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ON

DIABETES MELLITUS

AND

GLYCOSURIA

BY

EMIL KLEEN, PH.D., M.D.

PHILADELPHIA
P. BLAKISTON'S SON & CO.
1012 WALNUT STREET
1900

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PREFACE.

Among the thousands annually visiting Carlsbad in search of health the diabetics present the greatest clinical interest, and from my first years as a practitioner in the Bohemian Spa I sought some relief from the monotony and many other unsatisfactory aspects of a practice of this kind in a careful study of the glycosuric dystrophy with its manifold complications.

Early in the nineties I conceived the project of publishing a book upon this subject, hoping thereby to fill a want in the medical literature of the day. Others, however, at about the same time undertook the same assiduous task. A few months after my reading, early in 1895, a paper on "Digestion, Metabolism, and Nutritive Needs in Diabetes" before the Swedish Association of Physicians,* v. Noorden's highly scientific work on diabetes was published, and almost simultaneously with the appearance of my own long-delayed book in the Swedish language, Naunyn's magnificent monograph was welcomed by the profession.

Still, the more than kind reception that has been accorded this book by the physicians of my native country has led me to entertain the hope that the most important part of my clinical, experimental, and literary work of recent years has not been entirely in vain. I resolved to give my book publicity in some more widely used language than the one most familiar to me, and myself, with some few additions and changes, translated my book into English. In doing this I derived considerable assistance from a dear American friend. Finally, Dr. Eshner, of Philadelphia, has revised the manuscript and added his most valuable aid to change my own

* See the "Transactions of the Association" ("Hygiea") for the same year, and the chapter on Metabolism in this book. In the latter I have added some references to the researches of the last few years.

somewhat deficient English into good English, for which work I hereby render my public thanks. For the substance and scientific matter of this book I am myself alone responsible.

I have treated the vast subject of diabetes and glycosuria with as much brevity as is compatible with my purpose of giving as full a view of it as the present time allows, never having out of sight that my chief aim is to facilitate for the general practitioner the acquisition of the knowledge of the glycosuric dystrophy, to which I have devoted considerable time and work.

At the end of the book I give a list of names of the chief authors on the subject of diabetes but no list of their works, as this alone would fill a small volume, and now that we have the "Index Medicus" and the "Catalogue," seems to me entirely superfluous.

EMIL KLEEN.

CARLSBAD, September, 1899.

CONTENTS.

Chapter		Page
I.	Definition and History,	9
II.	Geographic Distribution and Etiology,	15
III.	Glycosurias,	26
IV.	Symptoms and Complications of Mild and Severe Diabetes,	70
V.	Diabetes Infantilis,	157
VI.	Diabetes Mellitus Following Extirpation of the Pancreas,	164
VII.	Metabolism and Nutritive Needs,	169
VIII.	Investigation of a Case of Diabetes,	236
IX.	Treatment,	253
	Table of the Commonest Kinds of Food in Percentages of Proteid, Fat, and Carbohydrate,	295
	Personal Register,	299
	Index,	307

DIABETES MELLITUS

AND

GLYCOSURIA.

CHAPTER I.—DEFINITION AND HISTORY.

Under the name *diabetes mellitus* are included different pathologic conditions which, however imperfectly understood, undoubtedly in most cases affect the central nervous system, and which are characterized by a faulty metabolism, as a result of which, under ordinary diet, there takes place the excretion in the urine of an abnormally large amount of sugar.

Thus, diabetes mellitus, so far as is at present known, is not a clinical unit, but a syndrome, the chief and most constant symptom of which is glycosuria, and which is represented by very varying clinical types.

There are, however, numerous cases attended with the excretion in the urine of minute yet distinctly pathologic amounts of sugar, which cases differ widely in clinical aspect and in prognosis from the diabetic type, and which generally are not included in the designation diabetes mellitus.

When the power of consuming the ingested and digested carbohydrates is but little or momentarily impaired, and when the pathologic excretion of sugar, under ordinary mixed diet, only slightly exceeds the traces of sugar found in normal urine, or is but transitory, the condition is not called diabetes mellitus, but *simple glycosuria*.

When the excretion of sugar becomes considerable and more persistent, but disappears when the carbohydrates are decreased or

withdrawn from the food, the condition, which generally is accompanied by other more or less well-defined symptoms, constitutes the *mild stage of diabetes.*

The *severe stage of diabetes* is characterized by the occurrence of glycosuria even when the carbohydrates are withdrawn from the food.

We shall find that the limits thus fixed are far more distinct on paper than in the reality of clinical experience, in which we see represented all imaginable intermediate stages between the normal capability of consuming the sugar of the blood and the greatest possible deterioration of this capability.

Our knowledge of diabetes has essentially developed during the nineteenth century, but for many ages previously something was known of it, as is shown in notices occurring here and there in ancient works.

The term diabetes (*διαβήτης*: *διά*, through; *βαίνειν*, to go) is attributed to the Roman, Celsus, who lived in the beginning of the Christian era. The term then probably comprised both diabetes mellitus and diabetes insipidus.

In the Indian Yajur-Vedas we find definite statements upon this subject, and it seems from these ancient documents, discovered about a hundred years ago, that Susruta, whose existence was passed in the native land of the cobra, the Brahman, and the tiger during the seventh century, was familiar with both the clinical picture and the sweet urine of diabetes mellitus, which probably then, as now, was more general among the Hindus than among any other race.

Europe was far behind India in knowledge of diabetes mellitus during those times. As is always the case, single instances occur of correct guesses long before science had acquired the facts. Paracelsus suspected that a change in the blood is the cause of the symptoms of diabetes. It was, however, not until as late as 1674 that the sweet taste of the urine was first noticed by Thomas Willis (1622–1675), and a whole century more elapsed before Dobson showed that this sweetness is due to a variety of sugar. The idea of the presence of sugar in the blood of diabetics then began to gain ground, and we find this opinion general at the commencement of the nineteenth century. Rollo and Cruikshank accepted the existence of blood-sugar in diabetes; but Nicolas and Gueudeville, Segalas and Vauquelin, as also Sobeiran, tried in vain definitely to demonstrate its presence. Wollaston at first (1811) denied, but afterward acknowledged, its existence. Maitland and Ambrosiani (1835) believed they had found it. McGregor observed fermentation of diabetic blood, and Simons found in the blood of a diabetic patient after a hearty meal 0.25 per cent. of sugar, although only traces had been present before the meal.

All of these observations, however, concerned diabetes exclusively; but as early as 1826 Tiedemann and Gmelin deemed sugar a normal ingredient of the blood, and considered that they had proved its presence in dogs, whether

the animals were fed with carbohydrates or with meat. Early in the forties this observation was confirmed by Magendie and by Frerichs, and in 1845 Thomson, by fermentation, made (far too low) a determination of the sugar in the blood of fowls.

At the close of the forties Claude Bernard began his all-important investigations, which proved successively the presence of sugar in the normal blood under all dietetic conditions; its production from glycogen in the liver; its dependence on nervous influences; its increase above the normal ratio in cases of diabetes, and many other facts, a knowledge of which is essential for a comprehension of diabetes mellitus, and to which we shall have to return in the chapter on Metabolism.

The enormous amount of work afterward performed in this field by others has, on the whole, simply served to prove the correctness of Bernard's observations and conclusions, and it is only within quite recent times that experimental pathology has provided us with any material additions to what that most admirable physiologist taught us.

In 1848 Traube observed that sugar disappeared from the urine of a diabetic patient when carbohydrates were withdrawn from his food, and that the same individual exhibited glycosuria at a later period, in spite of this withdrawal. He thus discovered the difference between the mild and the severe stage of diabetes, on which others, especially Seegen, afterward attempted to found a division into two different forms of disease.

Toward the close of the fifties Brücke and Bence Jones, independently of each other, found small traces of sugar in normal urine, an event of importance chiefly because it led to further investigations for small amounts of sugar in urine and brought to light many instances of slight glycosuria, pathologic though often unessential, that present themselves under different conditions. Our knowledge of the simple glycosurias, however, has been chiefly developed during the last two decades, and is still increasing year by year.

Gerhardt, in 1865, discovered that a solution of ferric chlorid causes a wine-colored reaction with the urine of patients suffering from severe diabetes. This observation has proved of immense importance, as it greatly facilitated the diagnosis of severe diabetes and promoted the study and the comprehension of certain pathologic metabolic products, and of those acid blood-toxins that essentially invest the severe stage of diabetes with its clinical peculiarities.

Lavoisier had, in the latter part of the eighteenth century, laid down the principles of metabolism, but it was not until the middle of the present century that our knowledge of this most important subject began rapidly to develop through the works of Liebig, G. Lehmann, Bidder and Schmidt, Bischoff, Reignault and Reiset, and others. In 1867 Pettenkofer and Voit—though they themselves at first misinterpreted their own results—taught us that the consumption of oxygen, the excretion of carbonic acid, the production of heat, and the nutritive needs in the diabetic are governed by the usual laws, and that they are not attended with other deviations from the normal than those that arise directly from the loss of sugar through its excretion with the urine. When, later, Rubner (in the middle of the eighties) gave us his calorimetric tables of the nutritive value of different articles of food, the conditions were

fulfilled for arranging a rational diet for diabetics, as for others, and we have been enabled more effectually to obviate the mistake of dieting diabetics, with the one view in mind of eliminating hyperglycemia and glycosuria, and with out due regard to dietetic possibilities and to nutritive needs.

