglycæmia. The kidneys are not prepared for this. The sugar, rejected by the cells of the body, flows away through the kidneys. But when, by choosing particular carbohydrates, *e.g.*, lævulose and allied substances, we force, as it were, the formation of glycogen, we attain at the same time a better combustion of carbohydrates.

I must, however, at once mention that the capacity of the diabetic patient to elaborate lævulose is not unlimited. In the most severe cases of diabetes even this faculty is lost, and then the glycosuria is increased almost as much by the administration of lævulose as by that of glucose. There is another phenomenon which should be mentioned here. It has recently been discovered that in almost all severe cases of diabetes lævulose appears spontaneously in the urine by the side of glucose even when the food contains no

lævulose and is moreover free from carbohydrates. From my experience of this occurrence during the last two years I consider this symptom to be a very grave one. What is it that gives rise to it? It appears that in every organism small quantities of lævulose are always formed at the same time with large quantities of grape-sugar. In normal blood and in all pathological fluids (exudates and transudates) traces of lævulose have been found. In a healthy man this lævulose has, however, but a very brief existence. It is very readily converted into glycogen and is then accordingly selected by the liver and by the muscles. The same holds good also in slight cases of diabetes. It is only when the assimilatory power of the organs in severe cases is totally exhausted that the transformation of lævulose into glycogen is also checked, and thereafter in addition to the grape-sugar, fruit-sugar also appears in the urine.

I will take this opportunity of mentioning that there are a few individuals who suffer from spontaneous lævulosuria, although the urine does not at the same time contain grape-sugar. We have to do here with a special peculiarity of metabolism. The largest quantities of the different carbohydrates are all excellently tolerated, or if anything slightly increase the lævulosuria. It is only towards lævulose itself and its precursors that a lessened power of assimilation obtains. We have probably here to do with the want of some particular ferment in the body. We may place this spontaneous form of lævulosuria in the same category

with the spontaneous pentosuria already referred to, and the rarely occurring spontaneous excretion of sugar after ingestion of maltose. Strictly speaking, people with spontaneous lævulosuria may also be termed diabetics, because they exhibit, in common with ordinary diabetics, the peculiarity of being unable to turn carbohydrates to their proper account. But in their clinical relations the two forms differ widely from one another. Lævulose plays so small a part either as food material or in the formation of sugar inside the body that the disadvantage to the patient in its not being sufficiently made use of is but slight. The peculiarity of the disease of the true diabetic—the failure to make efficient use of grape-sugar—is much more serious, for almost all carbohydrates which enter the body as food, or which arise endogenously, go through a grape-sugar stage.

2. *Causes of Defective Formation of Glycogen.*

Having so far as we have gone now established the fact that the diabetic individual has a difficulty in making use of grape-sugar, whatever its origin, and having recognised as highly probable that this anomaly of metabolism immediately depends upon defective formation of glycogen, we must approach the question as to what the deficient formation of glycogen depends upon. He who can answer this with certainty has solved the riddle of diabetes. To the pancreas we must first direct our attention.

(*a*) *Experimentally Produced Pancreas Diabetes.*—It is well known that even the earliest workers expressed the opinion, as the result of careful post-mortem investigations, that diseases of the pancreas played an important part in the ætiology of diabetes. Frerichs and Lancereaux may be especially mentioned in this connection. Sixteen years ago there followed the experimental investigations of v. Mering and Minkowski: total extirpation of the pancreas was shown to produce a severe and fatal diabetes, whose symptoms and course resembled in every particular the spontaneous form of diabetes as it is manifested in man. In other instances, it may well be doubted whether it is permissible to draw conclusions with regard to spontaneous diseases in man and diseases artifically produced in animals, but in this case the agreement is so complete that all such doubt vanishes. Every single feature of the experimental pancreas diabetes was shown to have its counterpart in human diabetes and vice versa. The experiments were originally made on dogs, but pancreas diabetes has been now produced in a whole series of animals and with the same result in all, the deviations according to the species of animal being only slight, except in the case of birds in which pancreas diabetes exhibits certain peculiarities to which there is nothing analogous in other groups of animals. On these details, however, I will not here dilate. Only the most important of the points necessary for the understanding of what is to follow shall at this time be selected from the large

quantity of material that has since accumulated in regard to experimental pancreas diabetes:

(1) In a very few hours after total extirpation of the pancreas,—in one day at most,—the condition designated as *total* pancreas diabetes occurs. All the carbohydrates, which in the intestine or beyond the intestine are usually transformed into grape-sugar, now reappear almost completely in the urine. Lævulose is still, however, utilised by the body to a fairly large extent, a phenomenon the significance of which we have already discussed. A large proportion of the sugar which has been formed in the body out of proteid material also appears in the urine. On an average, to 1 part of nitrogen in the urine as much as 2.8 parts sugar are excreted; the proportion is not a constant one but varies with the kind of proteid on which the animal has been fed. This is a subject on which I shall have more to say later on. The symptoms, therefore, are those of the so-called severe form of diabetic glycosuria, *i.e.*, the type in which the glycosuria does not disappear even when carbohydrates are absent from the food.

(2) If about 20 per cent. of the substance of the pancreas is allowed to remain, only what is termed *slight* diabetes results, *i.e.*, a condition in which the glycosuria only occurs if carbohydrates are present in the food. Owing to the gradual degeneration of the portion of the pancreas that has been left, this slight form of diabetes frequently passes into the severe form.

(3) If over 20 per cent. of the gland substance is allowed to remain, diabetes is not induced.

(4) Cutting off the pancreas secretion from the intestine has certainly nothing to do with the causation of diabetes. It occasions great disturbances in the digestive processes, especially in the absorption of fat, but never gives rise to glycosuria.

(*b*) *Theories with Regard to Pancreas Diabetes.*—The discoverers of pancreas diabetes concluded from their experiments that the normal pancreas "gives off something by internal secretion," the presence of which in the blood is essential for the elaboration of the sugar. Starting from this hypothesis, which at the time met with universal acceptance, the theory of pancreas diabetes has not been further developed up to the present day.

There has certainly been no lack of attempts to discover the nature of the action of the pancreas in this regard.

Lépine's Theory.—In the first place R. Lépine, from the results of many very laborious investigations, maintained that the amount of "glycolytic ferment" in the blood was diminished both after extirpation of the pancreas and in spontaneous diabetes in man. This theory gave rise to a lively and extensive discussion in the current literature and it was ultimately decided that the methods employed by Lépine were not sufficiently accurate for the purpose in view.

Glycolytic ferments, whose identity with the oxidising ferment universally present in the organism was

asserted by some and denied by others, do certainly occur in the blood, but their action is so feeble that only a very small part of the enormous quantity of sugar which a normal man actually transforms during each 24 hours could be destroyed by them. Careful test experiments have also shown that any difference between the amount of ferment in normal and in diabetic blood is very slight, if indeed there is any difference. We must, therefore, to-day conclude that Lépine's theory has been robbed of all the foundations on which it was based. Moreover, to work further on the same lines means an almost fruitless quest, since all that we know of the more minute processes of metabolism is in favour not of the blood but of the tissues being the actual seat of the decomposition of the sugar. Lépine himself has now also recognised these necessary conclusions.

Cohnheim's Theory.—Another new point of view presented itself when O. Cohnheim published his observations that neither the pancreatic juice alone, nor the muscle juice alone produces any considerable glycolytic effect; although when the two juices are together allowed to act on sugar, a most energetic destruction of the sugar ensues. This seemed to prove that, in accordance with the theory of v. Mering and Minkowski, the pancreas gives off something which, when led to the tissues by the blood, enables them to destroy the sugar. Cohnheim gave the name of "activator of the pancreas" to this substance, and ascribed to it the property of being heat-resisting. Although

a few expressions of agreement with this view soon appeared, the careful testing of it by G. Embden and R. Claus in my laboratory brought about the immediate collapse of Cohnheim's whole doctrine. If the muscle juice can be kept free from bacteria, its glycolytic power is not altered by the addition of pancreatic juice. Cohnheim had not sufficiently attended to this point and had so fallen into the same error that had rendered valueless many earlier works of glycolysis.

V. Noorden's Theory.—I believe that it is in another direction that we must seek for the solution of the problem. The alterations which occur in the deposition of glycogen which I discussed in detail in my last lecture occupy such a central position in the disturbances of metabolism in diabetes and have obviously so powerful an influence on the fate of the carbohydrates that an exact investigation of just these processes promises the most fruitful results. Again it is to the pancreas that we have to direct our attention. We have to ascertain whether this organ supplies to the blood a substance which has something to do with the building up or with the breaking down of glycogen. This might be a ferment which favours the act of polymerisation in the formation of glycogen, or it might be an antiferment which prevents too rapid destruction of glycogen. All tissues, muscle especially included, have an enormous power of destroying glycogen; one cannot therefore work quickly enough to obtain correct quantitative determination of the amount of gly-

cogen in the organs. Glycogen during this diastatic process is always transformed into sugar which, as is well known, cannot be fixed by the tissues. If the pancreas furnishes a substance which acts as an antiferment, *i.e.*, serves as a restraint to the diastatic ferment, a deficiency of such an antiferment would produce exactly the same result as the deficiency of a ferment favouring the fixation of glycogen. In both cases, poverty of glycogen in the organs and hyperglycæmia would be the inevitable consequence, and, as already discussed, the cardinal symptoms of diabetes would follow of themselves. Further investigation will in my opinion disclose the existence of the one or the other of these two processes. Which of them is the more likely to occur can hardly as yet be foretold. The fact that diabetics can still form glycogen out of lævulose, and that glycogen is found to be deposited in the cells of the liver and muscles after feeding on lævulose seems to point to the probability of its being rather a question of faulty formation of glycogen from grape-sugar than of its too rapid destruction. We must, however, bear in mind that as yet we do not know the exact constitution of glycogen, and that lævulose may give rise to a different and more stable form of glycogen than may glucose.

I am here treading on purely theoretical ground, but it is a train of thought that I felt I ought not to suppress, as it may serve as a stimulus to future work. In my laboratory many experiments have been already made with a view to settling the question one

way or another and I hope before long to be able to communicate a definite result. You will see that these hypotheses tend in quite a different direction to those of Lépine and Cohnheim. These authors concern themselves with anomalies in the *glycolytic* process, while I have in view anomalies in the formation of glycogen or in the *diastatic* process. The two views, however, have this in common, that they assume the action of some substance formed by the pancreas and both aim at explaining the important fact, mentioned even by the oldest exponents of diabetic conditions, namely, that somehow or other the normal metabolism of carbohydrates is disturbed in the body of a diabetic.

(*c*) *Disturbances in Formation of Fat.*—It is not only the breaking down of the carbohydrates molecule by oxidation that is affected by those disturbances in the sugar metabolism, but also a synthetic process, viz., the formation of fat out of carbohydrate, that is altered. Were only the changes in the splitting, and the consumption of the carbohydrates concerned, there would be no more necessity for the supervention of glycosuria than there is in a healthy individual fed continuously on large quantities of farinaceous food and other carbohydrates. A strong and persistent glycosuria could not occur on a diet poor in carbohydrates, with which the whole quantity of sugar which gets into the circulation is relatively small, and at all events does not nearly equal the quantity which is taken up from the alimentary canal and fully elaborated in a richly-fed healthy man. The carbohydrates,

not utilised by the glands, muscles, etc., would be selected by the fat-forming cells and by synthetic processes would be built up into fat just as in the healthy body. Hyperglycæmia and glycosuria can only ensue when the carbohydrate molecule has become inaccessible not only for the oxydising but also for the fat-forming cells. It is possible also that the formation of fat from carbohydrates does not occur from glucose directly, but only by the intermediate agency of glycogen; we have, however, no information on this point. All that we do know is that in severe cases of diabetes not only the consumption of sugar, but the process of formation of fat, also suffers.

On the basis of the foregoing considerations I think that we are justified in adopting the following view:

We can conceive cases of diabetes in which, to begin with, the sugar-consuming capacity has been only impaired while the synthesis of fats from carbohydrates continues. Under such circumstances, the working cells of the body would be richly bathed with nutrient sugar solution, but would nevertheless degenerate because they could not, or only with difficulty, attack the sugar molecule. As a consequence a form of tissue-hunger occurs which later reflexly leads to increased appetite and a consequent large intake of food. In such a case this is the immediate cause of obesity. Obese individuals of this type have already an altered metabolism for sugar, but instead of excreting the sugar in the urine, they transfer it to the fat-producing parts of the body, whose tissues are still

well prepared to receive it. The ensuing obesity masks the diabetes. It is a case of "diabetogenous obesity" (diabetogene Fettsucht), as I term this condition in preference to the term "lipogenous diabetes," which expresses the doctrine more usually held.

We arrive, therefore, at the following conclusions:

1. There are cases in which the consumption of sugar and its transformation into fat are both simultaneously impaired, glycosuria of different degrees of severity and wasting commonly resulting. This is the commonest form of diabetes.

2. There are cases in which only the consumption of sugar, but not the synthesis of fat, is impaired: obesity, but no glycosuria, is the result; it is a form of diabetes masked by obesity. These cases develope later into:

3. Cases in which the consumption of the sugar is diminished and the storage of the carbohydrates in the fat masses is also suffering a moderate and gradually progressing impairment. These are cases of obesity with superadded glycosuria and constitute the common form of diabetes in the obese. This theory I certainly do not regard as a hypothesis merely put forward to supply gaps in our knowledge, but I believe it to be well supported by the available facts. A similar opinion has been expressed by W. Leube. The connection between diabetes and obesity ceases in the light of my theory to be any longer an enigmatical relation, and becomes a necessary consequence of the relationship discovered in the last few years between carbohydrate transformation and formation of fat.

My opinion that these are obese people who are theoretically already diabetic before they begin to excrete sugar, is supported by observations upon patients which I communicated to the "Congress für innere Medicin" ten years ago. Certain of such people, in whom obesity was a hereditary family characteristic, although they could metabolise very large quantities of starch, exhibited marked alimentary glycosuria after 100 grammes of glucose. As I thought likely at the time, and as I have elsewhere recently communicated, a few of the then-mentioned obese patients have since become really diabetic. It is advisable therefore to test the urine of obese people from time to time for alimentary glycosuria, in order to recognise in good time any tendency to diabetes, and thus by immediate regulation of the diet to afford real assistance to the patient, saving him perhaps from a later attack of diabetes.

(*d*) *Pathological Processes in the Pancreas Itself.*—Although we cannot as yet obtain a clear insight into the disturbing processes to which the metabolism of carbohydrates is exposed in the tissues after removal of the pancreas, the line in which future researches must be carried on is pretty clearly indicated. The methods of the unravelling of the processes which take place in the pancreas are far less intelligible. The numerous post-mortem examinations which have been made since the discovery of experimental pancreas diabetes show, it is true, that no organ of the body of a diabetic so frequently exhibits anatomical alterations as the pancreas, simple atrophy and sclerosis of

the pancreas being the most frequent structural changes. But all observers have been struck by the fact that the anatomical alterations in the pancreas even in very chronic and very severe cases of diabetes are only slight. More than one author has on this account cast some doubt on the "pancreas" theory of diabetes. Such dissentient voices are, however, now hardly taken seriously, so firmly rooted has the doctrine of pancreas diabetes become. For the last few years it has been taught that the pancreas really consists of two glands which, although intercalated into one another, are quite independent in their development and function. The one part is said to alone furnish the secretion and the digestive ferments, the other part consisting only of solid ductless masses of cells, the so-called islets of Langerhans. These islets are supposed to form the substance which is essential for the metabolism of the carbohydrates and to pass it into the blood. It is certainly true—and Opie was the first to lay special stress upon this fact—that these two different parts of the pancreas may become diseased and degenerate independently the one of the other, and that anatomical alterations which occur in diabetes concern especially, sometimes even exclusively, the islets of Langerhans. Cases are, however, on record in which in spite of severe diabetic disease the islets remain intact. I have myself seen a few such cases. Quite lately it has again been asserted, and on the strength of very careful work, that an essential difference between the tissue of the islets and

that of the rest of the gland cannot be said to exist; that the islets are only early stages in the development of the secreting gland substance, and develop into this later. The question is one which is now being actively studied by pathological anatomists. It is as yet, in my opinion, too early to form a definite judgment on the matter, but whatever the solution finally turns out to be, this much is certain at the present time, namely, that the specific diabetic disturbances of the pancreas are not necessarily connected with visible anatomical alterations in the islets or in any other tissues of the pancreas. For those cases are very frequent in which the most conscientious anatomical examination has failed to bring to light any pathological change, or at most has revealed a very slight increase of connective-tissue. It is evident that severe disturbances of chemical functions may occur in this organ without impressing their image on anatomical structure. We are all still so much under the influence of that glorious epoch in which pathological anatomy was the only mistress from whom scientific medicine could learn with profit, that it is often difficult for us to realise that important disturbances of function may occur when miscroscopic examination reveals no distinctively pathological changes. In formulating any theory about diabetes, however, it seems to be necessary to let go such ideas and to seek for the root of the matter in those disturbances of the intra-cellular chemical mechanism which, though often accompanied by anatomical changes of the organ or

perhaps caused by them, may yet develop without any structural alterations. Of the nature of these chemical disturbances one cannot even hazard an hypothesis.

3. *Over-Production of Sugar as a Cause of Hyperglycæmia and Glycosuria*

So far we have only been considering the fact that in diabetes the consumption of carbohydrates is abnormally diminished, and that hyperglycæmia and glycosuria occur because the cells of the tissues permit the sugar of the blood to pass by them unmolested.

At the same time the question suggests itself as to whether it may not be an *increased* formation which gives rise to the overloading of the blood with sugar. The question is an old one and anyone familiar with the history of the doctrine of diabetes knows, that in the first few decades after its discovery, it was the over-production of sugar much more than the diminution of the amount used up, that was spoken of. Many authors are still inclined to this view. The question is an important one, and is the more interesting theoretically because it takes us into just that region of physiological chemistry which is receiving a large amount of attention from present-day workers. It refers to the investigations into the sources of animal sugar.

(*a*) *Definition of the Question.*—The matter is a complicated one, and it is only in roundabout ways that it can be unravelled. Let us begin by trying to make clear the question at issue. Over-production of

sugar can only be spoken of when substances which are not normally sugar-formers become such. We will assume that this is the case in diabetes. It probably is so. Then follows the question as to whether the over-production is a *primary* effect, *i.e.*, whether it is an *independent* consequence of those disturbances of metabolism characteristic of diabetes, and is the proximate cause of the hyperglycæmia and glycosuria. This question is probably to be answered in the negative. There remains, however, the other possibility, that the over-production of sugar is a *secondary* effect evoked by the demand made by the tissues for sugar. This requires some further explanation. Normal tissues are always utilising sugar for the performance of work and for the supply of heat. The cells get the required carbohydrates partly from the glycogen which is deposited in them as reserve food-material, and partly from the blood which brings sugar to them in an ever-steady flow. In the same measure that sugar is taken from the blood by the working cells of the muscles and glands, fresh sugar is supplied to it at some other place, so that the amount of sugar in arterial blood remains at the same level. The liver is the most important, perhaps it is the only, organ which provides for this supply. As long as its store lasts the liver yields the supply of sugar out of its reserve glycogen, but with hard work or long fasting this store soon becomes exhausted, and yet the formation of sugar continues; the sugar concentration of the blood remains unaltered even when there has long ceased to

be any store of glycogen at all in the body, as after very severe exercise or after several weeks' starvation. In any case, after the exhaustion of the reserve glycogen and perhaps much sooner, some other sources of sugar must be tapped. We shall see that proteid material and probably fat can be also drawn upon for its formation. The important fact is that the need of the muscles and other tissues for carbohydrates prescribes to the regulating liver how much sugar it shall form and how much it shall give off into the blood. Whether or not the liver receives this intimation by nervous channels as was formerly universally assumed, is not yet decided. It is certainly a possibility, but we are more inclined nowadays to think of the influence as being chemical in nature, *i.e.*, that it is the *quality* of the blood flowing through the liver which informs the liver-cells whether much or little sugar is to be formed and given off. It may be that it is the sugar content of the inflowing blood which itself gives the regulating signal; but it is more probable that substances produced by the metabolism of the cells of the body bring the information that the tissues are famishing for sugar and so indicate the needs of fresh supplies.

In a diabetic individual the tissue-cells are bathed in a superfluity of sugar and are yet hungry for sugar because they are unable to utilise it. Consequently, from the tissues of the diabetic, especially in severe cases, continual stimuli are being sent to announce the sugar famine and to urge the mobilisation of fresh

quantities of sugar. The sugar-forming organs have, in severe diabetes, to work continuously in the same manner as they do in a healthy individual who has exhausted his store of glycogen and is yet performing heavy muscular work. The only difference is, that in the healthy body the mobilised quantities of sugar step into the breach and are there used up in the proper way; whereas in the diabetic the reserve called out does not reach the place where it is required, and is uselessly squandered.

We see from this description, which is far from containing anything hypothetical, and on the contrary is strictly limited to known physiological processes, that the specific diabetic disturbance in metabolism, *i.e.*, the diminution in sugar-consumption, may, and even must, entail *secondarily* an over-production of sugar. Material which the healthy man can leave for future need or for other purposes is brought into the field for the formation of sugar. It stands to reason that this process attains very different dimensions in particular cases of diabetes. It is greater the more the normal consumption of sugar is disturbed, and the higher the level to which the claims of the muscles and the glands have risen by reason of increased activity.

After these preliminary remarks, let us try to give an account of the sources from which the animal organism can derive its sugar.

(*b*) *Sources of Sugar, and Carbohydrates of Food.*

(*a*) In the first place we must, of course, name the carbohydrates themselves. In people who eat a great

deal of carbohydrate food the sugar taken up from the intestine is more than sufficient to supply the whole demand. It is doubtful whether in such cases other sources of sugar are at all brought into play. At any rate, the cells prefer sugar when it flows abundantly from the intestine to all other kinds of non-nitrogenous material. The respiratory quotient, which rises even in only a quarter to half an hour after the ingestion of carbohydrates and remains at the higher level so long as carbohydrates are being absorbed from the intestine, shows this. One may very easily, as the respiratory quotient shows, limit the oxidation of fat by limiting the amount of carbohydrate in the food; it is much more difficult to do the reverse, *i.e.*, to limit the consumption of carbohydrates by limiting the fat in the food. It is, however, only in some individuals that the daily uptake of carbohydrates is great enough to cover the whole consumption of sugar. There are many healthy people, *e.g.*, whole races in the northern regions of the world, and also numerous groups of animals, in which carbohydrates are hardly used at all for food. These people and animals subsist almost entirely on animal nourishment and, in spite of this, sugar is being continually produced and conducted to the tissues. In such cases the demand must be met from other sources of sugar.

(β) *Albuminous Substances.* — The question whether sugar can be formed from proteids has passed through many remarkable phases. Anyone who looks up the history of chemical biology will find that many

important pieces of evidence with regard to the origin of sugar from albuminates are drawn from our knowledge of the metabolism of diabetes. The conclusions are based on the fact that diabetics with severe glycosuria when strictly dieted so as to consume as little carbohydrate food as possible, for a long time continue to excrete an amount of sugar out of all proportion to the small amount of carbohydrate in the food. The sugar must, therefore, have been newly formed out of other material. One may even frequently find an approximately proportional relation between glycosuria on the one hand and decomposition of proteid on the other hand. The easiest way of convincing oneself that sugar can be formed from albumen is by feeding a diabetic who exhibits severe glycosuria for a few days on a diet poor in proteids and at the same time free from carbohydrates (*e.g.*, on green vegetables, yolk of eggs, butter, tea, coffee, wine, lemonade, etc.). The sugar in the urine then sinks to a minimum, or may even entirely disappear. The body has certainly by this time become quite free from glycogen. If, now, albuminates be added to the diet the sugar in the urine rapidly increases in amount. Out of an extremely large number of such observations I will relate one which illustrates this point.