In 1886 von Mering discovered phloridzin-glycosuria, which is curiously characterized by the excretion of large amounts of glucose, with a *diminished* quantity of sugar in the blood. Three years later von Mering and Minkowski, thanks to the great accuracy of their mode of investigation, had the good fortune to discover that severe diabetes can be produced by total extirpation of the pancreas—the one "artificial" method at present known of bringing about with certainty this variety of diabetes. By reason of these two discoveries, and in view of the far-reaching consequences of the latter, von Mering must be considered as the investigator that, next to Claude Bernard, has contributed most effectively to our knowledge of diabetes mellitus.

During the last few decades an extensive literature has accumulated, and many valuable contributions have been made to the knowledge of this dystrophy. In addition to those already mentioned, a great number of authors have distinguished themselves in this connection, among whom I may name Frerichs, Bouchardat, Cantani, Seegen, Pavy, Bouchard, G. A. Hoffmann, Griesinger, E. Kütz, von Voit, Naunyn, Ebstein, Chauveau and Kaufmann, Lépine, Weintraud and von Noorden—passing over no small number of others who have written more or less important works on the subject.

Diabetes mellitus, being in its "mechanism" a peculiarly mysterious disease, with an undiscovered, or at least not fully explained, pathologic anatomic basis, has been made the subject of many theories, at present amounting to more than thirty. In no other department has medicine made such extended excursions into the domain of purely speculative science, and nowhere has this led to greater liberties with the imagination. It is not my intention in this work, which is designed for the practitioner, to enter upon a consideration of all of these thirty theories; but in order to show how weak and uncertain our search for truth has been in this field, and how many different theoretic possibilities present themselves, I will cursorily mention the main currents of opinions that have prevailed.

In former times the cause of diabetes was looked for in those organs whose functions show the most manifest abnormity—*i. e.*, the kidneys. This idea, in all its naïveté, has been to a certain degree revived, though with numerous modifications, additions, and limitations by our views on phloridzin-glycosuria, and by the auxiliary influence on the excretion of glucose, attributed on strong grounds by many authors to the kidneys.

Rollo, the greatest authority on diabetes at the beginning of the present century, supposed the cause of the dystrophy to be *a disturbance of the digestive functions*, which resulted in an excessive resorption of carbohydrate. Similar opinions, however absurd they may seem at present, have been expressed quite recently by many authors, and, among others, by no less an authority than Bouchardat in his earlier days. The importance in the causation of diabetes of changes in the pancreas was suspected long before Lancereaux wrote his paper on this subject, and before we knew the effect of total extirpation of the pancreas, and could assign to this organ a rational position in the pathogenesis of diabetes. An intuition of such a relation was at the bottom of the views of Bouchardat and others, and later found expression in Popper's idea of faulty digestion, in consequence of a *defective* secretion of the pancreatic juice as a cause of diabetes mellitus.

Since Bernard's great discoveries and his theory of the formation of the sugar of the blood in the liver from glycogen, and of its consumption in the tissues for the production of vital force, two great schools have arisen, in each of which several divisions are apparent. One of these schools considers the cause of hyperglycemia and glycosuria—*i. e.*, of diabetes—to be a *diminished consumption* of sugar in the tissues. For the sake of brevity, we may be permitted to say that the other school considers the cause to be an *increased production of sugar* in the liver. According to some views, this excessive production, however, is of an entirely passive kind, and is more correctly expressed as a diminished capability of the organ of transforming into, and storing as, glycogen the sugar conveyed to it through the portal vein, so that a larger part of the sugar reaches the circulation by the hepatic veins than can be stored in the muscles as glycogen, or be consumed by them. A large number of authors consider this view corroborated by the frequency with which sugar appears in the urine in cases of cirrhosis of the liver. A positive participation on the part of the liver may also be conceived. Claude Bernard and his numerous followers believe this to consist in increased activity of a normal function pathologically excited by hyperemia. Pavy and Schiff thought the production of glucose in the liver an entirely pathologic phenomenon. In both views a diastatic ferment and a central nervous influence transmitted through the vasomotor nerves are accepted. The latter influence must be given a place in every general theory of diabetes.

Those that have conceived the idea of defective consumption of the sugar of the blood have either accepted the disappearance from the organism of a ferment that normally should cause decomposition of glucose into glycerin and its aldehyd, and the cessation of which embarrasses further oxidation (Schultzen, Schermetjewski, Nencki and Sieber, Bence Jones), or have thought of defective oxidation in the lungs (Araki), or have placed the fault with the muscles (Zimmer). Since the theory of an "internal secretion" of the various glands of the body was adopted, and the production of diabetes by total extirpation of the pancreas was demonstrated, a large number of scientists have come to consider the cause of diabetes to be the disappearance from, or the diminution in, the blood of a "glycolytic ferment," present normally, and sent into the blood by the pancreas for the combustion of glucose.

There are, moreover, a considerable number of observers who have supposed that there takes place a diminution in, or a retardation of, the entire "internal respiration," which goes on in all of the tissues,—an opinion which at first obtained some support from Pettenkofer and Voit's experiments on metabolism in diabetes by reason of their erroneous interpretation of their results (Cantani, Jaccoud, Bouchard, Lecorché, Naunyn, Huppert).

Diametrically opposed to this opinion is another advocated by Robin, who speaks of an increased metabolism, of a "*suractivité de la nutrition.*"

In this cursory retrospect I wish to mention also Ebstein's carbonic-acid theory, which, however ingenious, entirely lacks support in facts. Ebstein placed reliance on the incorrect but once wide-spread supposition that a diabetic *ceteris paribus* always consumes less oxygen and produces less carbonic acid than a healthy individual. The carbonic acid he supposed to act as a check on the diastatic (glucose forming) ferment, and also to render certain proteids—especially globulins—more tenacious. Thus, when the carbonic acid —in consequence of a defect in the protoplasm, with resulting disturbances of the "internal respiration"—is lessened in diabetes, in the first instance and in the milder stage of the dystrophy, the carbohydrate—*i. e.*, glycogen—is attacked by the diastatic ferment more vigorously than under normal conditions. In the severe stage the globulins are also decomposed more readily, and an excessive formation of glucose begins at their expense. After Schierbeck's investigations on the diastatic ferment in alkaline and acid solutions, Ebstein and Schultze, in 1893, came to the conclusion that carbonic acid in alkaline solutions *augments* the diastatic activity, and retards it in neutral solutions, while even a very slight degree of acidity inhibits it altogether. It is rather difficult to understand how these facts, together with the qualities of the blood under normal conditions and in the presence of severe diabetes, could be made to fit in with Ebstein's theory, which, moreover, falls to pieces in the face of the fact, now fully proved, that the diabetic produces as much carbonic acid as a healthy individual. Ebstein's citation, in support of his theory, that Hoesslin found a sojourn at a high altitude, which had been considered as increasing the production of carbonic acid, to be favorable for the diabetic, is an unfortunate one, as Hoesslin's experience in this respect, at the time his treatise was written, was limited to a *single* case. On such a foundation not even a supposition should be hazarded on the subject of diabetes, and far more reliable facts indicate that residence at great heights does not in any way counteract diabetes. (See the following chapter.) The opinion that a sojourn at a high altitude in rarefied air materially increases the production of carbonic acid (Mermod, Marcet) does not seem to be borne out by facts. U. Mosso came to the conclusion, a few years ago, from investigations conducted on Monte Rosa and in rarefied air, that the quantity of carbonic acid produced in respiration under these conditions at an altitude of 6400 meters differs but slightly from that produced at an altitude of 286 meters (Turin).

Of late years there have been advanced in France—where, since Bernard's time, diabetes mellitus has been the object of constant study—theories concerning its pathogenesis, in which the nervous system, the pancreas, and the liver are all involved. Even if these theories can not as yet be said to be

more than hypotheses, they are nevertheless founded on definite observations and are of actual interest. I shall, therefore, return to them in the chapter on Metabolism, when we shall see that the theories of an increased production and of a decreased consumption of sugar both have solid bases, and that they ought not to be pitted against each other as utterly irreconcilable. To the present comprehension of special pathogenetic factors in the dystrophic group, the future will assuredly bring many additions and corrections, and the present generation will, perhaps, in time be forced to confess that "all our wisdom was but folly."

CHAPTER II.—GEOGRAPHIC DISTRIBUTION—ETIOLOGY.

Diabetes mellitus is a common phenomenon among civilized humanity,* and is constantly increasing in frequency *pari passu* with the intensity of cultivated life.

Some time ago I saw it stated—I believe it was by Worms—that among men occupied in intellectual pursuits (statesmen, learned men, professional men, merchants) of an age between forty and sixty no less than ten per cent. are diabetics. Most physicians will be inclined to protest against this figure as far too high, as it is, if by the expression diabetic is meant a person that displays a clinical type of diabetes. It would be nearer the truth to place the number of diabetics among the classes named at one per cent. On the other hand, if we call every person a diabetic that, taking ordinary food, excretes habitually and daily an inconsiderable though pathologic quantity of sugar in the urine, Worms' figure would be rather too low than too high. If samples of urine be taken an hour after dinner from a hundred brain-workers between the ages of forty and sixty, it will doubtless be found, on testing with Nylander's solution, or with Trommer's test, verified by the fermentation-test, that about fifteen of the hundred samples contain an amount of sugar

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* In animals diabetes mellitus—unless designedly caused for experimental purposes—is very rare, but it has been observed in the ape (Leblanc, Beranger-Férand), the horse (Hübner), and the dog (Thiermesse, Schindelka). Slight glycosuria has also been noticed in animals.

that attains to hundredths of a per cent.—*i. e.*, are distinctly pathologic. It will, however, also be found that the greater part of the "patients" in question consist of quasi-healthy, or, to use a better expression, very slightly affected, persons, who neither for the moment present, nor are likely in the future to present, decided symptoms of the clinical type that we are accustomed to call diabetes.

Among the European and the American, Aryan, highly civilized races, the difference in the frequency of diabetes, on comparing large areas, will not be found to be very great: not greater than it may be in different parts of the same country. Different conditions of life—altitude, climate, and state of culture, even within very narrow limits—give rise to very considerable variations. Thus we find that diabetes is more common in Malta and Gibraltar than elsewhere on the shores of the Mediterranean, in Tuscany than in the rest of Italy, in Normandy than in the other provinces of France, in Vermont than in the other States of the Union.

The statistical figures that are available are assuredly far too low, as the diabetic type is often not very pronounced, and in the milder form does not cause death, except through complications which have no definite relation to diabetes. Moreover, these figures have doubtless been obtained in very different ways in various places, and allow of no absolute comparison. On learning from Saundby that the number of deaths annually from diabetes mellitus per 100,000 inhabitants is in London 5.88, in Berlin 5.04, in Paris 9.6, in Christiania 3.9, in Rome 1.67, in Malta 13.1 (the highest European figure), we can scarcely conclude with certainty that the *correct* figure for Berlin is higher than the *correct* figure for Rome, for which latter city the figure cited is assuredly far too low. In Malta, however, diabetes is undoubtedly very common.

In Norway, among 10,000 deaths, 21 are owing to diabetes mellitus (Kiær).

There is scarcely any doubt that in large communities diabetes mellitus is rapidly increasing. According to Bertillon's statistics (cited from Lépine), diabetes caused the following deaths per annum among 100,000 Parisians:

From 1865 to 1873, a total of	2.3	From 1885 to 1886, a total of	11
" 1873 " 1877, "	4	" 1887 " 1892, "	12.13
" 1878 " 1883, "	9		

In Copenhagen the mortality from diabetes has also increased rapidly and constantly during the past few decades. From 1860 to 1864, according to Caroe, there was but one death per 62,840 inhabitants, while from 1890 to 1894 there was one per 12,855.

Purdy's statistics for the United States are demonstrative and show :

In 1850, 72 per 10,000 deaths.	In 1870, 170 per 10,000 deaths.
" 1860, 98 " " "	" 1890, 191 " " "

Purdy, undoubtedly with due cause, ascribes the enormous increase after 1860 to the rapid increase of prosperity, the luxurious mode of life, and the more arduous struggle for existence after the Civil War.

Of all *races*, the Hindu is most susceptible to diabetes. In India and Ceylon diabetes is a very common disease among the upper classes,—so common that, according to the editor of the " Indian Medical Gazette," almost every family in Calcutta belonging to these classes of society has lost one or more members by death from this dystrophy, while another author (Bose) estimates the number of deaths from diabetes in Calcutta at 10 per cent. of the entire mortality (!!!),—a circumstance that must be attributed to the highly nervous constitution of the Hindus, their early marriage, and excessive sexual life in general, the high intellectual culture at present prevalent in India among these classes, their sedentary mode of life, and perhaps also their diet, so rich in sugars and other carbohydrates. The preponderance of male over female patients seems to be at least as great as in Europe. Among the Mohammedan population in India diabetes, though not rare, is not nearly so common as among the Hindus.

Next to the Hindus the Jews—who in many respects occupy the same relative position to Europeans in general as do the Hindus to the Jews—are highest in the scale of diabetic frequency. No specialist in diabetes can avoid noticing the comparatively large percentage of patients among Hebrews, who also are a nervous race, and who for centuries have devoted themselves almost exclusively to intellectual and sedentary pursuits.

It has been of interest to me to form some estimate of the frequency of diabetes among the Chinese, who seemed to me, during the few weeks I spent among a vast number of their race, to be a nation with a highly developed intellectual, but comparatively slightly developed emotional, life, rather difficult of comprehension for any other than a Chinaman. Saundby's statements seem to prove that diabetes is very rare among Chinese laborers. Graham, who at Sumatra practised among 15,000 of them, discov-

ered but a single case during his seven years' sojourn. In the United States, I have myself, from various sources of information, come to the conclusion that the disease is far more uncommon among the lower classes of the Chinese than among the same classes of Americans and Europeans. On the other hand, Dr. Cantlie, who for many years has practised in Hong Kong, has kindly informed me that among the *richer* Chinese diabetes is not at all uncommon, adding the interesting information that it more especially attacks those that change from the usual Chinese diet, with its preponderance of rice, to a more mixed European diet. I presume this observation to be perfectly correct;—just as I have repeatedly found that in cases of very slight glycosuria I can cause a larger quantity of sugar to appear in the urine by mixed test-meals than by those that consist exclusively of carbohydrates.

Among the contented Japanese, whose education has hitherto been Spartan in many respects, diabetes is not common. If, as is probable, they ere long provide reliable statistics, it will doubtless be seen that with the nation's wonderful and rapid adoption of European culture, the frequency of diabetes will quickly increase.

Among the Persians diabetes is said to be less general than among Europeans, and the same is stated of the Turks (Tholozan). Among the Arabs of the part of North Africa under French sway the dystrophy is not rare (Calmette and others).

It is interesting to learn that among the laborers on the sugar-plantations of the Mauritius and British Guiana, where, relatively speaking, the lower classes consume an enormous amount of cane-sugar, diabetes mellitus is rarely encountered (Blair, Saundby). From Venezuela the same statement has been forwarded to me. Almost all these laborers are "colored" and belong to those races among which diabetes mellitus is uncommon as a general rule. Circumstances, however, seem to indicate that a strongly saccharine diet has *per se* but little etiologic influence.

Among all people beyond the pale of culture, diabetes is very rare. This I believe to be the correct way of viewing the aforementioned immunity among Africans, and the reason why so little is heard of diabetes among the Indians of America, or among the numerous and various aborigines of Australia, or in the English

colonies of mixed but predominant colored population. With greater intellectual exertion, keener emotions, higher nervous development, more earnest struggle for existence, more urgent demands, a more intense culture, in fine, we are bound to find more diabetes mellitus.

From what we have already learned we should *a priori* be inclined to believe diabetes to be far more common among a given number of residents in cities than among the same number of persons in the country. There is, therefore, nothing remarkable in the large number of statements that support such a supposition. On the other hand, it is an interesting fact that statistics point, in some degree, in the opposite direction. In Great Britain there are several counties with a large urban population which are low in the scale of diabetes, while others with a far greater rural population are high in the scale. Purdy has compared the figures in the United States, and has come to the conclusion that in the North diabetes is more general among the rural population, and in the South among the urban population ; and he ascribes this difference to the better protection against cold afforded by the cities as compared with the country, which holds good only for the North. In the South other differences determine the result. These, in my opinion, do not, as Purdy supposes, consist in the better oxidation secured through the country air, but in the mode of life of the inhabitants of the country, which, as a general rule, is far more free from nervous influences. Except during the first decades of life, when diabetes mellitus is very rare, and attacks fully as many, or perhaps more, girls than boys, this dystrophy is far *more common among males than among females*—naturally, in consequence of the severe struggle for existence on the part of men, and their greater proneness to excesses. The difference plainly appears in the second decade, and is manifest in all following decades. Generally, there are three times as many male patients as female. Exclusive of the ages under twenty, Pavy had 928 males and 373 females ; Grube had 137 male and 40 female cases, while my own experience shows nearly three male to every female patient.

Diabetes is rare in childhood and youth, the greater number of the patients being attacked during the most exacting period of their life—from forty to sixty years of age.

Pavy's* table shows :

Age.	Male.	Female.	Total.	Male.	Female.	Total.
Under 10, . .	3	5	8	0.22 per cent.	0.36 per cent.	0.58 per cent.
From 10 to 20,	35	22	57	2.57 "	0.61 "	4.19 "
" 20 to 30,	69	28	97	5.07 "	2.05 "	7.13 "
" 30 to 40,	154	70	224	11.32 "	5.14 "	16.47 "
" 40 to 50,	260	79	339	19.11 "	5.80 "	24.92 "
" 50 to 60,	281	137	418	20.66 "	10.07 "	30.73 "
" 60 to 70,	138	44	182	10.14 "	3.23 "	13.37 "
" 70 to 80,	25	9	34	1.83 "	0.66 "	2.49 "
" 80 to 90,	1	. .	1	0.07 "	. .	0.07 "

A mild and warm *climate* seems to give rise to less diabetes than a severe and cold one. High *altitude* tends to increase the frequency of diabetes. The mortality among diabetics is also greater during the *cold* than during the warm season.