Three days of strict diet[1] with much meat: 48.2, 56.7, 57.1 grammes of sugar.

Three days of vegetables: 30.2, 11.9, 2.1 grammes of sugar.

[1] No carbohydrates.

Five days of vegetables and 300 gr. meat on each: 7.8, 22.8, 33.5, 36.7, 48.3 grammes of sugar.
Two days of vegetables alone: 8.1, trace only grammes of sugar.

Every physician experienced in the treatment of those suffering from diabetes must have made numerous observations of the same kind. The increase of the glycosuria which follows the addition of albuminates to the food is often even more intense than the example cited. Amongst practitioners, therefore, for a long time there has been entire unanimity of opinion, that, at any rate, in diabetes, sugar may be formed out of proteids. Amongst physiologists, E. Pflüger, of Bonn, is the only one remaining who has disputed the doctrine. Although we must gratefully acknowledge that by his critical studies he has taught us how careful we must be in interpreting all such experiments, yet we cannot help reproaching Pflüger with the fact that he has gone much too far and quite unjustifiably attacked the trustworthiness of more than one experiment. For this reason we must welcome the more Pflüger's own recent acknowledgment of his error, and the fact that he has himself adduced evidence of the formation of sugar from proteids.

I cannot here, of course, discuss all the phases of this regrettable dispute. We will accept the fact that sugar can be formed out of proteid and that, at least in severe cases of diabetes, such a formation actually happens to a very great extent.

Much more complicated is the question as to the

exact component of the proteid molecule from which sugar is formed. When at the end of the last century Kossel and Pavy produced evidence that carbohydrates could be split off from the majority of albuminates by treatment with acids or alkalies, the matter seemed to have become very simple of explanation. The proteid molecule, it was said, is built up after the manner of a glucoside. In the organism, as well as outside it, the carbohydrate group is split off when the proteid molecule breaks down, and it furnishes the sugar which the tissues require when the diet is poor in carbohydrates, and which appears in the urine in severe cases of diabetes in spite of a dietary restricted in carbohydrates. This doctrine agreed with the conception that had long before been formed with regard to the process, but for which up till that time experimental evidence had been sought in vain. But no sooner was such evidence apparently obtained than the doctrine had to be altered in some essential points. The fact that carbohydrate groups occur in proteid, and that these may be called into the service of sugar metabolism, of course remained, but it did not suffice to explain clinical and experimental observations.

It was next established that the quantity of carbohydrate represented in the proteid molecule varied greatly in the different albuminates, and, taken all in all, was never a large one.

The only proteid substances which contain much carbohydrate, *i.e.*, 25 to 35 per cent., are the glycoproteids (mucin, ovomucoid, etc.); the simple pure

proteid bodies contain much less. Among the pure proteids ovalbumen contains the largest amounts of sugar, viz., 10 to 15 per cent. carbohydrate; the proteid bodies of the blood serum contain not more than 1 to 2 per cent., muscle substance less than 1 per cent.; casein does not even contain any carbohydrate that can be split off.

The percentage of sugar which can be produced out of proteid substances by diabetic individuals is much higher than the highest of the above numbers. Proteids in such cases may yield as much as 40 to 50 per cent. of their own weight of glucose.

The conjecture, that the richer the proteid was in carbohydrate the more did it promote the formation of sugar, has not been confirmed. On the contrary, all observations, without exception, point to the conclusion that it is out of casein that sugar is most readily, and to the greatest extent, formed in the diabetic organism, *i.e.*, out of just that proteid body which contains no preformed carbohydrate; while on the other hand ovalbumin, of all the simple proteid bodies the most rich in carbohydrates, yields the smallest amount of sugar when administered to a diabetic patient. It must therefore be some other groups of atoms in the proteid molecule which contribute to sugar formation. It is now recognised that such groups are constituted by the amino-acids, which, as is well known, make up a large part of the proteid molecule. In casein, quite large quantities of these amino-acids are present. The most conclusive observations relate to alanin

(amido-propione-acid), but those with glycocoll (amido-acetic acid) and leucin (amido-capronic acid) may also be mentioned. My assistants, Dr. G. Embden and Dr. H. Salomon, found that in the dog, after extirpation of the pancreas, alanin is almost measure for measure transformed into sugar and excreted with the urine. As to the exact chemical processes which take place in the transformation of amino-acids into carbohydrates, it is the less desirable that I should now discuss them for the reason that the investigations so far made do not lead to any perfectly certain conclusions.

It is also doubtful whether, under all circumstances, the amino acids contained in the proteid molecule are first transformed into carbohydrate before being oxidised to form the final products, urea, carbon dioxide and water, or whether the transformation into sugar only occurs when the organism is in need of carbohydrates. An interesting observation made in our laboratory is in favour of the latter alternative. In a healthy man, large quantities of administered alanin are excreted unaltered in the urine; in a diabetic individual feeding with alanin results in the appearance of greatly increased quantities of sugar, but of very little unaltered alanin in the urine.

I have already mentioned that the different proteid bodies permit the formation of different amounts of sugar in the diabetic organism. It is both necessary and at the same time interesting to pursue this matter further, as it has an important bearing on the practical

dieting of diabetics. The large number of investigations which have been made on the subject have not all led to a perfectly definite result; this is hardly a matter for wonder, considering how difficult it is to obtain experimental results which shall be free from all errors of technique, etc. I believe, however, that we are already in a position to make the following statements:

Feeding with casein is associated with the most marked degree of glycosuria, then follow that resulting from the proteids of the leguminosæ (peas, lentils, beans). Egg albumin and the albumin of cereals (wheat, rye, rice, oats) have the least power of producing glycosuria. In severe cases of diabetes one must bear this experience in mind, and absolutely forbid casein and also limit the quantity of meat that may be eaten.

(γ) *Fats.*—The question as to whether fats also play a part in the formation of the sugar is a much more difficult one to answer. For the one component of fat—the *glycerin*—the question may be at once answered in the affirmative. From the chemical standpoint it is explicable that much of the detail of the process still requires clearing up. Clinical experiment has, however, removed all doubt as to the fact that glycerin increases glycosuria both in severe cases of diabetes in man and in dogs after extirpation of the pancreas. *Lecithin*, which contains a fair amount of glycerin, behaves in the same way. But while there is perfect unanimity of opinion about the behaviour of

glycerin, this is far from being the case with regard to the second component of fat—the *higher fatty* acids—and their property of yielding sugar. Weighty objections have been raised to their having such possibilities, especially since the formation of sugar from fatty acids is incomprehensible, from the chemical point of view. This objection is certainly not well founded. We know very well that the reverse process, *i.e.*, the formation of fats out of carbohydrates takes place to a very large extent inside the body, although we do not understand the details of the process. There is no assignable reason why the same procedures should not occur in the reverse direction, for we see such a type of reaction occurring in other domains of metabolism. The organism, for instance, splits up, on the one hand, the proteid molecule into its simplest components and, on the other hand, builds up proteid molucules out of quite simple materials. Moreover, wherever we find a ferment in the body, we find also, without exception, an antiferment which is able to act in the opposite way to it. We can, however, get no further by such general considerations and must now turn to the methods by means of which it has been tried to prove or disprove the formation of sugar from fatty acids.

Starting with the conception that the process takes place in the liver, J. Seegen mixed pounded liver and fatty acids together and kept the mixture at body temperature for some length of time. After a few hours he found more sugar in the mixture than in a

control piece of liver to which no fat had been added. His results were confirmed in Bunge's laboratory by Weiss, but, for chemical and technical reasons, serious doubt must be thrown on the positive result of these experiments. They have lately been tested on all sides with improved methods and the result is everywhere negative. I do not, however, regard the experiment as yet definitely concluded. It needs to be repeated with pressed-out liver juice, for it has been shown that most ferments are held very firmly by the cell-protoplasm and are only set free by great mechanical force or after complete destruction of the protoplasm and the objection may be raised to the earlier experiments that the ferment did perhaps not come into sufficiently intimate relation with the fat. In any case these earlier experiments tell neither for nor against the formation of sugar from fat.

Experiments have also been performed in order to discover whether feeding a diabetic individual on fat results in an increased amount of sugar in the urine. With one accord, both old and new experiments have demonstrated that this is not the case. The fact is of tremendous importance for the treatment of the patient, but it proves nothing with regard to the question immediately at issue. Fat, taken in as food, behaves quite differently from proteids. The latter are for the most part immediately disintegrated, *i.e.*, within the next 24 hours, and their final products appear in the excretions. The body can adapt itself so as to use much or little proteid and there is always a ten-

dency to regulate the amount broken down to the amount taken in. It is only under exceptional circumstances that the amount of proteid decomposed, exceeds the amount taken in and that the proteid substance of the tissue cells is drawn upon. It is quite otherwise with fat, the combustion of which is not regulated by the amount taken in, but by the amount of energy transformed in the body. It is a matter of indifference whether the food contains much or little fat: the same amount of fat is oxydised in either case. The only difference is, that in the one case the fat is taken from the food, in the other, from the reserve fat stores of the body. When more fat is taken in than the body requires, the superfluous fat is deposited in the fat store-houses. It is not, therefore, to be expected that increase in amount of fat in the food should cause increase of glycosuria. Any one who assumes that it does so, shows his want of comprehension of the rudiments of the doctrines of metabolism.

One other, indirect method of testing the point at issue still remains. It is based upon the assumption that we know exactly how much sugar can be formed out of proteid. This, unfortunately, we do not know. We have already seen that the amount of sugar produced depends largely on the kind of proteid employed. Even if we consider muscle proteid exclusively, *i.e.*, both that of the body substance and that consumed in the form of meat, the amount of sugar formed, according to the best authorities, varies from 44 to 64 grammes per 100 grammes proteid. The lower

figure is obtained from cases of experimental pancreas diabetes, the higher from those of phloridzin diabetes, and it is especially the merit of Graham Lusk to have established them. The same figures are proportionately represented in the contents of the urine. In the first case, to 1 gramme of urinary nitrogen, at most 2.8 grammes of glucose appear; in the second at most 4 grammes of glucose are present. If we now keep a diabetic for a long time entirely without carbohydrate food, and find that for a long period he excretes four times as much sugar as nitrogen, it is probable that sugar is being formed from some other source besides proteid. In by far the greater number of all cases of diabetes, even in the most advanced stages of the disease, the quotient 4:1 is not attained, and these cases are of no value for the theory. On the other hand, a few cases are known in which for a long period a considerably larger amount of sugar was excreted than would accord with the relation: 4 grammes sugar to 1 of nitrogen. A few of these cases have been described from my clinic, a few others I have seen since but have not yet published. As these patients, who were all suffering from the severest form of diabetes, had certainly no particle of reserve glycogen left, one is almost obliged to regard fat as the source of the superfluous sugar. The superfluity was in some cases so great that the glycerin in the disintegrated fat would not alone suffice to explain it, and the fatty acids must also be taken into consideration. Many objections

have been raised as to the value of the evidence yielded by these investigations. I cannot discuss them without going into all the details of the experiments. I confess that so far, no experiment exists which can give that conviction which a scientific experiment ought to yield; but in all *probability,* we may even now make the statement that there are a few cases of diabetes in which more sugar is excreted than can be accounted for by the amount of carbohydrate available and the maximum quantity of proteid that could have been disintegrated, and that in these cases fat must be looked upon as the source of the excess.

I, personally, would go much further and say that I am firmly convinced that the formation of sugar from fat is an actual fact. I expressed this view twelve years ago and laid the foundation of it by speaking of a "facultative formation of sugar out of fat," by which I meant to say that although in the ordinary course of things no formation of sugar out of fat takes place in the body, yet when the demand for sugar increases to an unusual extent, the organism is capable of making use even of this source.

(δ) *Answer to the Question as to Whether the Over-production of Sugar is Primary or Secondary.*— This brings us back to the point we started from. The question was asked whether sugar appears in the urine of a diabetic only because the consumption of sugar is arrested or also because it is being produced in excess. We may now answer this question in the following way:

Primary over-production of sugar as a source of diabetic hyperglycæmia and glycosuria is highly improbable. There is, at least at present, no fact which supports such a view. Only in cases of acute and transitory non-diabetic glycosuria, as, *e.g.*, in the experimental piqûre of Claude Bernard, does it come into question. In such cases more sugar is suddenly formed from the glycogen already present than there is actually a demand for at the moment; but as soon as the store of glycogen is exhausted the over-production immediately ceases.

Secondary over-production of sugar, on the other hand, plays an important part in diabetes. The cells are everlastingly hungry for sugar, although they are immersed in a medium which contains an abnormally large amount of it. They cannot avail themselves of this sugar, for reasons that have already been discussed. Consequently they are continually signalling for the mobilisation of fresh quantities of sugar. When the carbohydrates of the food and the stored-up glycogen can no longer supply the demand, as is the case in all severe forms of diabetes, then proteid and, as a last resource, fat are called upon to yield sugar. Thus groups of atoms are claimed for this purpose which are usually of service for other purposes. This process may be designated as secondary over-production of sugar.

III. THE ACETONE-BODIES

Since the discovery of acetone and aceto-acetic (or diacetic) acid in the urine of diabetics, an overwhelming amount of literature concerning the origin and significance of these substances has appeared. During the last two decades of the last century the interest they occasioned was even in excess of that in diabetic glycosuria. In the last few years a little light has been thrown on the acetone question, although we are still far from being able to explain all the known facts.

A. SOURCES OF THE ACETONE-BODIES

The acetone question has gone through some remarkable phases. At first it was the carbohydrates that were looked upon as the source of acetone and it was to the abnormal intestinal decomposition of carbohydrates that the formation of acetone substances was supposed to be due. This view was soon discarded on its being shown that neither in diabetics nor in non-diabetics is acetonuria increased by carbohydrate food, but that on the contrary it is somewhat diminished. The acetone was then thought to be derived from proteid, and for a long time this doctrine remained unassailed, the only matter for dispute being whether all varieties of proteid were capable of furnishing acetone or whether this could only be formed by the destruction of the body proteids. What appeared to

be an important confirmation of the view was attained when acetone was split off from proteid by treatment with strong acids in a test tube. But although it cannot be disputed that small quantities of acetone may arise from proteids inside the organism, and although new investigations in my laboratory show that acetone can rise from the disintegration of leucin, this process is certainly not an extensive one and cannot play any important part in pathological acetonuria. The amount of acetone bodies (acetone, diacetic acid, oxybutyric acid) excreted in diabetes and also in other pathological conditions, is often so large that the quantity of proteid disintegrated and measured by the nitrogen in the urine would not by a long way suffice for the formation of it, even if one made the, without doubt, false assumption that all the carbon of the disintegrated proteid was transformed into acetone bodies. Recently, *i.e.*, within the last four or five years, the doctrine that acetone bodies originate out of fatty acids has come into existence. This doctrine was at first only advanced with great caution and diffidence (Geelmuyden, A. Magnus-Levy, L. Schwarz). It has now fully established itself and a revision of all the known facts about acetonuria shows that this new theory is the one with which they chiefly accord.

B. GROUPING OF THE ACETONE-BODIES

There is one other point of view that must be considered. At first it appeared that acetone and aceto-

acetic acid on the one hand and oxybutyric acid on the other had quite a different significance and perhaps also a different origin. But now all investigators have come to the conclusion that the three bodies form a simple series, of which oxybutric acid is to be regarded as the first member, and the one from which aceto-acetic acid and acetone only arise. The chemical formulæ of the three bodies explains this:

Oxybutyric acid.....$CH_3—CHOH—CH_2—COOH$
Aceto-acetic acid (di-acetic acid)..$CH_3—CO—CH_2—COOH$
Acetone .....$CH_3—CO—CH_3$

We have no longer any justification for regarding any one of these bodies apart from the rest; we must consider them at the same time and class them under the common name of "acetone-bodies."

C. CONDITIONS NECESSARY FOR THE APPEARANCE OF ACETONE-BODIES

Although acetone-bodies may appear in the urine in other diseases and even in healthy human beings, they never, under any circumstances, occur in such large quantities as in diabetes mellitus, and especially in the severer forms of this disease. The reason is obvious as soon as one looks at the immediate conditions of their appearance. They arise out of fatty acids, but it is only when a second factor is present in addition, that they occur in any considerable quantity in the excreta. This second factor is the disappearance of carbohydrate out of the metabolism. As long as carbohydrates

are being abundantly disintegrated in the organism, neither the richest intake of fats nor the greatest increase in the destruction of fat leads to acetonuria. Why it is so we cannot fully comprehend, but it is a fact that the simultaneous consumption of carbohydrates either prevents the formation of acetone-bodies out of fatty acids or promotes their immediate destruction to such an extent that hardly a trace of them is left. The daily consumption of 80 to 100 grammes of carbohydrate suffices completely to put a stop to any acetonuria. On this account a healthy man under ordinary conditions of nourishment does not excrete more than traces of acetone. The quantity varies between 1 and 5 centigrammes a day. If, however, a healthy man omits for a time the carbohydrates from his feeding, and feeds only on fat and proteids, the acetonuria rises in the next few days to twenty or fifty times its normal amount; besides acetone itself, aceto-acetic acid and oxybutyric acid also appear. There are important individual differences in this respect; many people under such circumstances incline much more to acetonuria than others; children and young people do so much more than people in advanced years. Custom, also, has something to do with it. If the carbohydrate-free diet be continued for some time, the excretion of acetone bodies gradually diminishes again and finally reaches the normal small amount. We also find that people who, like the Esquimaux, feed almost entirely on animal food, do not have acetonuria in spite of the complete absence of carbohy-

drates from the food. The same is true for carnivorous animals: it is very difficult to produce acetonuria in healthy dogs. Many writers have, indeed, stated that it is impossible, but if one feeds a dog for a long time on a large amount of bread and then suddenly transfers it to a purely meat diet, severe acetonuria immediately follows, just as it does in man.

1. *Acetone-Bodies in Non-Diabetics*

All forms of non-diabetic acetonuria may be explained as due to want of carbohydrates, especially the long known acetonuria of inanition. A fasting man lives only on his own body-substance, such small store of glycogen as was present being soon exhausted. He can then only rely upon the proteid and the fat of his body as a source of energy. Acetonuria at once ensues. The acetone increases to 1 gramme or more, the urine gives a strong reaction with chloride of iron owing to the presence of diacetic acid, and closer inspection usually shows that oxybutyric acid is also present up to an amount of from 5 to 10 grammes a day and more. Acetone also appears in the expired air in such considerable quantities as to even exceed those in the urine. Careful clinical analysis of all cases in which acetone-bodies are excreted by non-diabetics has shown (L. Mohr) that everywhere similar conditions obtain as in inanition. It is always those patients who either are taking very little food or whose carbohydrate food alone is limited, who are concerned. Diseases with high fever, acute diseases of the

stomach and intestine, constriction of the œsophagus, etc., take the first place. If a patient with acute pneumonia is fed only on meat broth and eggs, he excretes several grammes of acetone-bodies a day, but if given much thickened soup, sugar-water and fruit juice, the acetone in the excreta is hardly more than the trace which normally exists. I might give instances from a whole series of different diseases; but this is not necessary as the tale to be told would always be the same. It is true that a few writers assign a special characteristic significance to the non-diabetic acetonuria occurring in certain diseases, but I hold this to be quite without justification. I have given this question my most careful attention in my practice during the last few years, and have found that acetonuria can in every case be prevented by the administration of abundance of carbohydrate food.

2. *General Conditions Which Promote or Hinder the Formation of Acetone-Bodies*

We may at the present time affirm that acetone-bodies arise out of fatty acids, but that they only then appear in the excreta when the organism has at the same time the opportunity taken from it of simultaneously consuming carbohydrates.

We do not yet know which fatty acids furnish the material for the formation of acetone-bodies. The lower fatty acids may certainly be indicted, although to the higher fatty acids a share in the process may be

assigned. In the latter case, however, the part they play is limited to the extent that they are capable of being split up in the body into chains of the lower fatty acids. The immediate material from which the formation of oxybutyric acid arises appears to be either butyric acid or acetic acid. As it would lead me into the domain of chemical hypothesis to dilate further on this matter I will now say no more about it.

A knowledge of the relations between fatty acids and acetone bodies has suggested to many practitioners that one ought not to allow diabetics to consume much fat. Such an assumption has, however, shown itself to be unwarranted; and the lack of sufficient reasons for their action must be at once evident to anyone who knows the peculiarities of the metabolism of fat in any detail. I have already insisted, when speaking of the formation of sugar out of fat, that the amount of fat decomposed is to a large extent independent of the amount of fat ingested. When a small amount of fat is ingested almost as much fat is destroyed as when the amount is large; only it is the body fat, not that of the food, that is consumed. Clinical experience also teaches the fact that the excretion of acetone bodies is hardly, if at all, influenced by the amount of fat in the food. In the first day or two very small differences are certainly noticeable. These are much too small to deserve attention, except in the case of the lower fatty acids. The lower acids behave quite differently to the higher; they are not—unlike the higher acids—conveyed to the fat store-

houses of the body but are further elaborated by the organism. Under normal conditions, the organism consumes them almost completely, but when the organism owing to dearth of carbohydrates inclines to the formation of acetone-bodies, then the ingestion of large quantities of the lower fatty acids gives to this process a distinct stimulus. We established in my clinic the fact that almost as much as 40 per cent. of the butyric acid given as food might reappear as acetone-bodies. In severe cases of diabetes it is, therefore, advisable to omit the lower fatty acids from the food as much as possible. Vegetable fats and the fats of meat contain very little of the lower fatty acids. Butter is the only ordinary article of food which contains a considerable amount of them, but as all the lower fatty acids and their salts are readily soluble in water, it is sufficient to knead the butter well through with cold water to almost completely remove the dangerous lower fatty acids.

Before discussing the special relations in diabetes, it must be mentioned that certain other substances besides true carbohydrates contribute to prevent the formation of acetone-bodies. Glycuronic acid, glyconic acid and saccharic acid, which are closely allied to true carbohydrates; also glycerin, lactic acid, malic acid and citric acid may be mentioned. The effect of the last four substances is, however, very much less than that of the carbohydrates. None of these substances come into practical consideration since they cannot be given to diabetic individuals in sufficient

quantity and for a sufficiently long time. The quantity of carbohydrate is really the only factor by which we practically can regulate at will the formation of acetone-bodies.

3. *Acetone-Bodies in Diabetes*

After these preliminary remarks, it will be at once understood that acetone-bodies occupy in no other disease so important a position as they do in diabetes. As long as we are only concerned with "slight" forms of diabetes, as long as the diabetic patient is utilising any appreciable quantity of carbohydrate, whether that of the food or that which arises in his body out of proteid, etc., so long the acetonuria remains, but barely more than its normal standard. As soon, however, as the capacity of the organism to attack the circulating carbohydrate is markedly diminished; when all carbohydrate of the food is reappearing in the urine, and at the same time the greater part of the sugar derived from proteid is being excreted, then we have before us the typical phenomena of diabetic acetonuria. The excretion of acetone-bodies may serve, like glycosuria, as a measure of the intensity of the diabetic disease.