The diabetic patient of Northern Europe passes the winter on the Riviera with decided advantage to his health, and his brother in misfortune in North America derives benefit from a sojourn in Florida, or in Southern California, during the severe cold season. Statistics from the United States speak strongly for the unfavorable influence of rigorous climates. According to Purdy, Vermont, with 6.3 deaths from diabetes per 1000 deaths, stands highest in the scale among all the States. It is remarkable for its cold winters, and a large part of the State is from 3000 to 5000 feet above the level of the sea. Next comes Maine, with 4.41 deaths per 1000, and having also a severe climate, though less severe than that of Vermont, and at a lower level. As a rule, the " northeastern hills and plateaus " constitute those parts of the United States that are most favorable to the development of diabetes. Purdy gives the mortality from diabetes in thirty of the most populous States, the average for *all* being 1.93 among 1000 deaths. Taking the figures from Arkansas, Alabama, Texas, Louisiana, Georgia, and the Carolinas, I find an average of 0.84 among 1000 deaths, while the corresponding figure for Connecticut, Massachusetts, Maine, Vermont, Illinois, Wisconsin, Michigan, and Minnesota is 3.21. Although I entirely agree with Dr. Purdy that cold and altitude are the chief climatic features that

*Schmitz, who (1892) had treated 2700 diabetic patients, and who has the largest private statistics, furnishes similar figures. I am unable, at this moment, to produce his latest table. He practised chiefly at a health resort, and his figures are, therefore, as will be easily understood, of less weight than Pavy's, who obtained his from an established urban practice. The English reports of the Registrar-General can not be used, as they include both diabetes mellitus and insipidus.

determine high mortality from diabetes, I can not escape the thought that this comparison of mine is only apparently so very demonstrative. The figures would be conclusive but for the larger colored population and less intensity of life and strife in the Southern States.

Hereditary influences are of great importance in the etiology of diabetes. In a large number of cases it will be found on careful investigation* that the diabetic patient is the descendant of a diabetic; and still more frequently, the nervous predisposition, which in the patient has found its expression in diabetes, has, in preceding generations, shown itself in the form of other affections with well-known changes in the central nervous system, in fully developed psychoneuroses, or in psychopathic manifestations of various kinds. It is often found that several members of the same family—brothers and sisters—are diabetic, sometimes exhibiting different forms of the dystrophy. Now and again I have found slight glycosuria and mild and severe diabetes in members of the same family.

All of the "learned" *professions* provide, comparatively speaking, a vast clinical material for the specialist in diabetes. Physicians especially—who are compelled to devote themselves to study assiduously, to sustain great responsibilities, are disturbed at night, and are harrassed by the suffering and unreasonable public—are often victims of diabetes or exhibit simple glycosuria. Statesmen and politicians are still more common subjects of the dystrophy in a greater or less degree. The position of the speculator and the business man is best illustrated by the adage from Wall Street, New York: "When stocks fall, glycosuria rises." Among the comparatively "unlearned" occupations it seems to

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* Close investigation, which in this connection is far more necessary in order to obtain reliable information than under ordinary conditions, is not only troublesome, but is attended with numerous difficulties. Many a layman considers neither hypochondria nor the slighter forms of melancholia as diseases of the mind, and, as a general rule, he is not willing in his own case or in that of his relatives to acknowledge any disorder as such that has not been treated in an asylum. Many laymen also entirely disregard Graves' disease, if not very pronounced, slight attacks of epilepsy, etc. Others consciously conceal a history of both psychoses and neurotic tendencies in their own family, and feel ill at ease and irritated by being questioned too closely on those subjects. In fully a quarter of all cases of diabetes there exists a direct *diabetic* hereditary predisposition, while a *neurotic* heredity is present in the great majority.

me that sailors furnish the largest contingent of cases of diabetes. It is not among the crews, but among the officers, that the greater number of diabetic patients will be discovered. I must have seen a score of sea-captains, usually affected but slightly, middle-aged, often corpulent, whose voices and figures often remind one of "Captain Cuttle." The great responsibility, the disturbed sleep at night, the good table, the drinks, and the limited exercise, possibly also the low temperature prevailing on board, all contribute to the development of diabetes.

The presence of pathologic quantities of sugar in the urine is far more common among the *higher classes*, with their more nervous, sedentary, and luxurious mode of life, than in the lower classes. On the other hand, a far greater percentage of cases of diabetes occurring among the last-mentioned classes is of the severe kind than is the case among well-to-do people. In making this statement I am perfectly aware that the less serious variety of diabetes is more often overlooked or neglected by the poor than by the rich, and that for this reason, also, far fewer mild cases are treated in the public hospitals than in private practice.

At Carlsbad, with a visiting public consisting almost exclusively of persons of some means, I not rarely discover a case of previously overlooked mild diabetes, and far more often cases of slight glycosuria. For a number of years, during the winter, in the capacity of physician in one of the dispensaries for the poor in Stockholm, I had ample opportunities of proving how comparatively rare glycosuria is among such patients.

Among occasional causes painful, depressing, or irritating *emotions* must doubtless be placed first. The patient often—and doubtless correctly—states the cause of his disease to be constant vexation in consequence of changes in external circumstances, grief at the loss of wife, husband, child, etc. In far rarer cases a violent fit of anger or fright—influences that invariably increase glycosuria in a diabetic and at times engender an occasional attack in a healthy individual—may give rise to a real, even severe, form of diabetes. One of my Carlsbad patients,—long ago deceased,—a brave and loyal officer of the Prussian Guards, dated both his Iron Cross and his diabetes from that fearful time outside St. Privat, before the longed-for order to storm was given. (See Glycosurias.)

Intellectual overexertion, and more especially the tiresome, unin-

teresting acquisition of sterile facts, also plays a certain rôle in the etiology of diabetes. In Sweden, where an enormous amount of time is spent at the universities in preparing for examinations, more than one case of diabetes in early years has come under my observation, in which the "corpus delicti" was probably the "cramming."

Sexual excesses, both natural and unnatural, doubtless are most deleterious. Here, as always, we find that what in one person causes diabetes, in another causes glycosuria, and the presence of small quantities of sugar in the urine in cases of sexual neurasthenia—especially in youths that have practised much masturbation—is not uncommon. Such an occurrence is sometimes only transient; but at other times diabetes develops in persons of middle age, in whose case no other point of importance can be discovered in the history than neurasthenia acquired in youth in the manner described. The sudden enormous increase in the frequency of diabetes just about the fifteenth year of life and the first manifestation of its preponderance among males as compared with females at this time, is doubtless owing partly to the strained intellectual activity often entered upon even at that early period, but also in part to masturbation, which is then so often practised. Both of these causes are far more prevalent among boys than among girls.

Some of our *habitual luxuries* that powerfully affect the nervous system certainly exercise a predisposing influence in the development of diabetes. This is principally the case with spirits for the occasional effects of which I must refer the reader to Alcoholic Glycosuria. I suspect, however, that a similar influence is exerted by other habitual poisons, and my attention has been called especially to the frequency of glycosuria in patients suffering from what we (incorrectly) term "nicotin poisoning," as a result of excessive smoking. This statement is made with a full realization of the difficulty, if not impossibility, of furnishing anything approaching statistical proof of its accuracy.

A *sedentary life* seems to favor the development of diabetes mellitus, which is seldom found in laborers, and is deemed by many to arise from decreased consumption of the blood-sugar in the muscles.

Profuse consumption of carbohydrates, especially of sugar, is often mentioned among the etiologic factors of diabetes. It stands to reason that any article of food that always increases glycosuria in diabetics will, if taken in large quantities, predispose to this dystrophy; nor can it be denied that a large number of diabetics have been fond of sweets. For my part, however, I am inclined to think that, on the whole, it is too rich a diet, both as regards the mixed nutriment, and more especially as regards alcohol, that plays the predominating rôle in this connection, and that the importance of large quantities of starch and sugar has been exaggerated. I beg to remind the reader that no carbohydrate other than grape-sugar causes glycosuria* in healthy individuals, and that laborers on sugar plantations show no special disposition to glycosuria or diabetes; and, finally, that just those classes in China and Japan that live almost exclusively on rice enjoy almost complete immunity from diabetes.

Starvation, especially if continued for any length of time, doubtless predisposes to diabetes. I refer the reader to the glycosuria following starvation, discovered by Claude Bernard, and more closely investigated by Hofmeister. (See the following chapter.) This form of glycosuria, however, is generally of short duration, although cases are sometimes encountered in practice in which insufficiency of food seems to be the immediate cause of severe diabetes.

Some time ago I attended a girl, eleven years of age, in whose case a careful investigation failed to reveal any other etiologic factor than insufficiency of food. For two months the child had been visiting some very poor relatives, and during that time had been constantly underfed. On her return, when she resumed her usual diet, severe diabetes set in. (See case, chapter v.)

Exposure to cold, if severe or often repeated, is universally considered one of the causes of diabetes.

Trauma now and then may undoubtedly cause diabetes, which sometimes follows immediately, but sometimes not until months have elapsed after the accident. The development of diabetes under these circumstances is more likely to follow trauma of the

* The glycosurias of the Trappists who make their liqueur (Charcot); of the German students who consume large quantities of ale (Kratschmer); or of Swedish students who drink arrack and sugar or Swedish punch, are examples of alcoholic glycosurias.

head; Griesinger was the first to call attention to the fact that contusions of various parts of the body, however distant from the nervous centers, may lead to a similar result. Nevertheless, only an exceedingly small percentage of traumata give rise to diabetes, and such accidents, though common, do not act as a cause in more than about one per cent. of all cases of diabetes in adults. Among nearly 200 of my own cases of diabetes in which the etiology has been carefully investigated, I find only two cases in which I consider trauma the cause with practical certainty. Among diabetic children, however, the percentage is larger.

Finally, *sunstroke* is, in rare cases, mentioned as a plausible cause of glycosuria or diabetes.

There are two dystrophies that have some, though as yet unexplained, connection with diabetes mellitus, and which undoubtedly constitute a predisposition to it—viz., *obesity* and *gout*.

All three of these dystrophies are not rarely present in the same family, and sometimes even in the same individual.

For other pathogenetic points I must refer to the next chapter. All the evidence seems to indicate that whatever may, as a transient or less profound influence, cause glycosuria, may, as a more persistent or more profound influence, cause diabetes in a mild or in a severe degree.

Diabetes, like all other dystrophies, is sometimes found in husband and wife, and Schmitz conceived the original, but not well-founded, idea that this may be the result of direct diabetic infection. I have myself seen several such instances in practice, just as I have seen married couples suffer from gout and adiposity, and I have always favored other explanations, too evident to any one to detain us further, which seem more rational than the theory of a diabetic infection. Tessier, however, has written a thesis in which this association receives further consideration.

CHAPTER III.—GLYCOSURIAS.

Since Brücke and Bence Jones found a reducing and fermenting substance in normal urine, the presence of minute quantities of sugar in the urine of healthy persons, and its possible amount within physiologic limits, have been much discussed. As representatives of the extreme views on this subject I may mention, on the one hand, Seegen, who, particularly in the beginning of his career, attributed vast pathologic significance to the slightest trace of sugar in the urine; and, on the other hand, we have Kühne, who considered 0.1 per cent., and Roos, who even mentioned 0.3 per cent., as possible under normal conditions. Breul has recently estimated the amount of sugar in normal urine as varying between 0.04 and 0.2 per cent. The larger amount is reached especially, he thinks, with a small expenditure of heat, high surrounding temperature, and bodily rest.

From the researches of Abeles, Wedenski, Schilders, Moritz, and Baisch, and a large number of my own investigations, I have come to the conclusion that there is a trace of glucose in normal urine, and that the amount in twenty-four hours scarcely exceeds a thousandth of 1 per cent. Some slight or occasional increase beyond this may often occur without noteworthy significance, but as soon as we reach hundredths or tenths of a per cent. we are within pathologic limits. The finding by Worm-Müller of sugar in 18 and by Nylander in 14 samples of urine from 100 "healthy" individuals by their tests, of which neither yields a reaction in the presence of less than a hundredth of a per cent.; and a similar experience on the part of Breul with Fischer's test, are for me evidences of the great commonness of slight but pathologic glycosuria, and I have always observed that such individuals, though they can not be pronounced diabetics, are not perfectly healthy, but will be found to suffer from nervous or gouty or other disorders.

As experimental pathology has of late proved that various operations, especially on the nervous system, cause excretion of sugar, so also has clinical experience shown that glucose may occur, over and above the normal traces, under several pathologic, but otherwise entirely dissimilar, conditions, some of which are of

a passing nature, though others may last for the greater part of a long life. We should never disregard or pass over without thorough investigation a measurable quantity of glucose in the urine; but we must avoid attaching too great an importance to the excretion of minute amounts, even if repeated daily, and pronouncing at once as diabetic every person whose urine yields a positive reaction to tests for grape-sugar. It is now impossible to change the clinical and prognostic idea that physicians and laymen alike for centuries have attached to the expression diabetes mellitus. A person that, upon an abundant mixed food, excretes, *e. g.*, 0.5 gram of glucose in the twenty-four hours is no diabetic in this sense, even if this insignificant excretion is maintained for years. Such manifestations occur more especially, and in large numbers, among neurasthenic and among gouty patients. The division of all the various forms and conditions attended with pathologic excretion of glucose into simple glycosuria, mild and severe diabetes is the one that best corresponds to the clinical reality, and the only one that seems to me possible at the present day.

A rational classification of the different forms of simple glycosuria is at present entirely impossible, owing to our defective knowledge of pathogenetic details; we must, for the time being, content ourselves with a table. At the head of the list we place *alimentary* glycosuria, common alike to healthy and to diabetic persons after the ingestion of large quantities of grape-sugar. Next come the glycosurias that arise from disorders in those organs that, even though the modus operandi is not as yet completely understood, undoubtedly influence directly the metabolism of the carbohydrates: the nervous system, the pancreas, and the liver. The *nervous glycosurias* may be subdivided into *organic* and *functional*, with known or unknown lesions of the nervous system. (The former include a number of experimental glycosurias.) Lesions in the pancreas may give rise to simple glycosurias, or to mild or severe diabetes; but the *pancreatic glycosurias* are treated of at length in a special chapter, and are therefore omitted from further consideration here. There are also *hepatic glycosurias*, but these are only known imperfectly from experimental and clinical observations.

Among *toxic glycosurias*, that due to *alcohol* possesses the

greatest practical importance ; and those due to *phloridzin* and to *carbon monoxid*, the greatest theoretic interest. Among *glycosurias from infection*, those that complicate malaria or influenza are the most common. In this category we include also that excretion of sugar in the urine that has been observed in association with purulent processes. Among "concomitant" glycosurias, special stress should be laid on those that occur in conjunction with *obesity*, *gout*, and *diabetes insipidus*, all of which are allied to diabetes mellitus. Glycosuria sometimes arises, further, from *cold*, from *starvation*, and from *fatigue*. It may occur, also, in the *fetus*, and it may be of *puerperal* origin. Finally, pathologic quantities of sugar are often observed in the urine in *senility* and in *cachectic states*. Of late years much has been written of *renal* glycosuria, and there seems to be no doubt that the kidneys have some influence on the excretion of sugar. The glycosuria from phloridzin may also be included in the renal variety. With regard to the glycosuria that is attributed to *cardiac disease* (Reynoso, Neumann), our knowledge seems at present to be too scanty to permit of any conclusion.

Of all these forms of glycosuria the acute alcoholic and the chronic functional neurotic, and the equally chronic gouty, are the most common, occurring much oftener than all the others together.

One attribute is common to all nondiabetic glycosurias with the exception of the one caused by phloridzin : viz., the excretion of sugar in varying, though never considerable, amount. The glycosurias are, so far as measurable quantities are concerned, transitory in some sense. Thus, after the ingestion of a large amount of glucose, after intoxication, cold, starvation, fatigue, or violent emotion, the sugar appears in the urine only for a short while,—sometimes only for hours,—and then generally disappears, never to return. After infections, childbirth, etc., sugar may appear in the urine for a number of days, but rarely persists for more than a few weeks. In cases of neurasthenia, gout, and obesity, or in senility and other more permanent states, the glycosuria may reach measurable amounts for only a short while some time after meals, and it may remain stationary at this point for years ; though every now and then, as sometimes happens also after transitory influences, it may be converted into true diabetes.

Glycosuria is in most cases an immediate effect of hyperglycemia, or the presence of an increased amount of sugar in the blood, though the relation between the blood-sugar and the urine-sugar is not a perfectly fixed one, and some influence on the part of the kidneys must be accepted. (See below.) Claude Bernard found that the dog, whose blood contains normally about from 0.10 to 0.15 per cent. of sugar, begins to exhibit glycosuria when the hyperglycemia reaches from 0.25 to 0.30 per cent. I accept the normal glycemia in man as varying between 0.10 and 0.15 per cent., and from the figures of Seegen and others it must be concluded that glycosuria may appear when the amount of sugar in the blood is only slightly above the last-named figures (even below 0.20 per cent.).

Hyperglycemia is, however, not a necessary prerequisite for glycosuria. The quantity of sugar in the blood is abnormally low in phloridzin-glycosuria. The same condition exists, according to Dastre, in the glycosuria due to *slow* asphyxiation. Hibernating animals, according to some observations, exhibit glycosuria; although the quantity of sugar in the blood diminishes during hibernation, and increases rapidly as the animals resume their accustomed activity (Claude Bernard), and their glycosuria disappears. According to Bernard, the amniotic fluid of the fetus (its urine) often contains sugar. The normal glycemia of the fetus is, so far as I know, not yet satisfactorily determined, but it seems to me possible that we might have here another example of hypoglycemia with glycosuria.*

Alimentary glycosuria occurs normally after the ingestion of large quantities of glucose, and it is of great importance to remember that, so far as human beings are concerned, this is the sole physiologic variety of purely "alimentary" glycosuria—which expression is often incorrectly applied. The largest possible quantities of ingested starch cause no glycosuria in healthy persons. After the ingestion of large quantities of sugars other than glucose

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* On the other hand, Naunyn mentions cases in which the amniotic fluid of the fetus contained no sugar, even when the mother suffered from diabetes; this fluid, in other cases of diabetes, may contain quite a considerable quantity of glucose (0.7 per cent., Husband).

the urine will be found to contain normally only a small part of the same kind of sugar; we thus may have a physiologic saccharosuria, a lactosuria, lævulosuria, etc. (see below).

Alimentary glycosuria evidently is caused by failure on the part of the liver to transform into glycogen very large quantities of glucose entering into that organ through the portal vein. The excess that is not transformed or is not stored or consumed in other organs (muscles) passes into the urine.