(*a*) *The Three Stages in the Excretion of the Acetone-Bodies.*—For practical purposes we may distinguish three stages in the excretion of acetone-bodies. They cannot, however, be very sharply marked off from one another.

First Stage.—Only acetone in the urine. The

quantity varies from the normal limit of 5 centigrammes to 5 decigrammes. Acetone is also given off in the expired air, often as much as, and even more than, in the urine.

Second Stage.—Di-acetic acid is also present in the urine, and the latter, therefore, turns red on addition of ferric chloride. This reaction usually occurs when the daily quantity of acetone excreted in the urine has reached 4 decigrammes. When 5 decigrammes is exceeded, I have seldom failed to find diacetic acid in addition.

Third Stage.—Oxybutyric acid occurs in the urine in addition to acetone and diacetic acid. Its presence may almost always be shown when more than 1 gramme of acetone occurs in the twenty-four hours' urine. When the excretion of acetone-bodies once exceeds these lower values the oxybutyric acid begins to predominate more and more. The daily amount of acetone does not usually increase beyond 5 or 6 grammes. It is rare to find 7 or 8 grammes. This quantity includes the diacetic acid, since the diacetic acid cannot be quantitatively estimated apart from acetone. In addition to these few grammes of acetone, enormous quantities of oxybutyric acid are found. It is not rare to find 30 to 40 grammes; even twice this amount—60 to 80 grammes—is often attained. The acetone in the urine, therefore, only gives a true measure of the whole amount of acetone-bodies present when the acetonuria is slight; when it is more marked, this means of measurement fails, since the

curve of oxybutyric acid rises so much more steeply than that of the acetone. A quite considerable portion of the acetone never reaches the urine; the substance being extremely volatile, it evaporates from the blood in the lungs and gives a characteristic odour to the whole atmosphere in the neighbourhood of the patient. This odour often permits the diagnosis of diabetes without any analysis of the urine.

(*b*) *Grouping of Cases of Diabetes from the Standpoint of the Excretion of Acetone-Bodies.*—The exact following out of the excretion of acetone-bodies in diabetics is of the greatest practical importance. As long as only small quantities appear in the urine the patient is not in danger of falling a victim of the specific diabetic intoxication. What this consists in will be discussed later. I consider that it is most important in practice to distinguish certain definite groups of cases. The distinction is founded on the behaviour of the acetone-bodies on the withdrawal of carbohydrates.

Group 1.—Numerous diabetics, on the diet that is usually prescribed for slight cases containing about 50 to 70 grammes of carbohydrate in the daily allowance, only excrete a few centigrammes of acetone, *i.e.*, hardly more than a healthy man does. When then carbohydrates are quite withdrawn from the food, the quantity of acetone soon rises to a few decigrammes; a few specimens of urine give also a slight reaction with ferric chloride and possibly also contain a little oxybutyric acid. The same effect would be produced

in a healthy man. If the same strict diet is continued the quantity of acetone-bodies gradually diminishes and a week or two later the amount is again quite low. The body has in the meantime adapted itself to the want of carbohydrate just as it does in the healthy body, as I have already stated. By far the greater number of diabetics belong to this group. From the clinical point of view, they would all be designated as cases of "slight diabetes."

Group 2.—On the usual diet containing 60 to 80 grammes of carbohydrate a day, we again find only a little acetone and no reaction with ferric chloride. On withdrawal of the carbohydrates, the acetonuria increases rapidly from 1-2 to 1 gramme and more, and the presence of both diacetic acid and oxybutyric acid may be easily demonstrated. I must emphasise, in opposition to an opinion that is widely spread, that there is no danger in this symptom. If we do not let ourselves be led astray by the increase of acetonuria but quietly continue the strict diet, after a few weeks we often notice a gradual diminution of the acetonuria until the original level is again reached. These cases behave like those of the first group, although the adaptation to the withdrawal of carbohydrates takes place much more slowly. These cases are, nevertheless, prognostically more unfavourable than those of the first group, since the inclination to acetonuria may increase considerably during the next few months or years.

In other patients of this group the adaptation of

the organism to the withdrawal of carbohydrates does not take place at all. The acetonuria remains high as long as carbohydrates are excluded from the dietary. It is only after the return to a diet containing carbohydrates that the acetonuria falls to its original value. One comes across such manifestations both in so-called "slight" and so-called "severe" cases of glycosuria. It is always a threatening symptom pointing to rapid advances of the disease. In children and young people especially, one has not long to wait for the confirmation of this bad prognosis.

Group 3.—Even on an ordinary diet containing 50 to 70 grammes carbohydrate, 1 to 2 grammes or more acetone is excreted. The reaction with ferric chloride is positive. Oxybutyric acid is permanently present. When once this condition has been arrived at, the excretion of acetone bodies shows itself to be to a large extent independent of the varieties of food consumed. It makes little difference whether much or little or no carbohydrate is given. The body has almost entirely lost its power of utilising carbohydrates, and therefore it is a matter of indifference for the formation of acetone-bodies whether the food contains carbohydrate or not. Large variations in the amounts of acetone and oxybutyric acid certainly also occur in these cases. They are, however, more dependent on the natural and autonomous variations of the diabetic process than on the nature of the food. There is no question as to the great permanent danger in which these patients exist. Many of them in spite

of this, however, with cautious dieting and care may maintain their powers for an extraordinarily long time. I know many diabetics who were excreting 50 to 60 grammes acetone-bodies daily six years ago, and have continued to do so since, and who yet enjoy relatively good general health.

D. DANGERS OF ACETONURIA (COMA DIABETICUM)

In what do the dangers of acetonuria consist? Anyone who has had the opportunity of seeing a diabetic patient die in typical diabetic coma takes with him from the death-bed the indissoluble impression that it was a matter of severe poisoning. I shall have occasion to refer later to the clinical peculiarities of coma diabeticum. Here I will only dwell on its relations to the acetone-bodies. Since the days when Kussmaul described the characteristic diabetic coma this question has been continually discussed. There is no advantage to be gained in reviewing all the theories here. We will turn at once to that theory which is now most generally accepted. We shall then have to consider whether other opinions are equally grounded.

1. *Theory of Acid Poisoning (Acidosis)*

I have already mentioned that oxybutyric acid is to be regarded as the primary acetone-body. Its precursors, the fatty acids, are completely used up in the normal organism. When this does not happen, as in

the diabetic, the acid substances themselves, as oxybutyric acid and diacetic acid, appear in the blood. Such a charging of the blood with acid we denote by the name of "acidosis," following the precedent of B. Naunyn. The normal body assumes the rôle of satisfying large quantities of acid and so of protecting itself from the danger which a diminution of the alkalinity of the blood and tissues would entail. If there is not enough preformed alkali at disposal, this is brought about by ammonia. A large part of the ammonia which is set free by the breaking down of the proteid molecule attaches itself to the acid and is thus prevented from passing over into urea. We find, therefore, that whenever abnormal quantities of acid arise in the body the relation of urea to ammonia in the urine is altered. In normal urine, 3 to 5 per cent. of the nitrogen exists in the form of ammonia, and about 80 to 85 per cent. in the form of urea. With the production of acid in diabetes, this relation is altered: 20 to 25 per cent. of the nitrogen may appear as ammonia, while only 60 to 70 per cent. remains over for the urea. Between this extreme degree of urinary change and the normal, the possible intermediate stages actually occur. There are, it is true, other factors on which the excretion of ammonia depends, but they are of much smaller significance, and we may, therefore, justly regard the excretion of ammonia as an indication of the extent of acid present in the blood, provided that alkalies are not at the same time being administered medicinally. From the quantity of

ammonia ascertained, it is allowable to come to a conclusion with regard to the approximate quantity of oxybutyric acid which is being excreted in the urine at the same time:

0.5 to 1 gramme ammonia per day is normal.
2 grammes of ammonia correspond roughly to the excretion of 6 grammes oxybutyric acid.
5 grammes of ammonia correspond roughly to the excretion of 20 grammes of oxybutyric acid.
8 grammes of ammonia correspond roughly to the excretion of 36 to 40 grammes oxybutyric acid.

These numbers are given as a result of the experience of a large number of observations and are in close agreement with theoretical calculations.

The neutralisation of the acid by the combination of ammonia has, however, its limits. Only a certain portion of the nitrogen arising from the breaking down of proteid can be set free for disposal as ammonia. If the production of acid continues with undiminished vigour, then the abnormal amount of acid must be neutralised by the fixed alkali of the tissues. This is recognised most plainly in the case of calcium and magnesium, as first demonstrated by F. van Ackeren and confirmed by the well-conceived experiments of D. Gerhardt and W. Schlesinger. In spite of all this, the alkalinity of the blood and the tissues cannot be kept at its normal level in the severer stages of diabetic acidosis. The "alkalinity" value of the blood was found to be 30 to 50 per cent. below the normal

average. Such a diminution of alkalinity is very disadvantageous for the general nutrition and for the excretory functions or washing out of the tissues. The central nervous system suffers the most from the changed conditions. According to the theory of Naunyn and his school the diminution of the alkalinity of the blood and tissues is at the root of the essential nature of the diabetic intoxication. This they regard as a true acid poisoning, the culminating point of which is eventually diabetic coma. The doctrine is supported by the results of experiments on animals. If rabbits are fed for a long time on acids, so as to remove the fixed alkali from their tissues, they eventually succumb under symptoms which closely resemble those which occur in the coma of diabetics. The main point of this doctrine is, that the surcharging with acid, or rather the diminution of alkalinity, is the most important and decisive factor for the diabetic intoxication. No special variety of acid is indicated. We cannot but acknowledge that Naunyn and his pupils (A. Magnus Levy in particular) have, with much ingenuity, endeavoured to support their theory by an extraordinary amount of experimental and clinical work. Yet the theory has its weak points. If it were unconditionally true, it ought not to be difficult to avert the disastrous consequences of over-production of acid by the continued administration of large doses of alkalies. For ten years or more it has been the general custom to treat every diabetic with large quantities of alkalies as soon as he shows the first signs of acidosis, *i.e.*, as

soon as the urine begins to yield the ferric chloride reaction. This is, without doubt, most useful, as it facilitates the neutralisation and excretion of the acid.

It is a useful procedure, whether it is only the *quantity* of acid or also its special *kind* that is regarded as the cause of the intoxication. Diabetic coma has not, however, become less common by this "alkali" treatment. Its onset, it may be granted, is in many cases deferred, but the coma nevertheless eventually supervenes. I know of quite a number of cases in which for months so much alkali was given that the urine gave permanently an alkaline reaction, in which, therefore, certainly no acidity of the blood or of the tissues could have developed, and in which, in spite of this, coma ultimately appeared.

In consideration of these facts, which are not disputed, though the evidence they afford is not sufficiently valued by Naunyn and his school, the acid theory shows itself not to be sufficiently far reaching. Its limitations at once suggest that attention should be directed to the nature of the acid. For a long time it was taught that oxybutyric acid was not particularly toxic. Professor Herter and Dr. Wilbur made new experiments on this point in my laboratory two years ago, from the results of which it appeared that the earlier view was not correct. Oxybutyric acid is much more poisonous than its actual acid value would lead one to suppose. The neutral salt of oxybutric acid is also poisonous. I do not,

therefore, hesitate to ascribe at least a certain part of the specific diabetic intoxication to the specific poisonous effect of oxybutric acid. This does not, however, explain everything. We are not yet acquainted with the entire number of chemical substances which are formed as intermediate products in the breaking down of proteids and fats in the organism, and we do not know whether other poisonous substances which possess some significance for the diabetic intoxication may not be found amongst them. I believe that many physiologists and pathologists agree with me in considering this highly probable. On such an assumption we must regard the diabetic intoxication on the one hand, and the over-production of acid on the other, as common consequences of the diabetic anomalies in metabolism. We must allow that both the nature and the quantity of acid formed are of equal significance, and contribute an equal share in impressing their stamp on the clinical form of the eventual auto-intoxication.

The standpoint I advocate in this matter is not only of theoretical scientific interest, but is also of practical significance. He who maintains that it is only the quantity of acetone-bodies that conjures up the danger of diabetic intoxication, will direct his chief attention to the suppression of these acetone-bodies. His clear course is to limit to the utmost the intake of fat and to increase to the utmost the intake of carbohydrates. By such treatment good momentary results may be attained, but they are not permanent. But he who,

while seeing only in the appearance of acetone-bodies what is truly an important symptom and a danger signal deserving all attention, does not see in this the essence of the danger, is much more inclined to keep to the old and tried method of limiting the carbohydrates, even though it leads to an unavoidable temporary increase in the amount of acetone-bodies. With certain exceptions, of which I shall have to speak later on, I have myself always upheld this last point of view. Whenever I have allowed myself to be led away from this standpoint I have always had to regret it.

2. *The Clinical Form of Diabetic Intoxication (Coma Diabeticum)*

Th. Frerichs in his well-known work on diabetes said twenty years ago: "Anyone suffering from diabetes is liable to the danger of a sudden and unexpected death by the supervention of coma." We can now no longer grant that this statement is fully justified. We have in the meantime learnt to distinguish between cases which are liable to this danger and those which are almost safe from it. It is not the glycosuria but the acetone-bodies which serve us as guides in the matter. The diabetic individual is certainly always in greater danger than a healthy man, for even in slight cases his tissues are less resistant; complications of different kinds, inter-current diseases of the most different organs, all affect him much more severely in the average, and are more dangerous to

him, than they are to the non-diabetic. But only those succumb to the specific diabetic intoxication,—the coma diabeticum,—in whom the chemical symptoms of acidosis have first developed. I have already said that the final coma is not to be regarded as something quite new, as a complication of diabetes arising spontaneously, but that it only represents the culmination of the specific diabetic intoxication. Apart from the chemical peculiarities of the urine, there are usually other harbingers of this approaching climax: drowsiness, mental haziness, rapid fatigue of body and mind, dyspeptic symptoms such as loss of appetite, marked constipation, nausea, vomiting, and, above all, strong gastric hyperæsthesia. When a diabetic begins to complain of indigestion after every meal, it is always a grave and disquieting sign. This prophase may extend over days, sometimes even over weeks. Then the drowsiness suddenly increases. The patients are still, it is true, easily to be waked from their semi-torpor, they can arouse themselves with a certain amount of energy for a short time, in such a way as to give the impression of being psychically normal, but this becomes from hour to hour more difficult; in their clear moments they are like people who have waked from a heavy alcoholic intoxication; they soon fall back on the pillows again as though drunk. Meanwhile, the breathing has altered, the respiratory movements have increased until both the inspiration and the expiration are at a maximum, without their frequency being such as obtains in the ordinary dyspnœa of heart

and lung patients. The pulse is quickened, but remains strong and full. The clear moments become rarer and shorter, the coma becomes complete, and about twelve to thirty-six hours after the commencement of the drowsiness, death ensues.

It is not always that the just-described prognostic symptoms are observable. The coma often attacks people who have felt themselves well and strong up to the time of its sudden outbreak. In ignorance of the danger, they subject themselves to a specially strong bodily or mental effort. This seals their fate. The overstrained brain-centres suddenly collapse under the diabetic intoxication which they have successfully withstood up to that moment. To such cases, which are never anything but rare, the just-mentioned statement of Frerich applies. If the after-history of the case can be obtained, it is always regularly found that serious symptoms of diabetes have previously appeared and that the excretion of acetone has been going on for a long time. It was only that the symptoms were not sufficiently heeded and the patient not sufficiently warned.

Besides strong efforts which overtax the powers of the individual, many acute infections of different kinds favour the onset of coma, especially septic infections, *i.e.*, such as phlegmonous inflammations or gangrene. Acute alcoholic intoxications are also dangerous, and the same is true of chloroform and ether narcoses. A similar process always takes place: the brain-centres are weakened by the chronic diabetic intoxication, but

they still resist; then a new weakening factor supervenes—overstrain, infection, intoxication—and the power of resistance is broken. Fate takes its course.

With regard to the treatment of these dangerous conditions and the outlook which the treatment offers I shall have to speak later.

IV. OTHER DISTURBANCES OF METABOLISM IN DIABETES

Having spoken at some length of the diabetic glycosuria and the diabetic acidosis, we can now give a considerably shorter representation of the other disturbances of metabolism.

A. THE ENERGY BALANCE, OR TRANSFORMATION OF ENERGY

Pettenkofer and Carl Voit, using their large respiratory apparatus, estimated forty years ago, by an observation extending over seven days, the intake of oxygen and the carbon dioxide produced in a patient with severe diabetes. Calculation of the entire amount of the energy transformed shows that 34 calories per kilogramme body weight were developed. Oxygen-intake, carbon dioxide production and formation of heat were all equal to the average amounts formed by the healthy man, reckoned per body weight. In their first publication the authors had wrongly interpreted the data, and so expressed themselves as to imply that in the diabetic individual an enormous diminution of oxydation, or in other words, of heat produced or of energy transformed, took place. This important experiment of the two famous Munich *savants* has had a remarkable literary history. C. Voit soon saw the error

in his first estimation and specially corrected it in his text-book on metabolism. But this correction for a long time did not attract the attention of other writers, and in later publications the false statement continued to be made that Voit and Pettenkofer had discovered a considerable lowering of the metabolism of energy in diabetics.

With the large respiratory apparatus of Pettenkofer, the respiratory metabolism of the diabetic has now once again been investigated by W. Ebstein. Most extraordinarily, the same error which Voit and Pettenkofer had made forty years before, again crept in. Ebstein also came to the conclusion that the oxydation processes were greatly diminished in his diabetic. An exact revision of the experiment shows, however, perfectly normal relations and a surprising agreement with the results obtained by Voit. Voit had estimated the amount of CO_2 produced in twenty-four hours as 11.5 grammes per kilogramme. According to Ebstein the value is 11.02 grammes.

More extensive experiments for the determination of the amount of oxydation in diabetics have been made with Zuntz's respiratory apparatus. By this procedure, the respiratory gas-exchange is determined in the fasting condition and in one of absolute bodily repose. Each experiment lasts half an hour or at most an entire hour. It is not technically possible to extend it for a longer time. The objection has been raised to the method that the experiments are too short and that it is not allowable to draw conclusions with regard

to the consumption of oxygen in a whole day from the consumption of oxygen which takes place during one hour. It must be granted that the method is difficult and somewhat precarious, but in the hands of a skilful experimenter it is perfectly reliable. This is shown by the most surprising and startling agreement of the calculated results with the results obtained by other good methods serving for the detection of the metabolism of energy.

In order to judge of the results, it is usual with Zuntz's method to give the amount of oxygen in cubic centimetres per kilogramme which is consumed in a minute. I have estimated, from about twenty good and perfect unexceptionable experiments which have so far been published, that 3.55 cubic centimetres is the average minimum value and 3.70 cubic centimetres the average maximum value. The separate values from which these averages were obtained vary very little from one another. The result agrees well with what one finds in perfectly healthy individuals. The values are certainly no smaller, rather, if anything, slightly higher than the normal average. We, therefore, arrive at the conclusion that, judging by the respiration experiments made both with the large Pettenkofer apparatus and with the more convenient apparatus of Zuntz, the formation of heat and the metabolism of energy in the diabetic is not appreciably different from that in the healthy man.

This signifies, in other words, that the demand for food is as great in the diabetic as in the normal in-

dividual. The statement requires, however, some qualification. It is of course only what the organism actually oxydises that comes into consideration as a source of energy. If we now give a diabetic exactly the same food as we give to a healthy individual, the value of the food to the two people may be quite different; for in the diabetic a portion of the material ingested is lost again in the urine.

An example will serve to make this clear. The following food was given:

150	grammes	proteid equals.....	615 calories
100	"	fat equals.....	930 "
200	"	carbohydrate equals.....	820 "
		Total.....	2365

On this diet there occurred in the urine of

Diabetic A.	20	grammes sugar equals.....	82 calories
" B.	150	grammes sugar equals.....	615 "

If, therefore, we want to make use of the fact that the oxidation processes are of the same intensity as in the healthy body, we must either take care that the diabetic is no longer excreting sugar, in which case we shall find that the same calorific value of food that is sufficient for a healthy man is also sufficient for him; or we must raise the heat value of the food by the sum of the energy which is lost by the glycosuria. Carbohydrates cannot of course serve as dissipators of energy in this case; they would run out unused as from

a vessel without a bottom. Other food-stuffs must come to the rescue: proteids, fats and to a moderate extent also alcohol. These matters already touch upon the therapeutics of diabetes and will have to be discussed later in greater detail.

Although exact quantitative investigations upon the details of metabolism showed with one accord the equality of the demand for heat in the healthy man and in the diabetic, and although common experience and practical rules of diet have long decided in favour of the same things, yet there have been heard recently a few dissentient voices expressing the opinion that diabetics need considerably less food than normal individuals (B. Naunyn, R. Kolisch, W. Schlesinger). Examples have been quoted which seemed to show that diabetics might for a long time maintain their body weight or even increase it on a diet whose calorific value did not reach that required by a healthy individual of the same body weight and under the same external conditions for the maintaining of his weight. I have something to say about these statements. For fifteen years I have followed very closely the dieting of all my patients—diabetics and non-diabetics—from a quantitative point of view, perhaps more exactly and on a broader basis than anyone else has ever done. I have also perhaps at my command, by reason of the numerous analyses made in my laboratory, a wider knowledge of the composition and of the calorific value of the food-stuffs employed by me, than others possess. I have never, amongst over two thousand

diabetics whom I have treated for weeks and months in my clinical institutions, come across a single case to which that assertion would apply. If we wished to maintain or increase the body weight of a diabetic patient we always had to incorporate at least the same total heat that would have been needed for the same purpose in a healthy man. I even had frequent opportunities of convincing myself of the extreme difficulty of raising the body weight in many diabetics, in spite of the most abundant feeding on available calories. By "available calories" I mean those which are left after deducting the calories of the sugar in the urine. I cannot, therefore, help suspecting that those who think they have seen something different have been the victims either of delusions or of faulty calculations. I am obliged to say this, because in the interest of the patient I should greatly regret if such an erroneous opinion should once obtain a firm footing. The consequence would be insufficient nourishment and gradual weakening of the body.

If we reflect on the just propounded relationship between the heat value of the original food-stuff and the actually available heat value, we can easily understand a much talked-of symptom of diabetes, viz., polyphagia. Anyone suffering from diabetes, whose diet is not regulated according to medical advice, eats large quantities of food, and amongst other things, also much of carbohydrates. The "stomach's hunger" is for the moment appeased, but it soon makes itself felt again, for the "tissue hunger" remains unsatis-

fied. The carbohydrates flow uselessly past the tissues. The strong appetite of the diabetic disappears, however, immediately when the unusable carbohydrates are limited and replaced by a sufficient amount of proteid and fat. When this happens both the emaciation of the patient and the polyphagia soon disappear.

B. THE NITROGEN BALANCE

It has long been known that in diabetes the destruction of proteid attains quite unusual dimensions. As much as 30 to 40 grammes of nitrogen have often been specified as occurring in the daily urine, especially in early days when the patient suffering from sugar disease was fed more on proteid than is now customary. In order to recognise the significance of this excessive elimination of nitrogen the point at issue must be sharply defined. The diabetic may excrete such large quantities of nitrogen for many very different reasons.

1. *Excessive Intake of Albumin*

The nitrogen elimination may be high because the diabetic takes much more proteid than a healthy man. For instance, if his diet contains 200 grammes of proteid, the metabolised nitrogen might according to calculations be 32 grammes or more. "Azoturia," as French authors designate this phenomenon, is hardly then surprising.