Numerous experiments of my own with glucose in normal and diabetic individuals have confirmed essentially several facts previously observed by Worm-Müller, Külz, and others, and have taught me: (1) That normal individuals can take, some hours after a light breakfast, and before the second meal of the day, generally 100, often 200, grams of glucose without excreting a measurable amount in the urine. The maximum average amount that can be taken under such circumstances is probably below 150 grams of glucose. (2) That this maximum amount—or, in other words, the limit of assimilation (Hofmeister)—varies vastly, even in normal individuals, under different, and sometimes even under apparently similar, conditions. (3) That the capacity for taking glucose without the development of glycosuria is often greater earlier than later in the day. (4) That a healthy individual excretes, as a rule, far less after the same amount of glucose than does a diabetic; but (5) that a diabetic in the mild stage of the disease may, by prolonged abstinence from carbohydrates for the time being, attain an equally high power of assimilation as a normal individual; and (6) that, consequently, a simple ingestion of glucose can not, for more than the time being, determine the limit of assimilation, and can not always establish the absence or presence of diabetes.

Under *organic nervous glycosuria* are included those cases of slight excretion of sugar in the urine that occur in conjunction with known lesions of the cerebrospinal and sympathetic nervous system. Experimental pathology has evolved some valuable contributions to our knowledge of central action in this connection; but this knowledge, however, is very imperfect.* Clinical experience

* The technical difficulties in the way of full and exhaustive investigation are scarcely to be overcome. Kahler's experiments, which, unfortunately, only concerned polyuria,

throws but a faint light on the subject, which is somewhat increased by pathologic anatomy. (See below.)

Though isolated observations as to the connection between certain lesions of the nervous system and glycosuria (or diabetes) had previously been made, it was Claude Bernard who, in 1849, first demonstrated this relation by his celebrated "piqûre" in the floor of the fourth ventricle between the centers of the pneumogastric and acoustic nerves. This lesion causes a transitory hyperglycemia, coupled with polyuria, and the presence in the urine of glucose to the amount of several parts to the hundred for from five to six hours in the rabbit and about forty-eight hours in the dog.* Puncture a little higher, in a frontal direction, causes albuminuria, while another somewhat lower causes simple polyuria. Bernard and many others have considered these phenomena symptoms of irritation, not of paralysis. As irritation of the chorda tympani causes increased functional activity (and hyperemia) of the submaxillary gland through the influence of sympathetic fibers, which preside over the vessels and lead to their distention, so is a vasomotor center in the brain irritated by Bernard's puncture. The stimulation is then transmitted through the upper part of the spine, and afterward through the splanchnic nerves to the vessels of the abdominal organs in which hyperemia plainly manifests itself. By the increased flow of blood to the liver its glycogen is attacked more actively than usual by the diastatic ferment in the blood, and the production of sugar is increased, according to Claude Bernard. The great physiologist undertook the experiment for the purpose of irritating the center of the pneumogastric nerve, and expected glycosuria from this excitation. He discovered, however, that glycosuria appeared after the puncture even if both pneumogastric nerves were

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seem to have given technically the best results. He injected a concentrated solution of silver nitrate through a fine cannula, and thereby caused circumscribed destruction in different parts of the brain of the rabbit. Lesions of Eckhard's "lobus hydruricus et diabeticus" caused transitory and inconstant polyuria, which also resulted from a lesion of Deiter's nucleus and adjacent parts of the crura cerebelli. A lesion of the acoustic tubercle and acoustic striæ caused polyuria within forty-eight hours. Although these results hold good for rabbits, they can not be applied without further experiment to other animals. Kahler favored the theory of stimulation.

* Bernard's puncture also caused glycosuria in pigeons (Bernard) and in frogs (Schiff, Kühne).

cut; that no glycosuria followed irritation of the peripheral stump; that glycosuria may be caused by reflex action, if the central stump is irritated, but that no glycosuria follows the puncture if previously both splanchnic nerves are cut or if the pancreas and the liver are separated from the nervous system. The puncture is now known to have the usual effect even if the pancreas is extirpated, and then increases the hyperglycemia (Kaufmann) and the glycosuria (Hedon), but it does not have that effect if the celiac plexus is extirpated (Schiff). After the glycosuria is over, the glycogen of the liver has mostly disappeared. If this has been previously removed by starvation, no glycosuria follows the puncture. If a certain quantity of glucose is injected into the mesenteric veins of an animal that has lost its glycogen through starvation, a slight glycosuria follows. A much more pronounced glycosuria follows, under otherwise the same circumstances, if the injection is preceded by Bernard's puncture (Naunyn), and it is thus evident that the capacity of the liver for storing glucose as glycogen is diminished by the puncture. Though the glycosuria following Bernard's puncture is transitory, and not very considerable, postmortem observations (see below) indicate that permanent changes in the floor of the fourth ventricle cause real diabetes, and Bernard's puncture has been a factor of great importance in our comprehension of diabetes mellitus.

Eckhard found that stimulation of a part of the vermis ("lobus hydruricus et diabeticus") is followed by polyuria and glycosuria.

Lesions of various parts of the brain may cause glycosuria, as Schiff saw after section of the optic lobes, the pedunculi cerebri, and the central and posterior parts of the pedunculi cerebelli.

Glycosuria often occurs after trauma of the brain. Higgins and Ogden found it in 20 out of 212 cases. This glycosuria generally passes off in a few days; now and then true diabetes mellitus or insipidus remains. Though Asher has collected 124 cases of traumatic diabetes mellitus, I repeat that trauma is a rare cause of diabetes mellitus in adults.

Section of the spinal cord down to the fourth cervical vertebra is followed in the dog by glycosuria (Pavy, Chauveau, and Kaufmann).

Section of the spinal cord between the fourth cervical and the

sixth thoracic vertebra is at first followed by slight and transitory hyperglycemia, but subsequently by *hypoglycemia.* Incisions below the sixth thoracic vertebra cause no alteration in the quantity of the sugar in the blood (Chauveau and Kaufmann).

Claude Bernard severed the spinal cord of a rabbit between the last cervical and the first dorsal vertebra. The animal became paralyzed below the division, and respiration became slower, and the temperature sank. The quantity of sugar in the blood also diminished,—as Chauveau and Kaufmann found also subsequently,—and the amount of glycogen in the liver increased. This last fact is denied by Chauveau and Kaufmann, who aver that though the liver, after this operation, certainly gives off less glucose to the blood, it instead discharges more glycogen (?).

If the pneumogastric of one side is cut and the central stump is irritated, glycosuria follows, and persists for a few hours. Sometimes it arises merely in consequence of the section (Bernard, Eckhard, Külz). Arthaud and Butte caused a more continuous glycosuria (amounting almost to 2 per cent.) by maintaining an inflammatory process in the central stump. Couvreur, after severing both pneumogastric nerves, saw glycosuria develop in the rabbit, and found, after the same experiment in the pigeon, that the amount of sugar in the blood first rises above, but afterward falls below, the normal.

Filehne saw glycosuria appear on irritation of the depressor branch of the pneumogastric nerve, perhaps from the passage of the stimulus to the latter.

Claude Bernard and others have found that irritation of the peripheral stump of the divided pneumogastric nerve does not cause any change in the amount of sugar in the blood under the same conditions. Arthaud and Butte and Lépine observed hyperglycemia, and Morat hypoglycemia. These differences in results may possibly be explained by differences in division of the nerve-fibers in the trunks of the pneumogastric.

Niedieck caused inflammation of the sciatic nerve in the rabbit, and found glycosuria develop. The neuritis had spread to the spinal cord, and at times it had passed over to the sciatic nerve of the other side. Niedieck considers that changes in the spinal cord cause the glycosuria, either by directly modifying the abdominal circulation or by transmitting the irritation to the floor of the fourth ventricle.

Schiff also found that irritation of the sciatic nerve caused glycosuria, which might last for several days and reach two per cent. This was afterward observed also by Ryndsjun, Böhm and Hoffmann, and others. The experiment does not always succeed in inducing glycosuria, although Külz obtained it in nine of ten cases.

Butte saw glycosuria after irritation of the first pair of dorsal nerves. Frerichs, Frazer, and others have observed glycosuria in the course of rheumatic inflammation of different nerves, and it is probable that irritation of any nerve, if sufficiently intense, may bring about such a result.

A number of observations illustrate the influence of the sympathetic nervous system on the sugar in the blood.

As early as 1859 Pavy found sugar in the urine after section of the nerves that proceed from the superior cervical ganglion, or after extirpation of the ganglion.

Cyon and Aladoff observed glycosuria after section of the inferior cervical ganglion, of the superior thoracic ganglion, and of annulus Vieusseni.

Külz found section of the cervical sympathetic trunk to cause slight glycosuria in four of ten cases; while irritation of the central stump several hours later was followed by glycosuria in six of the ten cases.

Irritation of the thoracic division of the sympathetic nerve also causes glycosuria (Pavy).

Morat and Duponc observed an increased production of sugar in the liver as a result of irritation of the splanchnic nerve.

Section of the splanchnic nerves often causes glycosuria. Hans Voit, however, failed recently to obtain this result in the majority of cases.

Pincus, Budge, and Lamanski saw dogs, rabbits, and cats die with profuse diarrhea and a violent gastro-enteritis about twenty-four hours after extirpation of the celiac plexus. By means of the same operation Munck and Klebs induced atrophy of the pancreas and glycosuria; while Lustig observed neither diarrhea nor atrophy of the pancreas, but considerable glycosuria (with polyuria), acetonuria, albuminuria, and death in coma. Peiper had a similar experience with rabbits, the glycosuria reaching from 2.5 to 4 per

cent., but neither it nor the acetonuria nor the albuminuria was constant.

A. and E. Cavazzani found a great increase in the quantity of sugar in the blood in the hepatic veins after mechanic and electric stimulation of the celiac plexus.

A. Cavazzani and G. Soldani, who consider the production of sugar in the liver to be a secretion, like all other secretions, found that atropin, which paralyzes the sympathetic centers and diminishes secretion, also diminishes the amount of sugar in the hepatic veins, probably by paralyzing the celiac plexus.

Clinical experience affords numerous illustrations of the dependence of the assimilation of carbohydrates on the nervous system. Sugar has been found in the urine in cases of general progressive paralysis (Lallier, Bequerel, Bond, Strauss), of tabes dorsalis (Smith, Oppenheim, Eulenburg, and others), of multiple sclerosis (Weichselbaum, Mlle. Blaine Edwards, Richardière), of paralysis agitans (Huchard, Topinard, Naunyn), of chorea minor (Demme, and others), of epidemic cerebrospinal meningitis (Mannkopf), and of cerebral meningitis (Naunyn), of syphilis (Leudet, Frerichs, and others), of aneurysm and of new growths (v. Recklingshausen, Frerichs, Seegen, Richardson, Spitzka, De Jonge, and others), of cerebral softening (Naunyn, and many others) and cerebral hemorrhage (Frerichs, Olivier, Schütz, Jacques Meyer, and others). Michael also found a cysticercus embedded in granulations in the floor of the fourth ventricle in a case of diabetes.

The numerous cases of disease of the brain, attended with the presence of pathologic quantities of sugar in the urine, permit us to conclude with certainty that a causal connection exists between lesions of different parts of the brain and glycosuria; but the statistics on the subject are of little value, on account of the great frequency of glycosuria independently of brain disease, the small number of cases, and the want of uniformity in investigation and of exact expression for the normal power of assimilation. It must be acknowledged that in a large number of cases of brain disease there is only an insignificant decrease, if any, in the power of assimilating carbohydrates. In only four of Kahler's twenty-three cases of organic disease of the central nervous system was there a distinct diminution in that power. Van Oordt (1898) found enfeebled power

of assimilating carbohydrates in 25 of 178 cases of diseases of the central nervous system. Several of the cases were neuroses (neurasthenia, hysteria, traumatic neurosis). Epilepsy and diseases of the spinal cord seemed to cause a diminution in the power of assimilation. Van Oordt's twenty-five cases, however, do not seem to me to make up a greater percentage with decreased power of assimilation than is found, on the average, among brain-workers. Glycosuria seems to be most frequent in cases of tumor of the brain, of general progressive paralysis, and of cerebral hemorrhage. The intensity of the glycosuria is generally slight, and does not amount to a real diabetes. Still, in cases of general paralysis, the amount of sugar often reaches one per cent. or more, and in cases of tumor and hemorrhage as much as four per cent. has been observed. If the patient survive, the glycosuria following apoplexy generally is transitory; sometimes true diabetes may develop (Jacques Meyer). (For a consideration of glycosuria complicating tabes dorsalis and multiple sclerosis I refer to chapter II.)

Cerebral softening, or encephalomalacia, is much more commonly an effect than a cause of diabetes (Naunyn).

Exophthalmic goiter is sometimes attended with glycosuria (Chvostek, Dumontpellier, Panas, Pavy, Blocq, Kraus, Ludwig, and others), and sometimes with true diabetes (Bettman, Laache). I have at present under observation a case of diabetes with struma, tachycardia, and nervous symptoms, but without exophthalmos.

A diminished power of assimilation of carbohydrates in different degrees has often been observed in cases of akromegaly also (Pierre-Marie, Cunningham, Lancereaux, and others). Marinesco has recorded a case of akromegaly with diabetes mellitus, epilepsy, and bilateral hemianopsia.

Epilepsy is at times, especially after attacks, attended with glycosuria (Goolden, Griesinger, Lallier, Ringer, Barlow, and others). "Mais elle (la glycosurie) reste en somme une manifestation exceptionelle" ("Les Epilepsies," Ch. Féré, Paris, 1890).

Pathologic quantities of sugar have also been discovered in the urine in cases of meningomyelitis (Kunkler), of myelitis (Bequerel), of spinal hemorrhage (Siebert, Scharlau, Vogler), of fracture and contusion of the cervical and dorsal vertebræ (Schiff, Frerichs,

Fischer), and of spondylitis (Baum). May found glycosuria and levulosuria in a case of transverse myelitis.

Traumatic neuroses are often accompanied by glycosuria (Brouardel, Richardierè, Strauss, von Strümpell, Ebstein, Naunyn, and others).

Simple neuralgias also—especially of the fifth pair—and sciatica are often complicated by glycosuria. I recently found one per cent. of sugar in the urine in a case of violent sciatica without any other symptoms of diabetes.

I consider it one of my most important tasks to emphasize the glycosuria so often found in cases of acute or chronic "functional" nervous disturbances, and for which there is no better name than *functional nervous glycosuria.*

Such a pathologic excretion of sugar may be the effect of an entirely transitory nervous disturbance, and may appear in otherwise healthy individuals for only a few hours after some powerful emotion (as of fear or anger), such as in a case of more permanent glycosuria, or in one of true diabetes, may for a short while greatly increase the quantity of sugar in the urine. Almost every physician who has given much attention to a study of the urine will have encountered instances of such transitory glycosuria, of which a large number are recorded in literature. Many facts tend to show that a similar condition occurs not rarely in animals, especially among the higher classes of vertebrates. Paul Gib has recently given the account of a bitch that always objected strongly to being shut up, and was greatly agitated during her seclusion, and that constantly after such treatment, but never otherwise, presented small quantities of glucose (up to 0.55 per cent.) in the urine.

Such an effect of transitory emotions makes it difficult in many cases to determine the nature of an excretion of sugar both in man and in animals. Glycosuria following an attack of gall-stones (as observed by Finkler and Gans) may be caused by the simple irritation of peripheral nerves, or by hyperemia of the liver; but it may also be the effect of the mere mental anguish of the patient during the painful, and possibly dangerous, passage of a gall-stone. Students of experimental pathology should bear in mind this possible cause of a transitory glycosuria of doubtful origin, and there is

abundant evidence that it often occurs in laboratories, where the infliction of pain on animals is not always avoidable. Minkowski discovered glycosuria in 15 of 32 animals subjected to operative experiments, in which this phenomenon probably must be attributed to mental influences. Examination of the figures given by Pavy, McDonnel, Seegen, Abeles, and others, for the quantity of sugar in the blood of the hepatic veins during experiments on animals leads to the conclusion that the experiment increases the production of sugar in the liver through the mere suffering it causes. It is not at all improbable that the glycosuria that follows extirpation of the salivary glands, so much expatiated upon by Reale and Rienzi, or that observed by Schiff after the ligation of the femoral artery, or by Minkowski after resection of the duodenum, as well as other slight and inconstant varieties of excretion of sugar in the urine, are to be referred to this category.*

Böhm's and Hoffmann's "Fesselungsglycosurie" in the cat, subsequent to its being tied experimentally, is well known, and can be explained most easily by the mental state and emotion produced by such treatment, though asphyxia may also be operative in this instance. The same may be said of Velisch's observation of glycosuria in the frog after tying it on its back, or after keeping it on its head in a narrow cylinder.

In some cases nervous glycosuria may last for some length of time, but finally disappears.

L, a medical student, works hard at his books, and is alarmed now and then to find distinct reactions with the ordinary tests for sugar in his urine, which after rest and a trip to a warmer climate becomes normal.

X, a youth of nineteen, was for several years addicted to masturbation, and every evening after dinner presented about 0.1 per cent. of sugar, which disappeared some time after he reformed his ways.

Mrs. T, now seventy-six years old, during middle age and after a period of great anxiety, excreted daily more or less than a gram of glucose with the urine. This caused her family some uneasiness, especially as a daughter had died of diabetes; but at present the old lady's urine exhibits no trace of reaction two hours after an abundant mixed meal.

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* Falkenberg and Külz observed, after extirpation of the thyroid gland, glycosuria that was not constant, though it sometimes lasted for weeks. Naunyn, in his recently published monograph, probably correctly explains this glycosuria by the starvation consequent upon the operation.

Count X Y Z, in a scientific controversy, both made and committed to paper a number of most absurd statements, for which he was subjected to severe but well-deserved criticism, by which he was greatly affected. During this time he availed himself of the opportunity to make some interesting investigations concerning the influence of emotion on metabolism, and on various occasions he found as much as 0.3 per cent. of glucose in his urine. After he had returned to the intellectual passivity for which nature evidently intended him, and time had consoled him for his disappointments, his urine returned to its natural condition.

If, on the other hand, the nervous causes of glycosuria are prolonged or become permanent, so will also the excretion of sugar with the urine, and this may continue for many years, and often for the rest of life. These habitual glycosurias have exactly the same etiology as true diabetes; and there will be found to exist hereditary influences of a diabetic, a nervous, or a gouty nature, and the usual accidental influences: viz., painful emotions, intellectual overwork, sexual excesses, etc.

Habitual glycosuria is found especially in persons suffering from those common functional disorders grouped under the name of neurasthenia, which disorders, when once they have appeared, seldom entirely leave the patient.