On the same diet the diabetic may excrete more

nitrogen than the healthy man. There may be two reasons for this:

2. *Loss of Nitrogen by Under-Feeding*

The breaking down of proteid is at a higher level than it is in a healthy individual because the latter has in the combustion of the carbohydrates of his food a strong protection for the constituent proteid of his body, while the diabetic excretes, without utilisation, a very large part of the carbohydrate he ingests.

Physiology teaches us that carbohydrates serve as proteid protectors, and that conversely the withdrawal of carbohydrates from the food increases the destruction of proteid. It was long ago pointed out by C. von Voit that these well-known physiological laws hold good also for the proteid metabolism of the diabetic individual. The conditions under which the diabetic lives may be imitated in the healthy man by diminishing the carbohydrates of his food by the amount excreted in the urine of the patient that one is comparing with him. Graham Lusk first made this striking and neat experiment: he showed that under these circumstances the proteid destruction in the healthy man was exactly the same as in the diabetic. The increase in destruction of proteid in so far as it depends on the absence of carbohydrates, is hardly to be called pathological. It is certainly a phenomenon intimately connected with the nature of the disease, but nevertheless is only the consequence of known

relations which normally exist between the utilisation of carbohydrate and destruction of proteid.

If we take into account these peculiar relations of diabetic metabolism, it appears that in by far the larger number of cases of diabetes the organism defends itself with the greatest obstinacy against loss of body proteid. I have already remarked that in late years it has become customary to give diabetics much less proteid food than formerly. So long as ten years ago I recommended, under certain circumstances, the intercalation of periods of from three to six days in which the food should consist almost entirely of green vegetables, yolk of egg, bacon, and butter. In such a period, not only is the carbohydrate reduced to a mere trace in the diet, but the food also contains an extremely small amount of proteid. The proteid sinks to 30 grammes a day. The extreme difficulty of keeping a healthy man in nitrogenous equilibrium on so small an amount of proteid is well known. Physiologists tell us that this is only possible when at the same time a large amount of carbohydrate food is being taken. When these carbohydrates are excluded, no one has succeeded in keeping a normal adult in nitrogenous equilibrium on so small an amount of proteid food. This does, however, succeed in the diabetic, not always it is true, but still remarkably often. The nitrogen in the urine sinks on the days of vegetarian diet, or, as I may also call them, on the green days, often to as little as 4 to 5 grammes. The total nitrogen in the urine and in the fæces remains below the total

nitrogen of the food or only very slightly exceeds it. Evidently, the diabetic is much better adapted by long custom to protect the proteids from destruction by the use of fat than is the healthy man.

3. *Loss of Nitrogen by Toxogenic Disintegration of Albumin*

We notice in many diseases that more nitrogen appears in the excreta than is contained in the food, although the quantity of proteid and of non-nitrogenous substances in the food would fully suffice to ensure nitrogenous equilibrium in a healthy state. This shows that an abnormal destruction of the body-proteid is taking place. We meet with this phenomenon in most febrile diseases, in severe cases of Graves' disease, in progressive carcinoma, and in various forms of intoxications, especially in cases of phosphorus poisoning. The cause lies in the presence of poisonous substances which injure and destroy the protoplasm. The dead proteid in the cells is then further disintegrated in the same way as the proteid of food, and its nitrogen appears in the urine. We call the process *toxogenic proteid disintegration.* For a long time it has been tried to ascertain by experiments in metabolism whether this process plays any part in diabetes, but no one has yet succeeded in proving it with certainty. Not even in the most extreme cases, in the time of severe diabetic intoxication, before and during coma diabeticum can proof of it be obtained.

In spite of this, however, clinical observation makes

it probable that toxogenic proteid disintegration may occur. We often see that diabetics keep up their strength for years, or even for decades, but eventually, in spite of the most plentiful nutrition, succumb and exhibit extreme atrophy of the whole musculature, although the fat stores may still, to some extent, remain undepleted. There is something else which, in spite of abundant nutriment, inexorably breaks down the muscle protoplasm and strongly inhibits its rebuilding. I have often been able to obtain evidence that in such cases 100 grammes and more of nitrogen may be retained for a few weeks within the body and yet the muscles remain as flabby as before. What becomes of retained nitrogen is at present unknown; it certainly, however, does not serve for the regeneration of protoplasm. To sum up, I should like to express an opinion, based on clinical observation, that although toxogenic disintegration of protoplasm in diabetes has not yet been proved by exact experiment, clinical observations make its existence extremely probable in severe cases. When experimental methods are further perfected, experimental proof will surely follow.

4. *Decomposition of Nuclein-Substances*

I have already at my command a few observations which point in this direction and which deserve notice. They relate to the behaviour of the purin bodies in the urine. We know from the observations of Burian and Schur, Walker Hall, Kaufmann and L. Mohr that the uric acid occurring in the urine and the xanthin bases

related to it arise from two quite different sources. The one part has its origin in the purin bodies of the food and is designated exogenous purin substance in the urine. Its amount varies quite extraordinarily, according to the composition of the food. The remaining amount has its origin partly in the hypoxanthin of the muscle, partly in the nuclein substances of the body, certain quantities of which are used up daily. This endogenous part of the uric acid output is, under normal conditions, very constant. About 15 to 20 centigrammes of the nitrogen of the urine are due to it. The endogenous part of the purin in the excreta makes its appearance, and can be measured when we feed a man exclusively on a diet free from purin. For this purpose it is necessary to exclude from the dietary all meat and meat derivatives. If this is done in very severe cases of diabetes, in which clinical observation notes the signs of a progressive atrophy of the muscles, we often find quantities of purin substances in the urine far exceeding the normal amount. I found in several cases for quite a long period 25 to 30 centigrammes purin-nitrogen daily in the urine—an increase, therefore, of 50 to 100 per cent. This is the chemical expression for an increased destruction of the most important constituent of the cell, *i.e.*, of the nuclear substance; for it is only the nuclei and not the body of the cell that contains purin substances.

I will not here enter upon the further peculiarities of the diabetic urine. After having considered the glycosuria, the acetone-bodies, and the nitrogen excretion,

there remains certainly much that is interesting, but it is of far less importance and significance for the processes concerned in diabetes. It becomes a question of details which are more interesting theoretically than practically.

Before concluding the chapter on the pathological chemistry of diabetes, let us turn for a moment to the peculiarities which have been found to occur in the blood of diabetics.

C. PECULIARITIES OF THE BLOOD IN DIABETES

1. *Lipæmia*

The appearance of large quantities of fat in the blood plasma of diabetic patients is not an exceptional phenomenon. Its occurrence was well known to the old practitioners on account of their frequent practice of venesection. In more recent years a number of exact systematic investigations have been made upon the matter, but the question is still not thoroughly cleared up.

The clinical signs are simple and precise. Usually, the amount of fat in the blood of diabetic patients does not exceed the normal percentage, namely about one per cent. In the most severe forms of the disease, however, when the diabetic intoxication has reached a dangerous intensity, sometimes—but by no means always—a distinct lipæmia ensues. The blood plasma presents a milky cloudiness, or even a milk whiteness. If the blood is placed in a tall measure glass the fat

rises to the surface and a thick, yellow-white butter-like, superficial layer results. When this is treated with ether or with the ordinary fat-stains its nature is at once apparent. The emulsion of fat in the serum is so fine that the particles cannot be recognised by the unaided eye: they are, however, easily seen upon ultra-microscopical examination. Anyone who has had an opportunity to observe such a case will confirm my statement that the intensity of the lipæmia presents wide variations. These variations, moreover, run hand in hand with the general condition of the patient. Recently I saw a case of diabetes in which lipæmia accompanied the onset of coma; when the coma disappeared, the lipæmia vanished. This phenomenon repeated itself during the course of several weeks, until the patient finally succumbed during an attack of coma.

Attempts have been made in order to discover the origin of the fat. Recently, from the medium of the iodine coefficient, the saponification coefficient, and the melting point, it has been determined that the fat was identical with that of the chyle, and thus originated from the fat of the food. Still one may safely suppose that the stored fat of the tissue cells may also serve as a source of the fat found in the blood serum, for in some cases, although fat is ruled out of the dietary, the extent of the lipæmia diminishes, but it does not entirely disappear. Ebstein thinks that the blood fat in diabetics with lipæmia arises from a fatty degeneration of the tissue cells, or even of the

blood constituents themselves. There are good reasons, however, for the non-acceptance of this view. Fat is a normal constituent of the blood. Excessive intake of fat may lead to an increase in the quantity of fat in the serum; the latter may even become cloudy or milky. Physiologically, however, the fat contents of the blood rarely rise much over one per cent. But in the blood of diabetic patients much higher percentages have been discovered. The average results vary from four to six per cent., the highest have reached fifteen to eighteen per cent. (E. Stadelmann, B. Fischer).

In diabetic patients there is some ground for ascribing the high percentage of blood fat to the large amount of fat contained in the diet. But one must remember that relatively high percentages of fat may be also found in the blood of individuals in a state of starvation. During inanition, when a certain amount of energy must be furnished by the combustion of the fat of the tissues, large quantities of the mobilised fat appear in the blood stream, en route to the working cells. The necessity for an active transport of fat is much more marked in the case of the diabetic than in that of the hungered, since the tissues of the former have lost their capacity to utilise carbohydrates. The amount of fat, in part arising from the food, and in part from the fat depots of the tissues, is still much less than the quantity which in the healthy individual is circulated and assimilated without a trace of concurrent lipæmia. Thus one cannot explain the

occurrence of lipæmia in diabetes by any reference to the fat intake, the fat-needs or the thereon depending fat-transport.

This point, which was shadowed, although not fully delineated by earlier observations, has been more completely detailed by the discoveries of recent years. Under normal conditions the fat from the chyle disappears from the blood-stream with extraordinary rapidity—far more quickly than it can be either deposited in the tissues or oxidised therefrom. In the blood-stream the fat enters into a combination, being soluble in water, probably by help of the red blood corpuscles. The nature of the compound is not yet precisely defined—perhaps lecithin may play an important part. The process is termed *lipolysis,* and is supposed to result from the action of a ferment, *lipase.* This formation of a water-soluble fatty compound is supposed to be a necessary preparation for the passage of the fat into the tissue cell. Once arrived in the cells, the ferments of the cell produce a deposition of neutral fat. Various authors have now advanced the hypothesis that in diabetes the lipolytic ferment is insufficiently formed, or its power is weakened, while the simultaneously appearing anti-lipolytic ferment acts more strongly (L.Schwarz, B. Fischer).

When Fischer mixed normal blood with some lipæmic blood obtained from a diabetic and placed the mixture in a beaker, the blood developed lipolytic properties. The portion of the fat which was soluble in ether was considerably diminished. In addition, it

was observed that the derivatives of fat and fatty acids in particular markedly inhibited the lipolysis. The diabetic acidosis thus favours the onset of lipæmia, although it can scarcely be regarded as the only factor, since the cases of acidosis without lipæmia are still very frequent.

If, then, under the guidance of recent views, we seek for the cause of diabetic lipæmia in abnormal conditions of lipolysis, we have still to reckon with many unknown or at least insufficiently established factors. However, such a standpoint opens up a path for further experimental inquiry into this rare and at present unexplained condition.

2. *The Williamson-Bremer's Methylene Blue Reaction*

We have still to consider another phenomenon of diabetic blood, and one for which we cannot offer a sufficiently acceptable explanation.

When a weak alkaline solution of methylene blue is added to normal blood, a blue-green colour results. Williamson was the first to point out that after the addition of the methylene blue solution to diabetic blood the blue colour was reduced and the mixture became yellow-red. Working independently Bremer observed that when a thin smear of blood was allowed to dry and then heated on a slide for ten minutes at 135° C., the addition of one per cent. methylene blue solution gave an intense blue colour, while if the same

procedure was carried out with diabetic blood, a pale green colour resulted. Numerous other dyes also exhibit tinctorial differences when applied to normal and diabetic bloods respectively. Both Williamson and Bremer ascribed the reaction to the reducing power of the circulating glucose. We know that a 1.5 to 2 per 1000 solution of glucose is able to reduce the alkaline methylene blue solution. This percentage of glucose, of course, frequently occurs in diabetic blood. There is no objection to conclude that the reaction primarily depends upon the amount of sugar present in the blood stream. All recent authors have accepted this interpretation, but further investigations upon the nature of the reaction have demonstrated the simultaneous action of other factors. Diminished alkalinity of the blood intensifies the reduction of the methylene blue. This explains the more frequent and intense reduction (or deficiency of staining the corpuscles) in the blood of diabetics bearing the signs of acidosis, than in that of slighter cases. The observations of Loewy are also of interest. He centrifugalised blood obtained from a diabetic patient, which could not be stained with methylene blue solution. The blood corpuscles were then freed from sugar by washing them in isotonic sodium chloride solution. In spite of this treatment the corpuscles could not be stained with methylene blue. I have confirmed these results. When I repeated the experiment with similarly treated blood corpuscles obtained from a healthy man, I found that the corpuscles stained most elec-

tively. Either the blood corpuscles of the diabetic contained sugar, in spite of the washing,—a rather impossible supposition, — or the colour-combining chains of the hæmoglobin have undergone certain changes. In what these consist our present knowledge can offer no satisfactory account. We stand upon the threshold of a question whose further probing may provide valuable results.

The irregularity of this clinical sign also sustains the view that in addition to the sugar other factors contribute to the colour-reduction. The faculty of decolourising methylene blue solution is by no means a regular and consistent property of diabetic blood, and the intensity of the reaction does not exhibit any relation to the amount of glucose present in the urine. The reaction often appears when, as a result of a restricted diet, the last traces of sugar have disappeared from the urine. Some cases have been described, and I have also made similar observations, in which the reaction was more marked during the days of restricted diet than when carbohydrate was present in the food. There are also various other factors which may either intensify or diminish the reaction. We still require quantitative estimations (obtained by objection-free methods) of the relations between the percentage contents of sugar in the blood and its precise staining capacities. Such figures, indeed, form the first requisite step towards a well-grounded explanation of this still open question.

V. GENERAL COURSE AND PROGNOSIS OF DIABETES

As I stated in the introduction, I do not intend in these lectures to deal systematically with the clinical symptoms and the course of the disease. You will find all that is worth knowing on such matters put together in the current text-books of medicine. I cannot, however, refrain from giving here a short review of the dangers and of the prognosis of diabetes. Only one who knows these will be able to carry out a deliberate course of treatment. For, more than is the case with the majority of other chronic diseases, the nature of the treatment must vary *pari passu* with the course of the disease and its prognosis.

Although all cases of diabetes have one symptom in common, namely glycosuria, and although we may say that in all probability this most striking of the symptoms depends in all true cases of diabetes on the same cause, namely on a disturbance of the functions of the pancreas, yet the clinical form, the course and the prognosis of the disease, is so variable that in comparing diabetics one with another, one might almost believe one had to do with a number of entirely different diseased conditions. This strikes us especially as compared with other chronic diseases, *e.g.*, heart diseases, pulmonary tuberculosis, chronic Bright's disease or

chronic diseases of the stomach. The course taken in all these diseases and in others is remarkably typical. Anyone who has observed and studied a few of these cases at all exactly has no difficulty in recognising the underlying typical form in each new case. In diabetes, however, the variability is enormously greater, and this is the reason why the disease so often fails to be recognised until a late stage, and when it has gone far beyond its initial stages and has already worked great havoc in the body.

A. THE COMMENCEMENT OF THE DISEASE

The commencement of the disease is for the most part veiled in obscurity. For in the majority of cases it must be acknowledged that the disease existed long before the discovery of the glycosuria. Cases in which the beginning can be exactly denoted are extremely rare. The cases of so-called *acute traumatic diabetes* are perhaps the earliest stages known. They are cases in which an accident happens to people who were formerly in perfect health, especially such a one as involves shock or injury to the brain, and in whose urine sugar then appears. In some cases the sugar soon disappears again; it is not then a question of true diabetes but only one of transitory neurogenous glycosuria. In other cases, the glycosuria persists and it is then a question of true diabetes. Such cases are much talked about, and most physicians have no doubt as to the frequency of their occurrence. I had occasion a short time ago to go through the whole literature of

the subject for the German Imperial Insurance Office. I was astonished to find that the really well-established cases are extremely rare. There are hardly more than half-a-dozen cases known, of which it may be asserted with scientific exactitude that before the accident there was no diabetes and that after it the disease ensued. In the greater number of the cases there remains the possibility or even probability that the people had diabetes prior to the trauma, although they were unaware of the fact.

It is much more difficult to obtain information about the first beginnings of ordinary non-traumatic diabetes. I have collected a few data on the subject. They all relate to doctors or chemists who were accustomed to frequently examine their urine. In all the cases the sugar reaction occurred at first sporadically, then disappeared again for some time. Now and again, *e.g.*, after strong bodily or mental exertion or after excesses of different kinds, the reaction returned, to disappear again very shortly. It might be many years before the phases of the positive reaction became more frequent than those of the negative ones, and a true diabetes could be diagnosed. The important point is, that all these people at the time of the discovery of the presence of sugar and for many years later felt perfectly well, and there was not a single other symptom to be found in the body that could have any connection with the diabetic disposition. The same is true for a large number of people in whom sugar is accidentally discovered when they are examined for a life insurance

policy. There is, therefore, no question but that diabetic disturbances may be present for a long time before subjective or objective symptoms of illness lead to its being suspected. This, of course, makes the determination of its exact time of commencement extremely difficult.

In those cases in which the disease was detected in its early stages, the glycosuria was always a so-called transitory one. It was characteristic, however, in that it showed itself under circumstances in which glycosuria would not have occurred in by far the larger number of normal individuals. This transitory character of the incipient true diabetic glycosuria is, of course, extremely important both for prognosis and diagnosis. How gladly would we refuse to believe that any evil consequence could ensue from transitory glycosuria when we accidentally come across it! But it is to my mind the duty of a physician to take very seriously every case of transitory glycosuria that is not directly called forth by excessive intake of sugar and at least to keep the case under supervision and to examine for sugar carefully and continuously. I would even go further, and demand in every case a moderate reduction of carbohydrate food and especially a complete exclusion of sweet comestibles. I believe that in this way the outbreak of the actual disease may in many cases be guarded against.

One cannot, as a rule, trace the disease back to what I have just described as its very first beginning. Usually for some time before, say for a few months or

longer, complaints may be heard of wasting, irritation or inflammation of the skin, neuralgia, defects of sight, weakening of sexual powers, nocturnal cramp in the calf-muscles, increased thirst, frequent passing of the urine, quick fatigue of the muscles, mental depression, nervous excitability, etc., which are not heeded or are wrongly interpreted. The symptoms resist treatment which has otherwise proved itself useful in similar disturbances of a different ætiology. Then one day the urine is examined and at once the whole picture of the symptoms becomes clear.

Careful enquiry into the history of the case now shows us when it was that the diabetes began to develop its *effects,* but it is too late to learn anything about the first true beginning of the diabetic disposition.

When we consider how secretly the disease develops and how much more frequently it occurs than used to be imagined, it is the duty of the physician to examine more frequently than is now the custom the urine of people entrusted to his care. The most favourable time for treatment is at the beginning. It has become customary in many large manufactories in Germany to examine the health of all the employees at quarterly intervals; amongst other things, examination of the urine for proteid and sugar is prescribed. By this means already many cases of incipient diabetes and of incipient Bright's disease have been detected. This is not only of important practical significance, but also of great scientific interest, for of both these dis-

eases we know relatively little of the first stages. To the family physician belongs the same duty of making regular periodical examinations of the urine. He ought not only to treat those members of the family who are ill, but should keep an eye on the condition of those who are well.

B. THE LATER COURSE OF THE DISEASE

As I have already observed, the first stages of the disease usually remain unheeded and unattended to. The practitioner is usually confronted with the fully developed disease when he first has to prescribe appropriate regulations of diet. Very much, then, depends upon these directions and upon the conscientiousness with which they are carried out.

1. *Slight Cases*

If taken in time and deliberately treated, one may, in slight and early cases, count, almost without exception, on a good or even a striking therapeutic result. Certainly, a large amount of perseverance and conscientiousness is required on the part both of the physician and of the patient. It would be a dangerous game to play, to give these patients schematised rules to follow, imposing the same limitations of diet on all, regardless of the quantity of carbohydrate each can tolerate, and to rely upon a Carlsbad cure every now and then to repair injuries. Although it is just for slight and incipient cases of diabetes that I am most willing to recognise the great significance of the Carls-

bad water cure, I must emphasise that by the faith which both doctor and patient set on this cure, a lamentable old jog-trot is only too often allowed to take the place of the regular dietetic home treatment so necessary for slight cases. Unless this has already been aimed at in the home, the course of events is then usually such that the urine is first made free from sugar in Carlsbad and so it remains for some little time after the return therefrom. Then, gradually, the diet becomes more lax—often with the knowledge and permission of the doctor. Now and then the limits of moderation are exceeded, and some sugar appears in the urine; it disappears, but soon returns again. The same thing repeats itself several times in the year, until a second visit to Carlsbad brings about a fresh recovery. This goes on for a few years until the patients notice to their horror that even after the drink cure they no longer become free from sugar. Then they begin to lose faith in the watering place, and the latter loses its credit; next year a new place is visited, but there, too, the result is not satisfactory. As a matter of fact the disease has got much worse in the course of these few years. Even strict measures are no longer competent to render the urine free from sugar. Out of what was, to begin with, a slight form of glycosuria, a severe one has arisen which can only be brought back into its original slight form, if this is possible at all, by great self-denial and great perseverance.

The diabetic may consider himself especially fortu-

nate if, under these circumstances, it is only the glycosuria that has got worse. As a rule, all sorts of secondary disturbances have developed *pari passu* with it, although they are at first unnoticed and disregarded, viz., degenerative processes which so readily set in when hyperglycæmia is permanently present (arteriosclerosis, neuralgia, neuritis, dimness of the lens, neuro-retinitis, falling out of teeth, etc.). From these complications the patient suffers more, and by them he is put into more immediate danger, than by the glycosuria itself. Also the worst of all complications of diabetes, viz., gangrene, arises most readily in people who have been suffering for a long time from slight glycosuria but have not adopted precautions stringent enough to prevent it.

The course and prognosis shape themselves quite otherwise when the diabetic disturbance is combated from the beginning with all the earnestness that the matter deserves; when one is not satisfied with a temporary freedom from high sugar excretion but strives to avoid it permanently. To do this is not difficult with such fresh and slight cases of diabetes as are now in question. There is no need to talk of real privations. They are at any rate nothing compared to the dangers which threaten by neglect of the disease. There are often certain difficulties in the way of the practitioner who energetically interferes. The patient usually feels quite well, and rejoicing that the analyses show only one-half to one per cent. of sugar, he is not nearly so much concerned as he should be about the

choice of food and drink. He sees around him others who excrete more sugar than he does and yet enjoy a good state of health. That makes him careless and somewhat thoughtless. He enjoys the present and takes no thought for the future. It is in this that the physician must not concur. It is his business to act in the present so as to avoid future disaster.

It cannot, it is true, be asserted that by proper individual diatetic treatment every case of slight diabetes can be cured or even kept within such bounds that all injurious consequences are abolished; but for a large, a very large, number of cases it holds true. In many patients, as a result of the treatment, the tolerating power for carbohydrates is gradually increased. Patients, who in the first year of treatment can only stand 100 grammes of bread in the day, acquire in the next year the power of tolerating 150, 200, 300 or more grammes of bread. In such cases, which are not at all rare, one may practically speak of a true and complete cure of the diabetes, even though there remain the germ for a new spontaneous outbreak or one brought about by neglect. It is the same sort of thing as with pulmonary tuberculosis. Here, also, the germ persists, usually throughout life, when it has once established itself in the lung. As long as it is dormant we regard the people as healthy, although we know well enough that they are continually in danger of the recurrence of the disease. In the case of pulmonary tuberculosis we know why it is that even after a rest of many decades the danger of a fresh attack still exists.

But in the case of diabetes we do not know why the disposition to it, when it has once arisen, is never fully extinguished, although it may be reduced to a practically immaterial residue.

In other cases of diabetes, even with careful treatment, no cure, in the sense we have just used the word, can be obtained; but nevertheless the disease stops its advances, although it had previously shown a distinct tendency to progress. The number of patients is relatively large who, in spite of their limited power of tolerating carbohydrates, can yet, by careful regulation of their mode of living, remain permanently free from sugar, and who, in spite of a long duration of the disease, do not get a single one of the bad complications of diabetes. In the most unfavourable cases one may always succeed in putting off the evil day for a long time.

I may summarize these remarks by saying that in slight cases of diabetes one has it in one's power to hinder or at least to considerably delay the onset of dangerous degenerative complications and the transition into the severe form of diabetes.

I must emphasise this most strongly. I would further expressly assert that if the proper and serious treatment of diabetes could begin earlier and be carried out with greater consistency, one might with certainty suppose that the general average prognosis of the slight form of diabetes would be much more favourable than has hitherto been the case; it would be recognised that there is hardly any other chronic disease in man which

can be so readily controlled and whose dangerous tendencies are easier to direct.

This, however, does not apply—or only to a much smaller extent—to the diabetes of children and young people, viz., up to about the end of the third decade of their life, even when the disease at the beginning seems to be ever so slight. In children and young people transitory glycosuria occurs much more frequently than is generally supposed. That alone has no significance; but if a true diabetic disposition develops, it progresses relentlessly, however slight it may be at first, and even when the treatment is the best in the world. Infantile diabetes knows no mercy; one can at most only defer the end for a little time.

2. *Severe Cases*

We usually understand by the term severe diabetes those cases in which the urine can no longer be freed from sugar by simple removal of carbohydrates from the food. In order to entirely prevent the glycosuria, the intake of proteids must also be limited, and in some cases even this does not suffice. There are many reasons against this kind of classification. But practically such cases also are deemed to be severe when only a small quantity—not more than 50 to 60 grammes of bread a day—of carbohydrate can be well tolerated, for so small a tolerating power calls on the one hand for no essential difference of treatment, and on the other hand these patients are sure, in a shorter or longer time, to lose completely their slight assimilative ca-

pacity for carbohydrates. The reverse process occurs extremely seldom, *i. e.*, it is very rare for a diabetic who cannot stand more than 60 grammes of bread in the day to succeed later in consuming a larger quantity without excreting sugar. This is at most the case after acute infectious diseases. Many such diseases, *e. g.*, angina, influenza and pneumonia, have the property of severely depreciating the tolerating power of the diabetic individual. What was at one time a high tolerating power may be reduced thereby to nil. The injury is, however, not irreparable; a few weeks later the former high toleration level has frequently been restored.

The behaviour of the acetone-bodies must, more than formerly, also be taken into account in the classification of diabetes into slight and severe forms. There are cases in which the morbid processes leading to acidosis are much more strongly developed than the disturbances in the oxydation of sugar. The dangers are in such cases greater than in others with the same or even with more marked glycosuria. The reverse may also occur.

I have also to remind you of what every physician is aware, namely, that the intensity and the obstinacy of the glycosuria is certainly not the only measure of the danger to which the patient is exposed. There are numerous cases of slight glycosuria in which severe complications obtain, *e. g.*, arterio-sclerosis or gangrene, and in which the dangers are much greater and more immediate than in other patients whose glycosuria is much more marked.

Severe and slight diabetes is not therefore necessarily identical with severe and slight glycosuria, but in spite of this the division into severe and slight forms of glycosuria has practically held its own. It furnishes, apart from the secondary effects of complications, a useful measure of the stage which the disease has reached.

The cases of severe glycosuria are to be judged quite differently from the previously mentioned cases of slight glycosuria. It must at once be stated that a cure is now no longer to be expected. So far as I know, there is not a single case in the whole literature of the subject in which this has occurred. A slight improvement is possible, especially in cases which had been neglected up to the stage under consideration. As a rule, one must be content if further mischief can be prevented. Even when the influence on the intensity of the glycosuria remains but slight, an intelligent and deliberate treatment may often produce valuable secondary results. Disturbing and dangerous complications vanish. I have seen cases in which the sharpness of sight was reduced by neuro-retinitis to $\frac{1}{10}$ and was brought back again to normal by four weeks of rational treatment. Obstinate neuralgia, neuritis, pruritus may disappear, loose teeth become firm again, the muscles stronger, the diminished body-weight increase; one sees that the results repay trouble, even though the final goal, the cure of the diabetic disturbance in metabolism, cannot be obtained. The way which leads to this result is difficult to determine. For the so-called slight

cases the course is clearly indicated. The order goes forth that at all risks the excretion of sugar is to be prevented. In severe cases, this saying can no longer be taken into consideration, for it is a command which cannot be complied with. One might modify it and say, " Care must be taken that as little sugar as possible is excreted," but that is not of universal application. It is only applicable to a certain number of cases. With others, one gets no further by this statement, and one may even do an injury, rather than a service, by such treatment. It is only experience that can teach one the right course to pursue, and even the most experienced physician has in each case to make careful test experiments before he can give definite advice. Of this I shall have more to say later. The prognosis of the severe cases is also quite different. The extreme cases, in which a high degree of acidosis has already manifested itself, and in which the progressive diminution of strength strikes the eye, are easy enough to read.

In the earlier stages of severe glycosuria the prognosis is extremely difficult. When I first began to treat a large number of diabetics I shared the generally accepted view that a diabetic who, in spite of deprivation of carbohydrate, continues to excrete large quantities of sugar (40 to 60 grammes), and who has permanently present in his urine much acetone, diacetic acid and oxybutyric acid, is unconditionally a candidate for speedy death. I have had to alter this view. I have patients who showed these effects as much as ten years ago, and from whose urine I then obtained large quan-

tities of oxybutyric acid. They have retained these symptoms, and yet even now enjoy good general health and powers. These cases are of course rare, but they do occur, and this experience has been most useful to me and to my patients, for it has convinced me that there is no need to be too much concerned when acetone and oxybutyric acid suddenly appear in the urine in the course of earnest and deliberate treatment. Certainly, in other cases, matters are quite otherwise. Severe glycosuria may be withstood for a long time, but as soon as the first signs of acidosis make their appearance this signifies the beginning of the end. You see what right I have to say that the severe forms of glycosuria behave very variably from a prognostic point of view, and that a forecast of their termination calls for much previous experience. But all cases are eventually making for the same end.

While in the slight cases dangers can almost exclusively only be called forth by the supervention of complications, in severe cases coma is the ever-threatening danger. I have ascertained that of my patients who were already suffering from the severe form of glycosuria, and whose disease terminated fatally, more than 80 per cent. died of coma. The remainder either died of apoplexy or of acute intercurrent diseases; only 3 per cent. were victims of gangrene. Of patients who suffered from the slighter form of glycosuria, and yet succumbed, only 5 per cent. died of coma, very many dying from apoplexy, tuberculosis and intercurrent diseases, especially pneumonia and influenza. More than

20 per cent. of the cases were the victims of gangrene. As in their course, so also in their fatal termination, cases of slight and of severe glycosuria behave differently.

3. *In What Do the Dangers of Diabetes Consist?*

After this brief review of the course and prognosis of the disease, it will not come amiss to clearly define wherein the real dangers of diabetes lie before we begin to speak of treatment.

(*a*) *Carbohydrate Deficiency. Lowered Nutrition.*— In order to obtain the whole value required from his daily food, the healthy man makes use of large quantities of carbohydrates. In most people they cover about 40 per cent. of the entire daily intake, often more, seldom less. This important food-stuff is of minor importance for the diabetic. Only in very slight cases does he make any appreciable profit out of them for the production of heat and work. The greater the intensity of the diabetic disturbance, the greater the amount of carbohydrate food that flows away unused in the urine; in severe cases, indeed, it may all do so. I have already quoted instances to show how greatly these processes diminish the actual calorific value of the food. The consequence is that the patient is insufficiently nourished, even though he eats abundantly. He gets thin, uses up his body fat and proteid, and gets weaker and weaker. Theoretically, one may put a stop to this state of things by ordering food which contains less carbohydrate, replacing the loss of carbohydrate by adding more proteid, and especially more fat. As a

matter of fact, the rational treatment of diabetes strives to take this course. But its practical application is attended by very great difficulties, for it is a hard task for many people to consume a sufficient quantity of fat. Distaste for it arises after a short time; even gastric or intestinal catarrh ensues and interrupts the intensity of the nutritional process. The more carbohydrate is dispensed with, the more frequently do such things occur, and we then often find that the diabetic patients are getting thinner and thinner and weaker and weaker. They are in danger of undergoing a slow death from starvation. In many cases of diabetes it is in this lowering of nutrition that the chief danger lies.

(*b*) *Degenerative Changes in the Nuclein Substances of the Cells.*—I have already drawn attention to the fact that in severe cases of diabetes abnormally large amounts of purin substances are excreted, although the whole food supply is quite sufficient for the maintenance of the nitrogenous equilibrium. This points to a progressive atrophy of nuclear substances, due, it must be supposed, to toxic influences. As a consequence of such influences, the muscles lose their power of doing work and the patients become weaker and weaker, even when the body-weight can be maintained by abundance of nourishment.

(*c*) *Abnormal Production of Acids* (*Acidosis*).—I have already spoken on this subject in so much detail that I need not here return to it. I will only once more remind you that the danger of acidosis only applies to

severe cases, and that it is still an open question whether it is only the quantity or the quality of the acids formed which materially matters, or whether other simultaneously occurring chemical changes of metabolism are responsible for the occurrence of the auto-intoxication.

(*d*) *Diminished Resistance to Intercurrent Diseases.*—It is a common experience to find that diabetics who are accidentally attacked by other diseases are much more endangered by them than are other individuals of the same age and of the same constitution. Most to be feared are acute infectious diseases, and amongst these, infections of streptococci, staphylococci, the diplococcus of pneumonia and by the influenza bacillus have an especially bad name. Even when the complication does not end fatally at once, diabetic patients are much more pulled down by it than are non-diabetic individuals. Also their recovery and convalescence last much longer. One generally finds that after the attack the glycosuria is increased. Many cases of slight glycosuria have been described which have been transformed into severe glycosuria by an intercurrent disease. The mischief may, it is true, disappear again, but this favourable occurrence is the exception, not the rule.

This is the place to mention the dangers which result from injuries. It is much more difficult to guard against septic infections of wounds in diabetics than in healthy people. Even when operative or traumatic injury is thoroughly aseptic, the process of healing is often rendered more difficult. For the surfaces of the wound,

especially those parts of the skin in its immediate neighbourhood, tend to necrose. The skin is, in any case, one of the most sensitive parts of the diabetic organism. The numerous skin complications which accompany it provide sufficient evidence of this (eczema, furuncle, carbuncle, xanthoma, etc.). Amongst chronic diseases, tuberculosis of the lungs must be especially mentioned. It is not, indeed, so common a complication of diabetes as was at one time taught, but when once it combines with diabetes the prognosis becomes almost hopeless.

In all these instances the lessened power of resistance of the tissues of the diabetic patient is revealed. This shows itself almost as much in slight as in severe cases of diabetes.

(*e*) *Chronic Degenerative Processes and Chronic Inflammatory Processes.*—We often notice in diabetics that symptoms which normally belong only to old age occur in relatively young people: falling out of the teeth, cataract, arterio-sclerosis, atrophy of the skin. The diabetic, we may say, tends to fall a prey to early old age. Nervous symptoms which bear an inflammatory degenerative character may also occur: optic neuritis, other forms of neuritis and of neuralgia, with manifold clinical symptoms which I will not here enumerate. Of all these disturbances it is—*quoad vitam*—the diseases of the arteries that have the greatest significance, since they add to the diabetes all those well-known dangers which we have also to fear from arterio-sclerosis in non-diabetics. In cases of this strange and, so far as its ætiology is concerned, obscure disease of

the vascular system, we often notice that its distribution in the vascular apparatus depends very much on the nature of the fundamental disease. Diabetes also introduces peculiarities into the arterio-sclerotic process. The arteries of the lower extremities are specially liable to it. As a consequence diabetics incline to gangrene, the saddest and most gruesome danger to which they can be exposed. In this respect also diabetes simulates old age. Arterio-sclerosis induced by other circumstances, *e. g.,* by alcoholism, by lead poisoning, by aortic insufficiency, by syphilis, etc., only very seldom produces gangrene of the lower extremities. It is only in the arterio-sclerosis of old age and of diabetes that the vessels of the extremities are frequently attacked.

The ætiology of all these degenerative processes has been much discussed. They all exhibit marked toxic characters. What, then, is the poison? Most text-books expound the view that the sugar, as such, is poisonous. The disturbance of nutrition of the tissues is said to be a direct consequence of hyperglycæmia. Much may be said in support of this view—in the first place, the daily experience that the riddance of the glycosuria, or, which is the same thing, of the hyperglycæmia, very often produces a most wonderful effect on those complications. We cannot expect the arterio-sclerotic process to retrograde, and no one has ever to my knowledge asserted that it does so; but we see that wounds which for a long time would not heal get better quickly when the glycosuria is stayed, and neuralgia and neuritis of long standing, which have withstood every other

treatment, disappear; disturbances of vision which depended on optic neuritis are cured. I have often observed, as I mentioned above, that patients who before the treatment could not read a newspaper without a magnifying glass, have recovered their sharpness of vision completely four weeks after it. Teeth which were loose before become firm again; dimness of the lens does not, it is true, vanish again, but it is arrested. There are, in short, few therapeutic results in medical therapy which are so striking as the recovery from diabetic complications of a degenerative nature by diminution or abolition of the glycosuria. Nevertheless, I think it would be rash to conclude that it is the sugar itself in the blood that is the toxic poison. In overcoming the hyperglycæmia, we probably neutralise other poisonous substances, the constitution of which we do not know. Opposed to the indictment of sugar as possessing toxic properties is our experience that the complications referred to do not in any sense bear a direct relation to the intensity of the glycosuria and the hyperglycæmia; they occur just as frequently in slight cases of diabetes as in severe ones. We must leave it to the future to throw light upon this question.

On the other hand, the experience that has been obtained with regard to the effect of treatment on the prevention and the cure of diabetic complications demands our energetic fight against the early stages of diabetes. How often is a slight amount of glycosuria regarded as of no consequence! The slight loss of

sugar is truly enough somewhat unimportant, but when we are confronted by the well-developed complications we have to ask ourselves whether it would not have been possible by more careful attention to the glycosuria we treated with such contempt to have kept secondary disturbances at a distance and to have prolonged life.

VI. THE TREATMENT OF DIABETES

We learn from the history of medicine that the treatment of diabetes during the era following its first discovery consisted exclusively in the prescription of dietetic regulations. Nobody was blinded by the fact that this kind of treatment was only symptomatical and did not touch the root of the mischief. Since then, however, attempts have often been made to place the treatment on some sounder footing. These attempts have, of course, entailed much error and the pursuit of many false scents. Still we must not give up the hope that we may yet succeed in finding a treatment which will yield better results and attack the disease at its root. In the meantime, the fact remains that the dietetic treatment is still the chief method by which the disease can be combated and its injurious consequences averted. Since the infancy of our knowledge of diabetes, scientific medicine has always had to return to dietetic treatment. With the progress of our knowledge of metabolism and of the chemistry of food, the methods employed in this treatment have been considerably improved and refined, but the principles involved are still the same. This need not deter us from ascribing the proper value to those other factors which exercise a beneficial influence on the disease.

A. PROPHYLAXIS

Prophylactic treatment does not, unfortunately, play any large part in diabetes, as the disease is usually well advanced by the time we are in a position to take the first steps to combat it. Only under special circumstances can prophylaxis be spoken of:

1. When several cases of diabetes have occurred in one family; for diabetes frequently, though not always, indicates a family predisposition.

2. When a transitory glycosuria is accidentally discovered in an individual, the reason for which does not obviously lie in a diet excessively rich in sugar. I should like to urgently recommend that such an event be neither heeded lightly nor neglected. It is in most cases the warning signal of later diabetic disease, the outbreak of which may not occur for many months, or even years.

When either of these two circumstances arises, it becomes the duty of the physician not only to make frequent analyses of the urine, but also to advise against the consumption of much carbohydrate food. He should especially reduce to a permanent minimum the eating of sugar and sweets of any kind. These can be permanently abstained from by the organism without any injury. To abstain from them is very easy for most people. These precautions are based on an experience which also plays a great part in the treatment of the disease itself. Abundance of carbohydrate food gradually weakens the power of toleration for

them in every diabetic individual, while withdrawal of carbohydrate raises the toleration capacity. In other words, the functions of the organism which are concerned in the elaboration of carbohydrates remain steady or improve when they are only drawn upon to a slight extent.

This is the only thing of any importance that can be said about the prophylaxis of diabetes. Everything else is covered by the general regulations which must always be laid down for the maintenance of a strong and healthy body.

B. ÆTIOLOGICAL THERAPY

There is no true ætiological treatment of the disease, since we have no true knowledge of its ætiology. But we may mention a few therapeutic points of view which border on the domain of ætiological therapeutics.

1. *Neurogenous Glycosuria*

I have already stated that there is no such thing as a chronic disease which can be designated by the name of neurogenous *diabetes*.

On the other hand, I pointed out the necessity of recognising a neurogenous *glycosuria*. This occasionally occurs, as I have said, as a transitory phenomenon in non-diabetics. It is only of interest for the treatment of diabetes in that it is, perhaps oftener than is generally supposed, a harbinger of the later appearance of diabetes and therefore makes those regulations neces-

sary which apply to the prophylaxis of the disease. Neurogenous glycosuria plays, on the other hand, a large part in individuals who are already suffering from true diabetes, *i. e.*, in some diabetic patients nervous influences lead to increase of the glycosuria. I am even of opinion that this is the case in every diabetic individual. It is not, however, always obvious and easy to recognise; for in severe cases the influence of diet so greatly preponderates that the more delicate influence which the nervous system exercises is often obscured. In slight cases, on the other hand, in which the influence of diet is not so important, the connection between glycosuria and the condition of the nervous system is often clear and very surprising; *e. g.*, psychic excitement may cause a diabetic to excrete considerable quantities of sugar on a diet on which he would otherwise be quite free from sugar. I have already, as you will remember, in the first part of my lectures, given as an explanation of this—that a transitory neuro-hepatogenous glycosuria is here being added to the diabetic disturbances of the pancreas. Such a state of things occurs of course incomparably more frequently and more distinctly in people who are neuropathically inclined, or who have become neurasthenic in the battle of life, than in people whose nervous system is in perfect order; and it occurs so frequently in combinations of neurasthenia with diabetes that the former predominates in the clinical signs of the disease. These are the cases which practicing physicians designate familiarly as neurogenous diabetes,

or as glycosuria due to neurasthenia. The name is right enough, when only the form of the clinical symptoms is meant to be implied by it. It is, however, fundamentally wrong, and a source of fatal therapeutic error, when it is taken to imply that the diabetes of these people is a thing apart. All these people are true diabetics; they are diabetics in whom the alimentary factor of the glycosuria is still slight, and in which, therefore, the nervous factors are more obvious. But all these people run the danger that by neglecting the important dietetic factors, and by alone paying attention to the nervous factors, the slight form of diabetes may progress to the severe stage. I must emphasise this strongly, for the error of only taking notice of the neurasthenia in such cases, and neglecting the alimentary glycosuria, is unfortunately not the exception, but the rule. The error is furthered by the widely spread view that neurasthenics cannot stand the limitation of carbohydrate in their food. Many neurasthenic diabetics have been sent to me, together with this statement. It is only in the rarest cases that I have been able to establish the truth of it. These patients can quite well bear a moderate limitation of carbohydrate; the whole condition, including the nervous disturbances, is improved by it. It certainly requires great caution and a careful investigation into the peculiarities of each separate case. Both the diabetes and the neurasthenia demand this. Every neurasthenic has his peculiarities, and has the right to have these heeded and duly appreciated. If this is done in the right way,

one can do justice to the claims which the diabetic disease makes in just the same way as in all other cases of diabetes. It must not be forgotten that there is a great aim in view, namely, to prevent the as yet slight diabetes from passing into the severe form of the disease. I have many complaints to raise against the practices in common use in many institutions and sanatoria for nervous diseases. It is customary in many institutions to give to neurasthenic diabetics as much food as possible, and of as many kinds of food-stuffs as possible, the reason being given that every limitation excites and disquiets them. That is quite a false basis to stand on, and only tends to accustom the patients to gross neglect of the most necessary dietetic preventive measures. Temporary improvement of the subjective state of health is, it is true, often attained by it, but as time goes on the diabetes gets worse, and from the organic changes which it occasions there arise new sources of danger for the nervous troubles.

I am, of course, far from advocating a one-side treatment of the diabetic disturbances of metabolism in these cases. The reason why I have considered them under this heading of "ætiological therapeutics" is that I wish to emphasise how greatly one may benefit by a reasonable treatment of the nervous disturbances. I cannot here discuss the necessary procedures in detail, as they are in keeping with the regulations which are otherwise usually prescribed and known to be beneficial in cases of neurasthenia. Frequently, removal of the patient from the customary wearing and tearing conditions

of life suffices. Every experienced physician knows that diabetic neurasthenics excrete much less sugar, even when the same diet is maintained, when they turn their back on work and the worries of home life. The nervous factor disappears and only the alimentary factor remains. In other instances the aid of soothing medicines may be tried, such as potassium bromide and codein, or residence in a health resort or a sanatorium may be found desirable; but you must in such case always send your patient to a place in which you know by experience that attention is paid also to diabetes, and not to a place where interest is alone centred in the nervous system. Only in this way do you unite an ætiological therapeutical treatment, directed towards the neurogenous glycosuria, with the customary and well-toned dietetic treatment of diabetes.

2. *Diabetes of Syphilitic Origin*

Syphilitic infection may produce glycosuria. In a few cases it is again a question of neurogenous glycosuria, which is developed in the way I have already mentioned, viz., by disease of the central nervous system. Cases are known in which transitory glycosuria appeared as an accompanying phenomenon in syphilitic meningitis. These cases do not come into the category of true diabetes. It is much more frequent for diabetes to arise through the effects of syphilis on the pancreas. Gummata of the pancreas are certainly somewhat rare, but chronic vascular changes are frequent, amongst the

consequences thereof being chronic induration of the pancreas. Also the simple parenchymatous atrophy of the organ which one so often meets with in children seems to me to be due to the syphilitic virus. I have at least established that in some of these cases a not fully cured syphilis was present in the parents at the time of the conception of the child. You know that atrophies and chronic inflammatory indurations of organs belong to the same class of lesions as arteriosclerosis, and that these after-effects are most difficult to influence by mercury or by iodide of potassium. This is unfortunately also true of the syphilitic and metasyphilitic diseases which attack the pancreas and thus lead to diabetes. It cannot be denied, however, that good results may often be attained. In this I agree with Dr. A. Mayer of New York, who, a few years ago, recommended the energetic treatment of certain cases of diabetes with corrosive sublimate. But so far as my sphere of observation extends, the positive results are not more than of short duration, and may be altogether absent. Hardly half a dozen cases can be quoted out of the whole literature of the subject in which a true cure of a diabetic was brought about by anti-syphilitic treatment. In spite of this, the experiment is one that should be repeated, although with great caution, for diabetics are far more sensitive than non-diabetics to the injurious effects of mercury. I have seen many cases in which severe and persistent forms of stomatitis or of enteritis followed upon the course of mercurial medication.

3. *Organo-therapy in Diabetes*

In a certain sense the attempts which have been made to cure diabetes by organ preparations may be included under the heading of ætiological therapeutics. Experiments made with these were certainly not directed against the initial cause of diabetes, but against the causes of hyperglycæmia and glycosuria. They aimed at providing the organism with substances which assist or favour glycolysis.

We must first direct our attention to preparations of the pancreas, because it is supposed that certain secretions of the pancreas are wanting in diabetes and that their presence is necessary for the normal assimilation of carbohydrates. The discoverers of pancreas diabetes even made experiments with regard to this: after extirpation of the pancreas they fed animals on the substance of this gland. Later, a number of different extracts of pancreas having been placed on the market, administered some of them by the stomach, some of them by subcutaneous injection. I have examined at least ten different pancreas preparations. We are all perfectly agreed as to the fact that pancreas preparations are quite without any effect on the diabetes itself. But for certain purposes, which have really nothing to do with the diabetes, they may be used with advantage, *i. e.,* for disturbances in the digestion of fat. There are, as is well known, cases of diabetes in which not only the internal secretion of the pancreas is disturbed, but also the production or

the outflow of the pancreatic juice. In such cases the digestion of fat suffers severely, so that it becomes difficult to properly nourish the patient (Steatorrhœa). Pancreas preparations are very valuable in such cases; they assist the absorption of fat most strikingly. Of all pancreas preparations, the so-called "pancreon" has proved the best (4 to 6 grammes daily).

Cohnheim's work, to which I have already referred, suggested the trial of mixed extracts of pancreas and muscle. Dr. Croftan, of Chicago, has recommended this combination. I have no personal experience in the matter, but theoretically I have much hesitation in accepting this method, since the experiments of Cohnheim, on which it is based, have not been confirmed.

The endeavour to make organs extracts of service has brought other preparations into the market. Thyroid extract was praised for some time, but it has since been recognised that glycosuria may rather be produced than abolished by this extract. The same is true for suprarenal preparations. Liver extract, administered per rectum or subcutaneously, was recommended in France a few years ago. We have made a few experiments with it in my clinic; they yielded such lamentably negative results that we soon ceased to use it. In the meantime the praises of them which were then sounded in France are no longer to be heard.

In spite of all these disappointing results, it must yet be emphasised that many possibilities lie in all such

attempts. We must most certainly seek further to obtain from the organism itself those substances which stimulate glycolysis. Everything that we know about diabetes and about the conditions of hyperglycæmia and glycosuria point to the fact that such substances do exist. They are perhaps to be sought for more in the blood that carried them to the organs than in the organs themselves.

Herewith all is said that can lay any claim to be considered amongst the ætiological therapeutics of diabetes or of glycosuria.

C. THE DIRECT TREATMENT OF THE GLYCOSURIA

Apart from ætiological therapy, treatment can only be directed, on the one hand, to the improvement of the general hygienic conditions of the diabetic patient, and on the other hand, to diminishing the glycosuria and the production of acetone-bodies as far as is possible. Before I pass on to the most important therapeutical factor, viz., the regulation of the diet, I should like to devote a few words to the treatment by drugs and by balneology.

1. *Treatment by Drugs*

In looking through the literature of the subject we find that a surprisingly large number of drugs have been recommended for diabetes. In a monograph published a few years ago by my former assistant, M. Kaufmann (*Zeitschur. f. klin. Medecin,* Vol. XLVIII.,

p. 260, 1903), there was quoted about thirty different drugs.

The number is really much greater, as only those drugs were taken into account by him about which we had had personal experience, and amongst these only those for which an influence on the glycosuria would be claimed. This is the only effect which interests us here. That the many complications of diabetes may give occasion for the most different kinds of drug prescriptions goes without saying; I cannot here enter into it more fully.

There is also no object in reporting on all the drugs which have been recommended for glycosuria. Only the more important ones will be mentioned. Over the majority of them science has long ago read the death-warrant, and most of our younger colleagues know nothing of the fact that they once played a certain part in the treatment of diabetes. Anyone who is especially interested in this matter should consult Kaufmann's work. After studying the whole literature very thoroughly, more so than had ever been done before, he has reported on over a hundred cases treated with drugs in my clinic.

Opium and its derivatives deserve perhaps the first consideration. Opium is one of the drugs which first made for itself a name in the combating of glycosuria, and this name it has kept. The history of therapeutics teaches us that there has been much misuse of opium. In the middle of the last century, in many places it became the custom to give diabetics, almost without

exception, large quantities of opium. The patients were often turned into true opium eaters or morphomaniacs, without being released from the diabetes. We are now better informed concerning the effects and the consequences of opium. So long as the diabetic is allowed large quantities of carbohydrate food there is no object in giving opium, for under such circumstances he is hardly, if at all, affected by the opium. The action of opium is on the other hand very powerful in cases in which the glycosuria has already been reduced to a minimum by abstention from carbohydrate food. Amongst these are cases which stand on the boundary line between slight and severe glycosuria. The last traces of sugar cannot be made to disappear; 10 or 12 grammes a day remain. If now an energetic opium treatment is begun, the sugar disappears very quickly from the urine, often in only two to three days, and the toleration and assimilation capacities for carbohydrate becomes markedly increased. To this end as much as 12 to 15 centigr. of opium or codein each twenty-four hours is necessary. Codein is just as effectual as opium and it has advantages in cases in which the constipating effect of opium is to be feared. Diabetics stand opiates very well. In the first few days they complain certainly of great fatigue, relaxation of the muscles and mental lassitude; the appetite also suffers at the same time. But they soon become accustomed to these effects of the drug, so that the administration of opium may be continued for weeks without any difficulty. Opium is, therefore, a valuable remedy

for attaining the end one has in view when ordering restrictions of diet, namely, the complete removal of sugar from the urine. On what conditions the anti-glycosuric effect of opium depends is not yet known.

It may be that it depresses or cuts off the nervous components of glycosuria, so that the alimentary component of the diabetic disturbance alone remains. A certain amount of clinical experience is in favour of this, but we know nothing for certain about it.

Such, however, is the only indication I have mentioned which justifies us in confidently presenting opium as a remedy for glycosuria. We may also, it is true, as I have already remarked, repress to some extent the alimentary glycosuria of the diabetic by opium. The extent to which this is possible is, however, much too slight to justify long-continued administration of so strong a drug.

Salicylic acid and its derivatives take the second place. Amongst them, aspirin deserves most attention, because it injures the digestive organs the least. Antipyrin, the effect of which in other respects (fever, neuralgia, rheumatism of the joints) closely resembles that of salicylic acid, comes into the same category.

Salicylic acid is completely ineffectual in those conditions in which opium exercises its greatest effect. I recommended opium in severe cases during periods of restricted diet. Salicylic acid, on the other hand, acts best in slight cases of glycosuria and during the time when carbohydrates are permitted. It raises the power

of assimilating carbohydrates not inconsiderably. A diabetic who can only take 60 grammes of bread a day without salicylic acid can stand about 100 grammes without excreting sugar when taking about 3 grammes a day of salicylic acid. This result does not, it is true, occur in every case, but it occurs frequently enough to justify the trial of it

A few further remarks may be here included. Both salicylic preparations and antipirin cause, as is well known, a reaction of the urine to ferric-chloride. Anyone who knows the reaction at all well will distinguish it from the reaction given by di-acetic acid without difficulty. But as a matter of fact, errors are often made and the patients are quite unnecessarily frightened by being told that their urine contains acetone and di-acetic acid. It must further be mentioned that antipyrin in passing through the organism unites with glycuronic acid. A combination is thus formed which turns the plane of polarised light to the left. This effect is opposed to that of grape sugar, so that the usual polarimetric method of determining the amount of sugar in the urine makes it appear that there is less than there really is. The statement that antipyrin has a much stronger influence on glycosuria than salicylic acid has is based upon this error. In reality, it is the other way round: salicylic acid has a greater effect in reducing the amount of sugar than an equal quantity of antipyrin. The sugar must be measured by a reducing method if antipyrin is given, since otherwise the estimates obtained are false.

In no case should the good effect of salicylic acid, and of products related to it, call for its continued use. The disadvantages which attach to the use of all strong drugs outweigh the advantages during prolonged administration. Both salicylic acid and antipyrin also gradually lose their beneficial influence upon the glycosuria after a time. There is, however, nothing to be said against the employment of such drugs for a few weeks in the year in slight cases of diabetes. In certain complications, however, they must be forbidden, *e. g.*, salicylates must not be used in cases of renal disease, nor salicylates nor antipyrin in gastric disorders.

Syzygium jambulanum. About fifteen years ago Professor Binz and Dr. Graser discovered that the fruit of the East Indian plant *Syzygium jambulanum* possessed the property of strongly reducing phloridzin diabetes. As both the dried fruits and their extracts have proved themselves to be quite harmless even in large quantities, it is not surprising that new experiments are always being made in order to discover whether the glycosuria of true diabetes cannot also be alleviated or cured by it. Many praise it enthusiastically; others only report failure. The truth probably lies between these two extremes. I have myself employed and thoroughly studied the effect of jambul preparations by a large number of experiments upon cases of severe and of slight diabetes. The results showed that in some cases a marked effect on the glycosuria was without doubt actually attained. Many diabetics excrete only 10 to 20 grammes less of sugar after taking jambul

preparations for a short time, without at the same time having altered their diets or habits of life. Some of them were slight and some were severe cases of diabetes. But even in the most favourable cases the good effects of jambul ceased after three or four weeks, so that it cannot be said to possess a really satisfactory and permanent effect. I find myself herein in agreement with all other authors who have approached the question by reliable experimental methods and have not based their reports merely upon superficial impressions. It can never be said beforehand whether or not jambul will have a good effect; that can only be ascertained by experiment.

I should like to recommend the use of jambul preparations in the same way as those of salicylic acid, *i. e.*, occasionally for three or four weeks at a time. Of course the recommendation only applies to those cases in which by continual analyses the drug is found to diminish glycosuria and to increase the power of assimilation of carbohydrates. Our experiments showed the advisability of maintaining as strict a diet as possible at the commencement of the jambul treatment, and then gradually under the protection of jambul introducing small amounts of carbohydrates into the food. In suitable cases one may thus produce, at least for a few weeks, a higher tolerating power than could be expected on the same diet without jambul. Amongst the different jambul preparations the powdered fruits (20 to 30 grammes of the dried powder) and the macerated fruits, prepared in the cold, are to be pre-

ferred. The stomach stands them better than the bought extracts. They are also certainly more effectual.[1]

On what the effect of jambul depends is at least as obscure as the reason for the beneficial effects of opiates and salicylic acid. If you put together all that is known about jambul preparations you will come to the same conclusion as I have, namely, that under certain circumstances in the long battle which we have to fight with glycosuria in every case of diabetes, they form a pleasant remedy and one eminently suitable for temporary use. Really decisive results, such as were promised for them at the beginning and as even now are often proclaimed for them in mercantile advertisements, are, however, not to be expected of them.

I may here pass over all other drugs which have been recommended for getting rid of the glycosuria, and of which it has been boasted that they raise the assimilatory power for carbohydrates, for no result that is worth mentioning has been obtained from any of them. Arsenic, kakodylate, strychnine, uranium salts and many other substances come under this heading.

[1] The preparation we have chiefly employed is made in the following way: 200 grammes of dried jambul fruits of last year, including their seeds, are finely powdered. They are then macerated at body temperature for 24 hours in 2 litres of water, to which 10 grammes of common salt, 4 grammes of salicylic acid, have been added, the mixture being frequently stirred. Higher temperatures must be avoided. The jambul is then filtered off. The salicylic acid only serves for the preservation of the readily decomposable substance. 100 centigrammes of the mixture are ordered to be taken cold every morning fasting, and in the evening before going to bed.

I must, on the other hand, dwell for a moment on a less edifying aspect of the therapeutics of diabetes by drugs, namely, on the numberless secret quack remedies urged on diabetics by advertisement in all countries.[2]

Diabetics are a credulous people. Experience teaches us that they are entrapped almost more easily than people suffering from any other disease by every possible fantastic advertisement which promises them a certain cure. A large industry in quack medicines supports itself on this credulity. The advertised remedies secure for themselves an apparent good effect in so far as they are accompanied by strict diatetic rules. The decrease which may occur in the glycosuria depends, then, of course, not on the drug, but on these rules of diet, which are usually much more stringent than those usually prescribed by the practising physician. The patient cannot, of course, discriminate between the two factors—diet and drug. He is only too much inclined to ascribe to the drug essential effect. Even doctors have often fallen into this error, and have later had to confess it

[2] The quack medicines in the market change according to fashion. It is of no use to name them here. In Germany a preparation of jambul called "Djoeat" is the most widely known. It is a preparation of jambul, the essential constituent of which agrees with the maceration for which I have just given the receipt. In addition, it contains nearly two dozen different substances of no value. Although in itself not injurious to health, it must be designated as one of the most despicable preparations, because the legend accompanying the drug professes for it that it is an infallible "cure-all" remedy for diabetes and tries to make ridiculous the efforts of scientific medicine.

to their shame. Many doctors, at least with us in Germany, take up the standpoint that no objections need be raised to patients making use of such quack medicines if they like to do so. This in my opinion is contradictory to medical ethics. Such a standpoint often involves dangers to the patient. He loses his faith in the medical profession when he sees that his doctor is no longer drawing from the well of scientific medicine, but is allowing himself to be led by hard and fast rules and directions given at random by any chemist or druggist. When once the diabetic has lost his faith in the medicinal advice which he so greatly needs in both great and small matters, he never again alienates himself from the dangerous quack preparations, and he is no longer available for serious and systematic treatment until it is too late and his tide of life is at its last ebb.

These observations may seem superfluous to many of you, but I believe it to be my duty to make them, because I have so often seen what tremendously harmful consequences have ensued when the diabetic has once fallen into the hands of irresponsible quacks, and how difficult it is afterwards to set him free from them and their remedies.

2. *Treatment in Health Resorts*

Thousands of diabetics make their way yearly to some famous health resort. Carlsbad with its alkaline sulphatic water is the goal of the majority, but Vichy and Neuenahr, with their merely alkaline waters, and

Homburg, with its saline water, are also much visited. Diabetics derive great benefit from these spas. It would be absurd to deny it. Fashion, subject as it is to change and mood, would not serve to explain such a concourse of patients. To actual good effects can alone such power of attraction be attributed.

Experience as to the beneficial effect of Carlsbad and similar places dates back from the earliest era of the study of diabetes, and investigations into the nature of the effect produced by them also commenced during the first years of the scientific study of diabetes. It is usually taught that by drinking these waters the alkalinity of the blood and of the tissue-lymph is raised; and by this means their oxydative and glycolytic powers are increased. This is certainly not true. We often give diabetics at home much larger quantities of alkalis for combating acidosis than they can ever get by the water they drink at the spas. It has never been observed that the assimilating power for carbohydrates has been raised or the glycosuria lessened by large doses of alkalies.

All other explanations turning upon a direct effect of the spa waters on the glycosuria have also come to grief. It has often been attempted to carry out drink cures at home with Carlsbad and other waters instead of making the journey to the watering-place, and the same beneficial effect was hoped for. The late Professor E. Kuelz made some time ago a series of experiments on the subject, and many very exact repetitions of the same experiments have since been pub-

lished. Although a few positive results have been attained, most of the experiments have yielded negative results, and every physician now knows that he cannot by a long way expect from home treatment with Carlsbad water what Carlsbad itself promises, and often enough, indeed, performs. Lately much has been said about the water losing its properties when bottled. The doctrine of ions and the discovery of radio-activity has suggested this. It is possible that such things are of importance, but to base anything upon them now would be premature and would only provide a sheaf of wild hypotheses.

In the meanwhile we are not justified in regarding the drinking of the water in Carlsbad, etc., as the only effectual and determining factor.

The Carlsbad cure, which I will take as the type of all the others, must only be looked upon as a whole, if we would understand its beneficial influence on the health of diabetics and on the glycosuria in particular. The fact that we have to deal with is this: that many diabetics return from a Carlsbad cure greatly strengthened and refreshed and that their tolerating power for carbohydrates is raised to a considerably higher level for weeks and even for months afterwards. In order to be sure of this I placed many of my patients before the journey to Carlsbad on a very definite test diet; and when the cure was completed they were again put on the same test diet. As I have described elsewhere, the difference between the first and second series of results very often shows that a surprising diminution of

the glycosuria has occurred. There are, however, exceptions to the rule, and these I shall have to speak about later on.

The factors which may be taken into consideration in such a cure are the following:

1. Complete removal from the strain and worry of daily life, whether these troubles occur in the home or in the daily calling. I have already stated this to be an important factor which affects especially favourably the nervous components of glycosuria.

2. A long stay and plenty of outdoor exercise. I have, it is true, previously drawn attention to the fact that many diabetics stand strong and persistent muscular work but badly, and may even have their glycosuria increased by it. But for the category of patients who profit most from the Carlsbad cure, *i. e.*, for patients who are still strong—perhaps also somewhat obese or gouty—this certainly does not, as far as our experience goes, hold true. In them, almost without exception, the glycosuria either diminishes at once or after a very short time, viz., when they get accustomed to taking long walks. The whole musculature is strengthened at the same time; the total energy of the individual increases, and the mass of protoplasm which utilises the carbohydrates also gradually increases.

3. The diet in health-resorts in carefully regulated, although really strict diet-cures are not practised there, these having shown themselves not to be desirable, since the combination of the waters with a much restricted diet often leads to loss of power and nervous irritability.

Nevertheless the diet is usually much poorer in carbohydrates than at home. The doctor's orders with regard to diet are perhaps the same as, or very similar to, those previously given at home, but the orders are better attended to by patients who have nothing else to do but to devote themselves to the cure, while the time-honoured customs of the hotels in the place make it comparatively easy for the patients to follow the advice or prescriptions of the doctors. Herein is an important reason why the desirability of sending diabetics to certain definite places where already a certain tradition as to mode of life has established itself comes before us again and again. In numerous beautiful health-resorts in the mountains and at the seaside these conditions do not obtain, and a diabetic has always the greatest difficulty there, as far as diet goes, in getting proper attention.

4. The doctors there are well acquainted with the treatment of diabetes, and have also a knowledge of all its minor details, which, though appearing to be insignificant, are yet of the greatest importance for the effect of the whole cure. This factor must not be undervalued. In other health-resorts diabetics are rare visitors, and though doctors are eager enough to treat them, a number of the strangest and least well-formed experiments are made, such that one sees from them plainly that they are dictated by book-wisdom only, and not by personal experience.

5. By the internal use of mineral waters and by baths, etc., many complications of diabetes are favour-

ably influenced, and such improvements exert a good bearing on the progress of the whole disease and on the general health of the patient. I have especially in mind the numerous disturbances of the digestive system which in part represent quite independent complications, but which are in part called forth or maintained by the peculiar mode of life of a diabetic. To overcome these disturbances is one of the most important and most grateful tasks of the Carlsbad cures. The same is true for other complicating conditions, such as obesity, gout, uric acid diathesis, neuralgia, etc.

You see then that beside the drink cure itself, many other factors come into play to explain why it is that from the time-honoured Carlsbad and similar places we may expect more beneficial effects for our patients than from other holiday resorts.

At the same time it is necessary to guard against too high an estimation of all these health-resorts and watering places. Both doctors and patients are apt to regard them as the true means of cure of diabetes, so that the first discovery of the presence of sugar provokes the random advice: "Go to Carlsbad," etc. All these spas together, however, cannot produce a real cure; they are only desirable places of recreation for diabetics. By paying a regular visit to one of them, patients are prone to believe that they have in so doing fulfilled the most important part of what they had to make up their minds to do with regard to the disease. Against this way of looking at things which the *genius loci* to a certain extent suggests, an energetic stand must be made. It

is exactly the opposite that is right. Only a small, although it may be an important, part of the treatment is carried out in the health-resort. The fate of the patient is not decided there, but depends, apart from the benign or malignant character of the disease, essentially on the home treatment. Here are essentials:

1. The general regulation of mode of life. This applies equally to all chronic diseases. To hit just the right regulations for the patient must be the continual care of the family physician.

2. The regulation of the diet. This does not apply to any other disease to the extent that it does in diabetes mellitus.

As opposed to the hard and fast rules which it was customary to lay down in earlier days, it is now recognised that the diet must be carefully selected for every single case. The selection is based on extensive and careful investigations with regard to the influence which the food, and especially its carbohydrate and proteid components, has on the glycosuria, acetonuria and on the other products of metabolism. This important inquiry on which the whole diatetic treatment is based can very rarely be carried out with sufficient exactitude at home or in health resorts. It has to be supplemented by observation and treatment in sanatoria and hospitals. To have first stated this and to have put his words into action is the merit of the late E. Kuelz. The recognition of this principle is always being extended, and that means a great practical step in the progress of the therapeutics of diabetes.

3. *The Dietetic Treatment.*

(*a*) *Principles of this Form of Treatment.*—The dietetic treatment of diabetes may be based upon the experience gained from two groups of important facts:

1. If by therapeutic measures of any kind we can succeed in getting rid of the glycosuria in a diabetic, and in maintaining this aglycosuric condition for some length of time without his body otherwise suffering in any way, then the power of the diabetic organism for assimilating carbohydrates almost always increases. On the same diet the patient will excrete much less sugar than before. In one patient such an effect may be surprisingly good and of long duration, in another, slight and transient; but the result is noticeable and measurable in every case. Some of the numerous complications of diabetes improve *pari passu* with the aglycosuric periods, but of this I have said enough already.

2. If we do not combat the intensity of the glycosuria, or if we employ insufficient remedies against it, the power of assimilation for carbohydrates in the diabetic gets less and less—in some patients slowly and gradually, in others with disquieting rapidity. This decrease of tolerating power may, unfortunately, often occur in spite of the best treatment, but it is in every case visibly hastened by neglect of dietetic precautionary measures. At the same time complications of various kinds, especially degenerative processes, make unceasing progress.

I have already attempted to give a theoretical ex-

planation of these facts. Whether the theoretical interpretation is right or not, the future alone can decide; but there can be no doubt about the empirical facts.

Of all factors which diminish or abolish the glycosuria, the limitation or the complete deprivation of carbohydrates is without doubt the most important. If it were only a question of diminishing or getting rid of glycosuria in the treatment of diabetes, this factor alone would completely suffice for the attainment of good and brilliant results. But other things have to be taken also into account, namely, the formation of acetone-bodies, the behaviour of the stomach and intestine, the influence of the form of nourishment on the general comfort, on the condition of the nervous system and on the general strength of the body. It is men whom we have to treat, and not symptoms. Many deviations from the hard and fast lines of dietetic treatment laid down are therefore required in practice. It is not from books that we can learn to steer aright amidst the manifold difficulties which arise from the peculiarities of individual cases; personal experience also must be our teacher. Nevertheless we must in all cases keep to certain points of view, and the first rule that I must lay down is this: the reduction of the glycosuria to its smallest possible limit must be the goal that is never lost sight of. Deviation from this rule can be allowed or demanded when the dietetic measures taken to reach this end are evidently producing worse evils. We then have unwillingly to decide not to enforce it, but we must still hope that we

may later return to the more stringent measures. I cannot help expressing the opinion that the practitioner who has not this end continually in view cannot be regarded as providing the proper treatment for cases of diabetes. Only in quite hopeless cases may such an aim be forgotten.

(*b*) *The Recognition and Estimation of the Assimilative Capacity for Carbohydrates.*—Of all the food-stuffs, carbohydrates exert the greatest influence upon the glycosuria. It is essential in every case to determine the precise amount of carbohydrate which the patient can tolerate. We call this the *tolerating power* of the individual. Various methods may be chosen for such estimations, but it is well to employ one reliable and well-accepted method in order to obtain values which will permit comparing. I have introduced a " test diet " for this purpose, which is well approved and now almost universally accepted in Germany.

I divide the foods into two groups:

1. Principal articles of diet. These include substances which are practically free from carbohydrates. Foods and drinks of this group form the basis of the three meals of the day.

2. Accessory articles of diet. These include substances which contain carbohydrates.

Such a division of foods is also important for giving therapeutic instructions. For the purpose of the test diet I always at first choose white bread, and of this I commence wth 100 grammes per day, 50 grammes for breakfast and 50 grammes for lunch.

VON NOORDEN'S STANDARD TEST DIET

Breakfast.—200 grammes coffee or tea with one to two tablespoonfuls of thick cream.

100 grammes of hot or cold meat (weighed after cooking). Butter.

Two eggs, with bacon.

50 grammes of white bread.

Lunch.—Two eggs cooked as desired, but without flour; or any other *hors d'œuvre* free from flour.

Meat (boiled or roasted), fish, venison, or fowl, according to taste, about 200-250 grammes altogether (weighed when cooked).

Vegetables, such as spinach, cabbage, cauliflower or asparagus; prepared with broth, butter or other fat, eggs or thick sour cream, but without any flour.

20 to 25 grammes creamy cheese (such as Camembert, Brie, etc.); plenty of butter.

Two glasses of light white or red wine, if desired.

One small cup of coffee, with one to two tablespoonfuls of thick cream.

50 grammes of white bread.

Dinner.—Clear meat soup, with egg or green vegetable in it.

One to two meat dishes, as at lunch.

Vegetable dishes, as at lunch.

Salad of lettuce, cucumber or tomatoes.

Wine.

No bread.

Drinks during the day (exclusive of wine), one to two bottles of aërated water.

The total urine excreted during the twenty-four hours is collected, that of the day and of the night separately, and is examined quantitatively for sugar. Both the percentage contents, and more especially the whole quantity of sugar excreted in the twenty-four hours is noted.

Further investigations as to the quantity of acetone, oxybutyric acid, ammonia, nitrogen, follow as a matter of course. If on this fare, the only carbohydrate contents of which are the 100 grammes of bread, no sugar is excreted, the quantity of bread is then gradually increased until sugar does appear in the urine. If, on the other hand, sugar is excreted with this test diet, the patient is at first kept on the same fare until the daily quantity of sugar excreted has become nearly constant. Then the quantity of bread is gradually diminished. At each stage in the diminishing process we keep our patient on the same amount of bread long enough to allow the sugar excretion to get a constant value proper to this stage.

When the urine becomes free from sugar whilst there is yet bread in the daily fare, it is with a case of the so-called *slight form of glycosuria* that we have to do, and the testing has taught us at the same time how high the tolerating power of the patient is. One patient may be able only to tolerate the 100 grammes of bread, another perhaps 150 or 200 grammes, again another

only 80 or 50 grammes. The greatest differences occur in this respect, and it is only an exact knowledge of them which enables us to properly prescribe the diet regulations necessary for each individual.

When it appears from these test examinations that the urine only becomes free from sugar when bread is totally excluded from the dietary, we have then to do with the *severe form of glycosuria.* Here also there are many degrees. With some patients the urine becomes free from sugar as soon as the carbohydrates are absent from the food. With others this restriction does not suffice, and the quantity of proteid substances also must be considerably reduced before the urine becomes free from sugar. The first cases I call *moderately severe glycosuria,* the second ones *severe glycosuria.* In the *most extreme* cases the total exclusion of carbohydrates, even together with the reduction of proteid food, does not suffice to make the urine free from sugar.

Having become by careful investigations thoroughly acquainted with the influence of the food on the glycosuria, acetonuria, and on the general state of health of the patient, it is then time to make a few more special enquiries concerning matters which have great therapeutic significance—the influence of rest and muscular movement should be studied. Wide individual differences exist with regard to this matter. It is found that some patients can tolerate much more carbohydrate when they are taking plenty of exercise; with others this is not the case, muscular work doing them more harm than good.

The influence of the various times of carbohydrate intake should also be examined. Many diabetics are extremely sensitive to carbohydrates in the early morning, when they are taken into the empty stomach, while they can tolerate well the same or even very much greater quantities of carbohydrate taken at mid-day or with the evening meal. The tolerating power is usually greater in the evening than in the morning. Sometimes the carbohydrates are tolerated better when given in very small and frequent amounts during the day; in other patients, however, just the opposite occurs, and much less sugar is excreted if the whole quantity of carbohydrate is taken at one meal.

The toleration power for the various types of carbohydrate foods should also be studied, as the greatest variations occur in this respect. Some diabetics can stand the sugar in milk or in fruit much better than an equal amount in starch flour. Others can tolerate starch better. Differences also occur with regard to the various forms of amylaceous foods. A knowledge of these is important for the prescription of therapeutic measures. One often finds that the starch of oats or of potatoes is better tolerated than that of rye or of wheat. I shall have to return to this important fact later on. No theoretical explanation of it has yet been offered.

The influence of certain medicines, alcoholic drinks, and of mineral waters upon the most important constituents of the diabetic urine or on the general health should also be estimated. Thus all these special ob-

servations, the practical significance of which is quite obvious, have only an actual value, and may only be taken as a starting point for dietary regulations, when the relationship between the food on the one hand and the composition of the urine on the other hand has been previously determined. It is only in this way that a satisfactory basis for treatment may be arrived at, and the danger of treating a diabetic by schematic rules be avoided. Such schematic rules never hold good for more than a small number of patients; to the larger number their application results in harm.

When the estimations of the tolerating power and the additional investigations have been concluded, the treatment may begin. The greater the experience of the physician, the greater will be the variety of his treatments, and it will rarely happen that he gives precisely the same directions to two diabetics, so great are the differences between individual cases. I cannot, therefore, give you any prescription to suit all cases. I can only select certain groups of cases and specify for each the principles which, according to my experience of over some 2,500 cases, should be carefully observed.

(*c*) *The Diet in Slight Cases of Glycosuria.*—In all slight cases of glycosuria the patients must first go through a period of restricted diet, *i. e.*, one from which all carbohydrate is excluded. The duration of such a period may vary from two to three weeks. I advise this even for those cases in which the test for tolerating power showed that 100 or 200 grammes of bread could be borne without the onset of glycosuria. During this

period one succeeds in raising the tolerating power even higher than it was before, and in causing the retrogression of any degenerative changes of the different organs. After this period carbohydrate is gradually added to the food, use being made in doing so of the experience gained at the beginning with regard to the peculiarities of the case. Care must, of course, be taken that the amount always remains below the level of the toleration-limit as at first determined—for the greatest stress must be laid on the injunction that no more sugar must be excreted in future. This is the only way to protect the organism permanently from the dangers of the diabetic disease, and, if possible, to entirely controvert the diabetic disposition. It is advisable to direct the patients to abstain again from time to time, for a week or two, from all carbohydrate food. In all such periods of restricted diet care must be taken that the patients consume an abundance of fatty food, otherwise they become weak and thin. A weighing machine forms the best means for recognizing whether or not a restricted diet is being carried out in the right way. Small losses of weight are hardly to be avoided in the periods of restricted diet; but they should not exceed one pound during each week. The more practice and experience gained in the carrying out of strict diet, the more frequently can such small losses of weight be avoided, and one may even be rewarded by a considerable increase of weight.

Much has been said and written against strict diet cures. As far as slight cases are concerned—and it is

only of these that I am now speaking—all these objections are without justification. There is no need for the periods of restricted diet to be long, *i. e.*, of more than two or three weeks' duration. I myself was at one time somewhat shy of prescribing them, but I can now say that in slight cases of glycosuria they have never been attended by any evil consequences. There are three points I should like to discuss here:

1. It has been said that nervous people cannot stand the restriction of diet well. I have already shown that this is not true, and I should here like to emphasise once more that it is only a technical, not an essential, difficulty which stands in the way. Increasing experience teaches us how these may be overcome. The beneficial result is often very clearly evidenced in nervous patients, the whole gamut of nervous symptoms improving simultaneously with the diabetic condition.

2. It has been said that the restricted diet must not be allowed when albuminuria is present. I can only agree with this so far as to say that in the presence of marked albuminuria the restricted diet should not be ordered for any great length of time. Short periods, from two to three weeks, can, however, be most excellently tolerated, even when the albuminuria is a sign of true nephritis, which is by no means always the case with diabetics. The physician must in cases of albuminuria, of course, take special care that the quantity of proteids and of extractives is not inordinately increased; but this presents no great difficulties for one initiated into the technicalities of a diabetic cooking.

It frequently happens that during the first few days of the restricted diet the albuminuria increases somewhat, but after a few days it sinks again and often attains values which are considerably lower than those observed on a mixed diet. I could even quote many cases in which on the restricted diet, not only the sugar, but at the same time the albuminuria, completely and permanently disappeared. This is a sign to me that the disturbance of nutrition of the renal epithelia which leads to albuminuria is often the immediate consequence of diabetes, and is on a level with other degenerative changes, as, for instance, the changes we so often observe in the nerves and the skin of diabetics.

3. It has been said that the exclusion of carbohydrates leads to acetonuria and the formation of oxybutyric acid. This is quite true. But since in the last few years we have discovered that even in the healthy body, when carbohydrates are withdrawn from the food, acetone, aceto-acetic acid and oxybutric acid appear in the urine, this objection against the employment of the restricted diet has lost much of its value. It is true that during the first few days of the employment of the restricted diet marked reactions for acetone and for diacetic acid may be obtained. The same occurs in healthy men, only the opportunities for making such an examination in a healthy man are comparatively rare. Anyone not knowing these peculiarities of normal metabolism exactly is easily disturbed when, after the introduction of the restricted diet, he sees the dreaded reaction take place. He is afraid of driving

the patient straight into the stage of acidosis and coma, and immediately changes his dietetic plan. This is wrong. If with the exact knowledge of the physiological facts one continues unerringly the use of the restricted diet, the reactions of the acetone-bodies gradually become weaker and disappear completely after eight or ten days, just as they would do in a healthy man under the same circumstances. In the periods of restricted diet daily exact quantitative determinations of the amount of acetone-bodies must be made, for the qualitative ones are not sufficient. When these determinations show that the values remain within physiological limits, every danger is excluded. Cases of slight glycosuria do certainly occur in which the acetone-bodies increase far beyond these limits on the restricted diet, and then, of course, the greatest caution must be exercised. Under such conditions I should not like to be responsible for the further continuation of the restricted diet in a consulting or a general practice. In hospitals, or other such institutions, where we can keep the patients under continual observation, one can of course extend the time during which the restricted diet is taken, and then one often has the gratification of finding that the acetone-bodies gradually diminish in amount and regain their normal values. Here again, therefore, much depends on the observation and study of each separate case on its own merits. When this is done there need be no fear of the restricted diet leading by accident to the dangerous condition of acetonuria.

As you see from what I have said, the treatment proposed is an endeavour entirely to remove the glycosuria from cases of slight diabetes. In order that this end may be attained it is necessary that the doctor should not only conscientiously set to work to raise the toleration limits, but also that the patient himself and those responsible for his dieting should be well instructed in the choice of his food, as well as in the details of its preparation. The usual schematic division of foods into those which are forbidden and those which are allowed has proved itself by experience to be insufficient for the avoidance of marked errors. It is precisely for these reasons that the temporary treatment of the patient in a clinic or other similar institution is to be recommended. Here the patients learn by practical experience in a short time, and with an ease which is mere child's play, how they are to diet themselves in future, better than they could ever learn from theoretical admonitions. The pointing out of the tolerating power, which the patient usually follows with the greatest interest, has by itself an important educational and instructive influence.

I have said that the principles so far laid down apply to slight cases of glycosuria. But one cannot in practice draw the line between slight and severe cases where it is drawn in theory. One can only then attain complete and lasting absence of glycosuria by the use of the method described above, when at least 60 to 80 grammes of bread or a corresponding quantity of other carbohydrate can be well tolerated in the day.

When the quantity must be still further reduced in order to obtain urine free from sugar, one must in most cases give up trying to make this condition permanent. I know, it is true, a few diabetics who have contrived to keep themselves for months or even years free from sugar under such circumstances with the very smallest daily intake of carbohydrates. They form, however, an infinitely small minority. Usually it does not succeed, and then one must have recourse to a method which is the rule for cases of severe diabetes: 80 to 100 grammes bread, or a corresponding quantity of other carbohydrate, is allowed, and at the same time the intake of proteid is so much reduced that not more than 12 to 14 grammes of nitrogen appear in the urine. On this diet the patients of course excrete some sugar, and in order to counteract the harm caused thereby, an eight or ten days' period of the fully restricted diet, in which the urine again becomes free from sugar, should be intercalated after every fourth, fifth or sixth week. As a rule, one succeeds in this way for years in overcoming every impairment of tolerating power, and very often even a gradual improvement of this power takes place.

You will see that the measures which I am recommending for the treatment of slight forms of glycosuria are very stringent and demand energy, intelligence and strength of will on the part of the patient. This is not different from what is the case in all other chronic diseases, *e. g.*, in tuberculous diseases of the lungs, in diseases of the heart and of the kidneys. He

who wishes to protect himself permanently against the multitudinous dangers which lie dormant in even the slighter cases of diabetes must submit to these discomforts and restrictions. In opposition to the prevailing fashion, I consider that a much more stringent and consistent carrying out of rational diabetic treatment should be accorded to slight than to severe cases. For in the slight cases there is more to be gained and more to be lost. When everything is carried out in the way required, one may say indeed that slight diabetes is one of the least dangerous of all chronic diseases.

(*d*) *The Diet in Severe Cases of Glycosuria.*—The dietetic treatment of cases of severe glycosuria presents great difficulties from the practical point of view, but for a systematic representation of what is to be done the matter is fairly simple.

Wherever it is possible, I recommend in these cases also that the treatment should begin with a fairly long period of strict diet. In so doing, careful attention should from the first be paid to the proteid as well as to the carbohydrate constituents of the food. The intake of meat should be especially restricted (to about 200 grammes in the day, weighed when cooked). The albumen of eggs and of vegetables can be much better tolerated and affect the glycosuria much less. I have already mentioned this. One usually intercalates, soon after the beginning of the course of restricted diet, two or three days, during which the proteid fare is reduced to its utmost minimum. Such days I call vegetable

days or green days. It cannot be denied that the periods of strict diet at the beginning of the treatment involve certain dangers, in all cases of severe glycosuria, since the acetone-bodies very frequently increase to a disquieting amount. As a precaution against this danger, abundance of alkali must always accompany this restricted diet. Very exact observation and daily quantitative analysis for acetone-bodies is essential. A first longer period of restricted diet can in these cases hardly be carried out without danger, except in an institution (sanatorium, clinic, hospital). When, however, it has once been established how the patient's general health, the glycosuria and the acetone-bodies react to the restrictions, there is nothing to hinder shorter periods of restricted diet from being repeated at home. The dangers are small if the condition of the patient is rigorously and continuously controlled. I can well understand how it is that so many practitioners are afraid of the restricted diet in cases of severe glycosuria and well-developed acetonuria. I have myself had many failures with it, and at first these greatly discouraged me. But with increasing experience I have learned to avoid the dangers and to remain master of the situation in every moment of the strict diet cure, even when the patients at the beginning of the treatment excreted 100 grammes or more a day of oxybutyric acid. If the treatment with the restricted diet can be carried through successfully for two or three weeks, enormous advantages are, as a rule, obtained. The excretion of the acetone-bodies does, it is true, increase regularly in the

first week, but in the second and third weeks it usually sinks far below its original value. It is quite astonishing how much the muscular power increases and the general health improves; and almost always, when a diet containing carbohydrate is subsequently returned to, the glycosuria remains far behind what it was before the treatment was begun.

When this period of restricted diet is once got over, the further dietetic regulations are quite simple.

Usually, 80 to 100 grammes of bread, or a corresponding quantity of other carbohydrate are allowed, but special observations must be made to find out which kinds of carbohydrates are best tolerated and how best to distribute them over the day. The proteid permitted must remain permanently low; not more than 12 to 15 grammes of nitrogen should appear in the urine. I regard this continued limitation of the proteid as an important addition to our knowledge, gained by the investigation of the last decade. The glycosuria does not rise nearly so high under the influence of the definite quantity of carbohydrate allowed as when much proteid is given, and this makes it, technically, very much easier to provide proper nutrition.

This customary diet with small quantities of proteid and about 80 to 100 grammes bread must be frequently interrupted by intercalated days of diet free from all carbohydrate. I usually prescribe two or three days of this restricted diet and one green day, twice in the month. But no general rule can be laid down about it: it is sometimes better to have these short periods

of restricted diet closer together, or in other cases to let longer pauses intervene between them. By this intermittent treatment with periods of restricted diet, none of which lasts more than a few days, and which can neither harm nor weary the patient by becoming monotonous, the glycosuria is, to a large extent, held in check and the progress of the diabetic disturbance in metabolism is better opposed in this way than in any other.

Once or twice in each year the patient should, however, return to a longer period of restricted diet, which, of course, must be gone through with all precautionary measures and exact observation of details.

The question often arises as to whether it is more advisable to order such patients with severe glycosuria either a Carlsbad cure or a period of restricted diet of some duration. The question should not be put in this way. There is usually a distinct indication calling both for the one and for the other. The two things have quite different tasks to perform, and each works beneficially in its own way for the general health and strength. If it is desirable to unite the two, it is better, as far as my experience goes in cases of severe glycosuria, to let the diet cure follow the Carlsbad cure, while with slight cases of glycosuria incomparably better results are obtained by the reverse process, *i.e.*, by the diet cure preceding the Carlsbad cure. No theoretical explanation of this can be offered, but it is a noteworthy fact of experience.

I cannot conclude this part of my subject without

drawing attention to one kind of treatment of severe cases of diabetes which from a practical point of view is of extreme importance, although the theory of it leads us into great difficulties. A few years ago I introduced the so-called OAT CURE into the treatment of diabetes. It was quite accidentally that I came to recognise its significance. A few patients in my clinic were suffering from severe disturbance of the stomach and intestine. I therefore permitted them nothing but oatmeal gruel. To my surprise the glycosuria did not increase, but became much less than it had been on the very strict diet. This was the starting point for further investigation, which was carefully continued for two years before I ventured, three years ago, to publish the paradoxical fact. The oat cure, as now prescribed by me, consists in the daily administration of 200 to 250 grammes of oatmeal, best given in the form of gruel, every two hours; 200 to 300 grammes of butter and often about 100 grammes of vegetable proteid, or a few eggs, may be taken in addition. Otherwise, nothing else is allowed, except black coffee or tea, lemon juice, good old wine or a little brandy or whiskey. Such a diet is often disliked by the patient, but I have always succeeded in getting over this difficulty. After three or four days of it, follow one or two vegetable days. Often even in this short time the purpose for which it was intended is found to have been attained; in other cases the same performance has to be repeated two or three times. It appears to be advisable to let a few days of restricted

diet, or even one or two vegetable days, precede the oat cure; for, when it immediately supervenes upon a mixed diet, the desired effect follows rather late.

At the commencement of the oat cure treatment one notices, it is true, even in the most favourable cases, an increase of the glycosuria; but after a few days the sugar excretion diminishes, and the acetonuria even more so. During the oat days the urine may often be quite free from sugar, and if it is not entirely free, one may be fairly certain that it will be so in the succeeding vegetable days. The following table gives the details of one such favourable case. The estimations made before the oat cure was begun show plainly enough that it is a case of severe glycosuria combined with excessive acetonuria. With the most restricted diet it had not been possible to bring the sugar below 40 grammes; even on the vegetable days more than 20 grammes were excreted. In the course of the oatmeal treatment the urine became free from sugar, and it remained so on the subsequent return to the restricted diet. It even appeared that small quantities of carbohydrate could be well tolerated, whereas for several months previously there had been no question of such a thing.

Day	Sugar	Acetone	Ferric Chloride Reaction	Ammonia
1. Restricted diet..	50.4 grms	2.1 grms	++	3.2 grms
2. " " ..	48.3 "	2.4 "	+ +	3.8 "
3. " " ..	58.9 "	3.1 "	+ +	4.3 "
4. Vegetable day...	28.2 "	2.1 "	+ +	2.9 "
5. " " ..	20.3 "	1.9 "	+ +	2.8 "

Day	Sugar	Acetone	Ferric Chloride Reaction	Ammonia
6. Oatmeal, 250 grms	38.3 "	1.9 "	+ +	2.4 "
7. " " ..	40.3 "	1.3 "	+	1.6 "
8. " " ..	30.0 "	0.9 "	+	1.5 "
9. " " ..	20.1 "	0.6 "	+	1.1 "
10. Vegetable day ...	8.0 "	0.8 "	+	1.3 "
11. " " ..	2.3 "	1.2 "	+	1.8 "
12. Oatmeal	18.3 "	0.5 "	0	0.9 "
13. "	5.6 "	0.1 "	0	0.9 "
14. "	0 "	0.05 "	0	1.0 "
15. Vegetable day ..	0 "	0.1 "	0	0.8 "
16. " " ..	0 "	0.1 "	0	0.8 "
17. Restricted diet ..	0 "	0.15 "	0	0.7 "
18. " " ..	0 "	0.18 "	0	1.0 "
19. Same and 20 gms. bread	0 "	0.12 "	0	0.9 "
20. Same	0 "	0.13 "	0	0.8 "

I believe that a glance at this table, which is only one out of a large number showing the same thing, will suffice to show that a result has accrued which formerly would have been deemed impossible to obtain. Unfortunately, however, there are only relatively few cases in which the result is quite so surprisingly beneficial; in many others it is incomplete, although still satisfactory; in others again, no result at all is obtained. The following fact is noteworthy: cases in which the results of the treatment were most beneficial relate without exception to the very severe forms of glycosuria; many of them were in children or young people. On the other hand, the result was almost without exception a failure in cases of slight glycosuria, the exact opposite of what one might *a priori*

have expected. The *oat cure* rendered me immense service in severe cases, and I may even say that I have often succeeded in fending off incipient coma by its use. Another important experimental observation is, that one should under no circumstances allow other carbohydrates to be taken at the same time as the oatmeal; meat should also be strictly forbidden. These are all matters upon which we can offer no explanation at the present time, and which are in apparent contradiction to all our other experience with regard to diabetic glycosuria. The contradictions will certainly vanish in time. What I have described has been already personally confirmed by many observers; especially favourable reports have been given from those chiefly concerned with the disease as it appears in children. Others have been unable to obtain any benefit from its employment. This is quite comprehensible to me, seeing that amongst the nearly three hundred cases in which I have so far tried the oat cure, very many of this kind have occurred. I have already mentioned this. Positive results are, however, of much greater importance than negative ones in such a matter.

I must not neglect to mention that in a few cases the patients have developed œdema during the oat treatment, whereas otherwise, as we all know, the diabetics rarely exhibit œdema. This rare occurrence has but little practical significance, since the œdema has each time disappeared immediately after the cessation of the oat treatment. The administration of a

slight dose of theocin or diuretin, however, entirely prevents its appearance.

The enormous diminution of the glycosuria or even its complete disappearance, in spite of the very considerable amount of carbohydrate contained in the 250 grammes of oats (about 150 to 160 grammes oat starch), is not quite without analogy. Many years ago v. Duering described the same occurrence following the administration of nothing but rice food. His observations were unfortunately not very exact, and, therefore, at the time received but scant attention. Later it was stated that the glycosuria could often be strikingly diminished, even in severe cases, by restricting the diet of the patient to nothing but milk, given at first in very small and then in gradually increasing larger amounts. As far as my experience goes, a good result is very seldom attained, and much harm is usually done by such a treatment. Two years ago Mossé recommended a "potato cure," which in all essential points agrees with my "oat cure." Mossé also excludes all other carbohydrates at the time of the potato treatment, and recommends the reduction of meat to a minimum. I have thoroughly tested Mossé's statements and can confirm the fact that, with due attention to the principles laid down by him, potatoes can be much better tolerated than would be supposed from the amount of carbohydrate they contain. Mossé attributes the cause of this effect to the high percentage of potash contained in potatoes, but what he says on this point is hardly convincing. In com-

paring the potato cure and the oat cure, as I often did for the sake of comparison in the same patient, allowing the one treatment to follow the other, I became convinced of the decided superiority of the oat cure. Severe cases of diabetes react much more favourably on oats than on potatoes. I must, however, acknowledge that there are exceptions, and in appropriate cases I myself have gladly made use of Mossé's treatment. I must, however, express myself strongly against the view that a few panegyrists of the potato cure have maintained, namely, that it is a method for universal application. Such exaggerations belong, unfortunately, to the spirit of the age. They are misleading and harmful, and serve only too easily to bring into discredit things which doubtless are good.

Whether it is the rice cure of Duering, the milk cure, the oat cure or the potato cure, on which we fix our attention, we find that underlying them all there is a common principle—namely, the limitation of carbohydrate to *one particular* kind, excluding all others, and at the same time the exclusion or the maximal reduction of meat. It is to this point, which they have all in common, that investigation must be directed in order to explain the peculiar and paradoxical effect they produce. It would seem that the diabetic organism is able—temporarily at least—to regain the power of assimilation for one particular carbohydrate, while still unable to utilise the infinitely smaller amount of the various carbohydrates contained in ordinary food. In my laboratory we have tried to discover

whether under the circumstances mentioned particular diastatic or antidiastatic ferments which affect only one particular carbohydrate occur in the blood; but the investigations, so far as they have gone, have yielded no positive results. We are obliged to leave to the future the elucidation of this practically and theoretically important question.

Still I must once more emphasise the fact that those new methods, however obscure their fundamental principles may be, constitute an important advance in the practical treatment of diabetes; this is certain, especially of the oat cure, because the severe cases are chiefly benefited by its employment. It is of tremendous importance to possess, as in the oat cure, a means of mastering large quantities of acetone-bodies within a few days. Even though we may not be able to permanently maintain this favourable state of affairs, it is still of the greatest advantage to the whole organism to be given a period, of about a week or a fortnight, in which the tissues are practically free from acetone. I would now as little like to omit the oat cure in treating a severe case of diabetes as to omit the intercalated periods of strict diet of which I have already spoken. I am convinced that all my other colleagues will learn to appreciate the value of the oat cure; I must, however, beg of you to keep strictly to the directions given by me.

(*e*) *Concluding Remarks.*—In the therapeutic part of my lectures I have put before you in a condensed from the most important methods of combating this

uncanny disease. Drugs, muscular activity, treatment in health-resorts and in public and private institutions, and regulations of diet have been spoken of in turn. I fear that what I have said cannot have contained much that was new to my audience, but I hope that it may still have had a certain value because I have earnestly tried to arrange and to illustrate the material under discussion from the stores of a large personal experience. Of course I have only mentioned the most important principles; the many details which play a large part in the treatment of diabetic people could only be hinted at. In this connection, I must refer you to my other publications. But all detailed descriptions of treatment, except where technical matters are concerned, are only of subordinate value. They often do more harm than good because they are apt to lead the listener or reader into the error of slavishly following certain rules, rather than allowing himself, armed by the sure mastery of the important principles, to be guided in dealing with details by the peculiarities of the case, and thus creating a therapeutical piece of work as a result of his own deliberations. This is nowhere more important than in diabetes mellitus. A thousand-fold experience has shown again and again that just the slavish application of all the therapeutical details of one case to another case is the weak side of diabetic therapy, as well as the source of much mischief. If I have succeeded in convincing my audience on this point I have fulfilled one important object of my lectures.

Both the representation I have given you of the therapeutics, and more especially the picture that I have unfolded before you of the chemical pathology of the disease, must have shown you that, although in recent times we have made considerable advances, yet many large gaps in our knowledge and understanding still yawn before us. A number of great problems remain to be solved. Of these I may especially mention, as one of the most important and interesting, the problem concerning the actual production of sugar and the actual consumption of carbohydrate in slight and severe diabetes. This and many others are problems to the solution of which we can only approach by having a large material to draw upon and plenty of skilled assistance in making use of it. It is to this country where assistance to scientific investigation is given more freely and abundantly than elsewhere, and which in the two last decades has enriched the doctrine of metabolism with so many new facts, that science confidently turns in the expectation of further advances.

VII. APPENDIX (FOOD TABLES)

TABLE I

This table includes the foods which may be consumed by all diabetic patients. A few of them are not entirely free from carbohydrate ingredients, in the chemical sense of the word, but the quantities present are so slight that they may be practically disregarded. Such foods may therefore find a place in even the most restricted dietary. The majority of diabetic individuals may have as much of any of the following foods as they may desire; but if it becomes necessary for the intake of albumin to be diminished, then the practitioner must limit the foods containing large amounts of albumin: as meat, cheese, eggs, etc. There also are diabetics who cannot be allowed to take spices freely.

Fresh Meats.—All the muscular tissues of mammals and birds, braised, boiled or roasted with their own gravy, with butter, with meal or flour; free mayonnaise or other sauces made without flour—warm or cold.

Inner Parts of Animals.—Tongue, heart, lungs, brain, calf's spleen, kidney, marrow. Liver of calf, game and poultry up to 100 grammes (weighed after cooking).

External Parts of Animals.—Feet, ears, snout and tail of all edible animals.

Conserved Meats.—Dried and smoked meats, smoked and salted tongue, pickled meats, ham, bacon, smoked goose breast, American and Australian tinned meats, brawn, ox-chops.

Sausage.—All various kinds, if free from bread or flour.

Potted Meats or Meat Pastes.—Strasburg goose-liver, etc., provided they do not contain bread or flour—with home-made articles the absence of flour may be assured.

Albumin, Preparations of.—Somatose, sanatogen, casein, eucasein, nutrose, tropon, roborat, etc.

Meat Extracts.—Liebig's, Maggi's, etc.

Fresh Fish.—All fresh and salt water fish, boiled or grilled or served with flour-free sauce. Fresh melted or browned butter may be taken at the same time. If the fish is cooked in bread crumbs, the latter should be removed before eating.

Conserved Fish.—Dried, salted, or smoked fish, such as cod, shell fish, herring, mackerel, sole, plaice, salmon, sprats, eels, etc.; also pickled herrings, sardines in oil, mackerel in oil, anchovies, sardellen, tunny. Caviar.

Mussels and Crustacea.—Oysters, mussels, lobster, crab, turtle, crayfish, etc.

Meat and Fish Sauces.—The well-known English piquant or similar sauces; beefsteak, Harvey's, Worcester, anchovy, lobster, shrimp, Indian soy, China soy, etc., may be taken in small quantities, if not contra-indicated for special reasons.

Eggs.—From all birds, raw or cooked in various ways, but without added flour or meal.

Fat.—Of animal or vegetable origin, *e. g.*, butter, lard, fat of roast meats, margarine, olive oil, usual salad oil, cocoa butter, goose fat. Cod liver oil.

Cream.—Good fat-rich cream, sweet or sour, as drink or added to solid foods or to drinks (if not necessarily restricted) up to about 200 c.cm. a day. For cooking purposes cream may be substituted for flour when making special dishes of meat, fish, vegetables and eggs.

Baked Foods.—Very few baked foods are absolutely carbohydrate free. Those most nearly so are prepared partly from ground almonds, partly from gluten.

Known to the author are meal-free rolls of Callard and Company (65 Regent Street, London, W.).

Meal-free rolls of O. Rademann (30 Goethestrasse, Frankfurt on Main). They call them gluten-rolls or air-rolls. These have the advantage that they can be used when a month or so old; other varieties become uneatable after several days.

Dessert cakes of Groetsch (made by O. Rademann, Frankfurt on Main) prepared from almonds, cocoa and saccharin.

Almond bread to be obtained from the Conditorei Pokorny in Teplitz (Bohemia).

Fresh Vegetables.—Salads; lettuce, crisp and smooth endives, cress, dandelion, purslane.

Aromatic Herbs.—Parsley, dill, thyme, pimpernell, mint, leek, garlic, celery.

Fruits and Roots and Stalks.—Gherkin, tomato, young green beans, vegetable marrow, onions, rape-cole (so long as they are still green), radishes, sea-kale (in slight cases also root artichoke and stachys). White and green asparagus, hops, Brussels sprouts, Zichorie, English celery (except the root), young rhubarb sprouts.

Blossoms and Flowers.—Cauliflower, broccoli, Brussels sprouts, artichoke.

Leaves.—Spinach, sorrel, curly cabbage, white cabbage, red cabbage, butter-cabbage, savoy cabbage, red beet.

Fungi.—Fresh mushrooms, stone or egg fungi, morel, truffles in usual quantities.

Fruits.—Bilberries, unripe gooseberries, when prepared with saccharin instead of sugar.

Conserved Vegetables.—Asparagus, haricot beans, cut beans, salted gherkins, pickled gherkins, peppered gherkins, mixed pickles, sauer-kraut, olives, champignons and any prepared vegetables of those groups already mentioned.

Condiments.—Salt, white and black pepper, cayenne, paprika, curry, cinnamon, clove, nutmeg, English mustard, saffron, aniseed, caraway, bay, caper, vinegar, citron—if not otherwise contra-indicated.

Soups.—Meat soups prepared from fresh meats or meat extracts, with the addition of green vegetables, asparagus, eggs, fragments of meat, marrow, liver, Parmesan cheese or other foods contained in this table.

Sweets.—Prepared from eggs, cream, almonds, citron, gelatine, saccharin being substituted for sugar.

Drinks.—All varieties of spring and seltzer water. Good brands of brandy, rum, arack, whiskey, corn brandy, Kirschwasser, and other fruit spirits.

Wine.—All the well-known table wines (white and red) are almost sugar free—at all events those that have been kept for three or more years in casks. Bordeaux, Burgundy and Ahz wines come under this category. White Rhine, Moselle, Saar wines are also almost free from carbohydrates.

A large variety of wines, which, through long keeping in cellars, have become practically carbohydrate free, may be obtained from O. Rademann, 30 Goethestrasse, Frankfurt on Main, and Gebr. Steinbach, 8 Poststrasse, Frankfurt on Main.

The champagne which contains the minimal quantity of sugar is, in the author's experience, that of Ernest Irroy in Rheims (specially prepared and reserved for diabetics). The most of the other champagnes called dry or extra dry contain sugar.

Tea and Coffee.—With cream, but with saccharin substituted for sugar.

Cocoa.—Cocoa may be taken, if not specially contra-indicated. The quantity, however, should be restricted. 10 grammes of the pure cocoa of Van Houten or Stollwerk or 15 grammes of Rademann's cocoa for diabetics (sweetened with saccharin).

Lemonade.—Seltzer water with lemon juice, sweetened with saccharin or glycerin (lævulose may be used if specially permitted).

TABLE II

This table contains those foods which contain a very small, but still demonstrable quantity of carbohydrate. They must be prohibited during "strict" dieting. As a rule, however, all diabetic individuals may take one or the other portion of them daily. Each portion of the following list does not contain more than 3 grammes carbohydrate. The amounts will necessarily differ for each patient. If such determined quantities are taken, the permitted bread need not be diminished. For larger quantities see Table III.

Vegetables.—Cooked without the addition of sugar and flour. Dried white beans, dried yellow or green peas (whole or mashed) one tablespoonful. White turnips, red turnips, carrots, celery (root), scorzonera, stachys, green or preserved peas and beans, large broad beans, prepared as vegetables or salad; two tablespoonfuls.

Potatoes.—A small potato about the size of a large plum, or a tablespoonful of mashed or fried potatoes.

Rettig-radish.—A small rettig weighing about 50 grammes.

Nuts.—Up to about 50 grammes. About six walnuts or ten hazel nuts or eight almonds or eight para nuts.

Fresh Fruits.—Apples, pears, apricots, about 50 grammes. Raspberries, strawberries, black currants, a heaped-up tablespoonful. Wild raspberries, blackberries, two tablespoonfuls. Bilberries, three tablespoonfuls.

Cooked Fruits.—Prepared with saccharin instead of sugar. Mirabelles, damsons, plums, apples, pears, apricots, peaches, sour cherries, a heaped-up tablespoonful. Raspberries, gooseberries, blackberries, two heaped-up tablespoonfuls.

Dried Fruits.—Plums, damsons, peaches, well soaked in water, a heaped-up tablespoonful.

Milk.—1-10 litre.

Lævulose.—Chocolate, prepared by Stollwerk, 15 grammes.

Cocoa.—Without the addition of sugar, 15 grammes.

TABLE III

This table contains foods which are rich in carbohydrates. They cannot be used during a rigid dieting. However, for patients who are not upon a strict diet, they may sometimes find a place, but the quantities must be strictly defined. The quantities will vary for each case and should be regulated by the practitioner—according to the precise assimilative capacity of the patient.

We give the patient a definite quantity of white bread each day, say, for instance, 100 grammes. The whole, or part, of these 100 grammes may be replaced by any of the foods contained in

this table, the replaced quantity of white bread being then eliminated. The corresponding carbohydrate contents are herewith given in tabular form. Some diabetic individuals tolerate one form of carbohydrate food better than another. The relative numbers must then be altered to suit the personal idiosyncrasies.

In the following tables the carbohydrate content of white bread is taken as 60 per cent. starch flour, the average quantity ranging from 56 to 62 per cent. in Germany. The percentages here given are calculated in part from the average of Koenig's Analyses, in part from analyses made in my own laboratory.

The analyses marked with a star in the following pages have been made in my laboratory. To estimate the carbohydrate contents, the food substance was boiled with dilute hydrochloric acid; the reduced substance was then estimated after the method of Allihn.

In starchy flour foods the value is calculated as starch, otherwise it is expressed in terms of glucose.

TABLE OF EQUIVALENTS

I. Equivalents Table for White Bread

ARTICLE	Percentage of Carbohydrate	20 gms. of White Bread Represents	Remarks
Rye bread	about 50%	24 gm.	
Army bread	about 50%	24 gm.	
Stone cutter's bread*	about 50%	24 gm.	
Simons bread*	about 50%	24 gm.	
Pumpernickel	about 45%	26 gm.	
Graham brown bread	about 45%	26 gm.	
Rhenish black bread	about 45%	26 gm.	
Breakfast biscuit*	70%	17 gm.	Huntley and Palmer's.
Albert biscuit	88%	14 gm.	Huntley and Palmer's.
Triscuit* (Natural Food Co.)	70%	17 gm.	Niagara Falls Mills.

II. Special Breads for Diabetics

White bread*	30 %	40 gm.	O. Rademann, Frankfurt on Main.
Black bread*	38 %	32 gm.	
Zwieback*	45 %	26 gm.	
Cakes*	50 %	24 gm.	
Rolls*	25 %	50 gm.	
Oat cakes*	65 %	18 gm.	The numbers give the average of numerous estimations.
Graham bread	28 %	45 gm.	
D. K. coarse bread*	35 %	35 gm.	
Meal	51 %	24 gm.	
Almond bread (Dr. Lampe)	10 %	120 gm.	
Aleuronat bread*	33 %	37 gm.	Gunther, Frankfurt on Main.
Aleuronat Zwieback*	48 %	25 gm.	
Aleuronat cakes*	55 %	22 gm.	

Konglutin bread*	40 %	30 gm.	Fromm in Koetzschenbroda.
Ambrosius bread*	42 %	29 gm.	Gericke in Potsdam.
Double Porter bread*	33 %	37 gm.	
Double Porter Zwieback*	21.5%	57 gm.	
Sifar biscuit*	5.2%	240 gm.	
Sifar bread*	5.0%	240 gm.	
White bread	38 %	32 gm.	Salus, Braunschweig.
Black bread	35 %	35 gm.	
Kleber bread	50 %	24 gm.	Seidl. Munich.
Kleber Zwieback	45 %	27 gm.	

III. Parisian Breads for Diabetics

Bread in rolls	44 %	28 gm.	L. Blanc, 30 Rue St. Augustin.
Bread in flat loaves	46 %	27 gm.	
Pain sans mie	65 %	19 gm.	33 Avenue de l'opera, Panification nouvelle.
Soya bread	14.4%	80 gm.	Pharm. Desvilles, Rue Etienne Maral.

IV. Cocoa

Pure cocoa powder	30 %	40 gm.	Stollwerk or Van Houten.
Eichel cocoa	48.5%	25 gm.	Stollwerk.
Cocoa for diabetics*	18.5%	66 gm.	Platshek in Carlsbad.
Saccharin-chocolate	18 %	66 gm.	Hoevel, Berlin.
Lævulose chocolate*	55.6%	—	Stollwerk, Cologne. Of the 55.6 per cent., 50 per cent. consist of lævulose, the remainder being made up of other carbohydrates.
Cocoa for diabetics	12 %	100 gm.	O. Rademann.

V. Natural Flours and Meals

ARTICLE	Percentage of Carbohydrate	20 gms. of White Bread Represents	Remarks
Wheat, rye, barley, oat, maize, buckwheat, millet	75 to 80 %	15 gm.	
Beans, peas, lentils	38 %	20 gm.	
Soya beans	48.5%	25 gm.	Platschek, Carlsbad.
Gluten meal	7 %	170 gm.	Hundhausen, Hamm.

VI. Starch Flour

From potatoes, wheat tapioca, rice, sago, maize, mondamin	82%	14 gm.	

VII. Prepared Meals

Vermicelli, Macaroni	80%	15 gm.	
Vermicelli, macaroni for diabetics	55%	22 gm.	O. Rademann, Frankfurt.

VIII. Cereals

Oats	60%	20 gm.	
Barley	66%	18 gm.	
Rice	70%	17 gm.	

IX. Pulses

Peas, lentils, beans	53%	23 gm.	Dried seeds.
Peas, beans, broad beans	30%	40 gm.	In fresh condition.

X. Tubers

Potatoes (summer)	16 to 18%	70 gm.	
Potatoes (winter)	20 to 22%	60 gm.	
Celery	12%	100 gm.	
Chervil	28%	42 gm.	

XI. Fresh Fruits

Sweet cherries	10 to 12%	100 to 200 gm.	
Sour cherries	8 to 10%	120 to 130 gm.	
Mulberries	10 to 12%	100 to 120 gm.	
Apples	8 to 10%	120 to 150 gm.	
Pears	8 to 10%	120 to 150 gm.	
Damsons (German)	6 to 8%	150 to 200 gm.	
Strawberries	5 to 7%	170 to 240 gm.	
Gooseberries (ripe)	7 to 8%	150 to 170 gm.	After cooking.
Gooseberries (unripe)*	2 to 4%	500 gm.	
Black currants	6 to 8%	150 to 200 gm.	
Mirabelles	4%	300 gm.	
Round plums (German)	4%	300 gm.	
Apricots	4 to 6%	200 to 300 gm.	
Peaches*	4 to 6%	200 to 300 gm.	
Raspberries	4 to 5%	240 to 300 gm.	
Bilberries	5%	240 gm.	
Blackberries	4%	300 gm.	

XII. Fresh Fruits

ARTICLE	Percentage of Carbohydrate	20 gms. of White Bread Represents	Remarks
Cranberries	1 to 2%	600 to 1200 gm.	
Pineapples* (very sour)	8%	150 gm.	
Spanish oranges*	1.5 to 2%	600 to 900 gm.	Weighed, unpeeled, January and February.
Spanish oranges	2.5 to 3%	400 to 480 gm.	Weighed, peeled, January and February.
Oranges*	5 to 6%	200 to 240 gm.	March to May. Chiefly lævulose.

XIII. Fruits Preserved in Their Own Juice
(*Without Sugar*)

White cherries	6 to 8%	170 gm.	O. Rademann, Frankfurt on Main, Middle. Value of numerous estimations, 1897-1903. The analyses relate to the fruits themselves: The sugar rich juice should not be consumed. These fruits are of exceptional flavour.
Apricot	6 to 7%	175 gm.	
Gooseberries	2 to 4%	400 gm.	
Strawberries	5 to 7%	200 gm.	
Reine-Claude	5 to 7%	200 gm.	
Mirabelles	6 to 8%	170 gm.	
Apple	5 to 7%	200 gm.	
Pears	5 to 8%	200 gm.	
Bilberries	3 to 4%	400 gm.	
Damsons	6 to 7%	250 gm.	
Raspberry juice	1%	1200 gm.	
Fruits with sugar extracted* (several varieties)	4 to 5%	240 to 300 gm.	O. Rademann.
Fruits with sugar extracted*	3 to 5%	240 to 400 gm.	Remy und Kohlhaas, Erbach a Rh.

XIV. Milks

Milk	about 4.5%	about 275 c. c.	Numerous analyses.
Sour cream*	2.5 to 3 %	400 to 840 c. c.	
Sour milk	about 4 %	about 300 c. c.	
Kephir	about 2.5%	about 480 c. c.	

XV. Beers

Bavarian winter beer	3.5 to 4.5%	275 to 340 c. c.	
Summer lager beer (Bayern)	4 to 5.5%	215 to 300 c. c.	
Bavarian export beer	4.5 to 5.5%	215 to 275 c. c.	
Light Rhenish beer*	2.5 to 3.0%	400 to 480 c. c.	
Pilsener	3.5%	340 c. c.	Buergerl, Brauhans (Analysis April 11, 1891).
Pilsener export beer*	3.8 to 4 %	300 to 320 c. c.	
Lichtenhainer	2.0 to 2.5%	400 to 600 c. c.	
Grätzer*	2.1%	600 c. c.	

Example Showing the Uses of Table III. (I. to XV.)

120 gms. of white bread are permitted. This may be replaced by:

At breakfast, 35 gms. D. K. Schrotbrot, equals.....20 gms. white bread
At dinner, 42 gms. lentils (in soup), equals.....35 gms. white bread
At dinner, 120 gms. pears (raw), equals.....15 gms. white bread
During the day ⅓ litre of milk, equals.....25 gms. white bread
At tea or supper, 25 gms. of white bread, equals.....25 gms. white bread

120 gms. white bread