Among neurasthenic patients, again, we may expect to find pathologic quantities of sugar in the urine, especially in cases complicated by gout or obesity; and it is a matter of choice whether we ascribe the glycosuria to the neurasthenia or consider it a collateral symptom of the obesity or gout, which latter dystrophy, by the way, is accompanied with marvelous constant nervous symptoms. Among obese persons we also not rarely find glycosuria, especially in those that exhibit neurasthenic stigmata. There is among the upper social classes a not rare type of middle-aged man, with a bodily weight as often above as below 200 pounds, with ruddy cheeks and a general appearance of health, but with high-strung nerves, great sensitiveness, and often with some slight gouty trouble.* If we adopt the rule of testing our patients' urine an

* As has already been mentioned, diabetes insipidus, like obesity and gout, may be converted into diabetes mellitus or it may be attended with the excretion of a small amount of sugar in the urine (Senator, Legroux). Such cases, however, seem to be quite rare, even comparatively. In the rare cases of recovery from diabetes mellitus a distinct diabetes insipidus sometimes remains.

hour after dinner, we shall find in a large proportion of the representatives of the type described at least distinctly pathologic traces of sugar—simple glycosuria. In other cases we shall find a true, though mild, diabetes.

Wherever we turn we often see in practice illustrations of the close relationship between all stages of the glycosuric dystrophy.

In a family of eight children one sister died at twenty-nine in diabetic coma; another, who subsequently died of carcinoma, developed the mild type of diabetes when about fifty years of age; in a third, somewhat corpulent, but otherwise healthy, sister, I have, in the course of many years, found several times after meals from 0.1 to 0.2 per cent. of sugar in the urine. With the exception of the sister that died in coma, none of the family presents any nervous disorder, but on the father's side there are neuropathic individuals of closest relationship.

In different branches of another well-known and widely spread family I have seen simple glycosuria, mild and severe diabetes, gout, and obesity, with or without traces of sugar. The psychopathic element in this in part highly intellectual family has manifested itself in fully developed psychoneuroses, in dipsomania, in perverted sexual desires, and in eccentricity.

The son of a man who met his death by diabetic coma discovered in late middle age that he was excreting sugar, the condition being found to be one of slight simple glycosuria. The daughter of a woman who had presented slight glycosuria died in early life of severe diabetes, and so on.

The daily excretion of sugar in the urine in cases of simple glycosuria is always insignificant, and the amount is frequently so small that it can not with certainty be demonstrated in larger quantities of urine, even after abundant ingestion of carbohydrates. If in a sample of the urine collected during twenty-four hours a percentage of, for instance, 0.5 be found, the case can no longer be classed as one of simple glycosuria, unless special causes—such as excessive indulgence in alcohol, an acute infection, powerful emotion, and the like—have contributed to the condition. The quantity in small samples voided a certain time (from one to two hours) after meals varies from hundredths to tenths of a per cent., and may for a little while, under the influence of agencies that increase the secretion, reach a somewhat higher figure. A percentage of 1.5, even in small quantities of urine, is rare in cases of simple glycosuria; more than 2 per cent. scarcely occurs at all in an anomaly of this kind.

Simple glycosuria causes of itself—*i. e.*, by hyperglycemia and by loss of sugar—no symptoms at all or only ill-defined and transitory

symptoms. We find in these cases, beyond the small quantities of glucose in the urine, usually no pathologic manifestations except the various neurasthenic stigmata and symptoms in lesser or greater number, and these can not possibly be ascribed to the insignificant deficiency in the power of assimilating carbohydrates or to the small addition to the normal quantity of sugar in the blood, which addition probably amounts to determinable quantities only for a comparatively short part of the twenty-four hours. To avoid unnecessary repetitions, I refer to chapter IV for a consideration of those neurasthenic symptoms, of which the most frequent and the most distressing are an excessive emotional irritability, insomnia, and enfeebled virility. I wish here only to remark that the glycosuria stands in no fixed relation to the intensity of the neurasthenic neurosis. We may find glycosuria present in cases of but slightly developed neurasthenia, and we may look in vain for it in cases in which many stigmata and symptoms combine to bring out in strong relief the neurasthenic picture which is scarcely ever complete in the individual case.

The symptoms that may be caused by hyperglycemia and glycosuria in these cases are so vague that even a considerable experience and much attention have not enabled me to arrive at definite conclusions with regard to some points. Pollakiuria, or increased frequency of micturition, even though the quantity of urine expelled at each voidance be small, is a usual, though not constant, symptom in cases of simple glycosuria. It is, however, common also in "nervous" patients without glycosuria, and it is often noticeable whenever the urine contains any great amount of crystals of calcium oxalate, which is often the case in the presence of simple glycosuria.

I have found furunculosis in quite a number of cases, with such an insignificant excretion of sugar that I could not possibly class them among diabetics. Furunculosis is also one of the earliest symptoms of mild diabetes. With regard to furunculosis, also, we must remember the oxaluria so common in neurasthenic patients, and especially in those that show glycosuria. In the "idiopathic oxaluria" of Begbie, Cantani, and others, the clinical picture is made up of slight nervous and dystrophic symptoms, and among the latter the authors also name furunculosis. It is not improbable that other causes than hyperglycemia are here active, especially in view of the fact that furunculosis is much more frequent in mild than in severe cases of diabetes.

Other cutaneous eruptions, especially eczema, are sometimes found in cases of simple glycosuria, which, like diabetes, frequently arise in persons with vasomotor irregularities of different kinds. It is difficult to assert any direct connection between these cutaneous troubles and glycosuria; they are both often found in cases of gout—a frequent disease in glycosuric individuals.

Patients aware of the presence of slight quantities of sugar in their urine sometimes mention dryness of the mouth or increased thirst, but the quantity of urine rarely exceeds 20 cu. cm. to the kilogram of body weight.

The teeth, which in true diabetes are pretty certain to be carious and defective after some years, are often in most excellent condition after decades of simple glycosuria.

When the physician wishes to determine by careful investigation as far as possible the nature of a slight glycosuria, and to give it a name, he must fully understand that his task is entirely a practical one, and that he must give up all attempts to draw a distinct, scientific limitation between simple glycosuria and diabetes. While bearing in mind that simple glycosuria and glycosuria in mild and severe cases of diabetes represent only a dystrophic symptom of various pathologic states and processes, we must remember that exactly the same gradual differences are to be observed in the excretion of sugar as in other dystrophic manifestations. What intelligent physician would undertake to determine where gout begins? In obesity, which reveals itself to our senses much more readily than gout or diabetes, even the layman understands that the interval between the normal man and the representative of the highest degree of obesity may be filled by a thousand individuals in such a manner that only a minute difference exists between each man and his neighbor to the right and to the left in the long line. We meet with exactly analogous conditions in glycosuric patients. It is impossible to decide precisely when the faint trace of sugar that, we must allow, may appear in normal urine ceases to be normal and passes over into simple pathologic glycosuria. It is equally impossible to find the boundary-line between the latter and mild diabetes, and in the chapter on metabolism we shall find that mild and severe "forms" of diabetes are also connected by intermediate stages. The individual may sometimes, by slow degrees, and during a series of years, pass through all stages, from the normal state to that in which he is overtaken by death from diabetic coma. This, however, is not the usual course, and many patients remain in the vicinity of that place in the chain that they occupied a short time after the beginning of their dystrophy. Simple glycosuria, as already mentioned, often shows a decided tendency to remain unaltered for decades, in spite of all sorts of pernicious influences.

Mild diabetes certainly not infrequently develops gradually from simple glycosuria, but it also often appears at once or after a short time as mild diabetes, and usually remains mild diabetes. If we can not deny that the severe type sometimes has gradually been evolved from the mild, it much more frequently shows itself in its severe character a short time after a normal state.

In examining and forming an opinion on a case with a small amount of sugar in the urine, the physician must further always bear in mind that, as simple glycosuria may, under some temporary influence, momentarily resemble mild diabetes, so also may mild diabetes at times appear exactly like simple glycosuria, and that, consequently, repeated examinations are always necessary. Recently I examined two patients on the same day—Mrs. M. and Mr. R., both about forty years of age. An hour after a similar dinner of mixed food the urine of each contained fully 0.15 per cent. of glucose, although in the urine collected for the twenty-four hours there was a scarcely perceptible trace. The patients consumed 200 grams of cane-sugar each; the urine in neither case afterward yielded a distinct reaction with Nylander's solution, but in both cases reduced abundantly after boiling with a few drops of sulphuric acid.* In short, the two cases seemed for the moment to be as similar as they could be. They are, however, essentially different in nature. Mr. R. for fully ten years has exhibited a simple, neurasthenic glycosuria, which during all this time, and with ordinary food, has appeared as it does now, without ever reaching considerable quantities of sugar or giving rise to diabetic symptoms; it will in all probability remain stationary in the future. Mrs. M. suffers from a true, though mild, diabetes of several years' standing. A few weeks ago her urine contained over two per cent. of sugar, and there was some polyuria; she has reached her present power of assimilation only after several weeks of strict diet. If she should for any length of time indulge in a free diet, which now was occasionally allowed for a couple of days for the sake of the experiment, her old symptoms would be certain to reappear.

In other rare cases the same individual may, without any differ-

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* In other words, neither urine contained glucose, but both urines contained some cane-sugar, which, after being inverted by boiling with acid, reduced (see below).

ence in diet, and without any assignable cause, present a periodic alternation of simple glycosuria and true, though mild, diabetes.

This is the condition that now and again is mentioned in medical literature as *periodic diabetes*. In the cases of this kind that have come under my observation a distinctly pathologic, though comparatively insignificant, trace of glucose is found even during the "free" intervals. Such a case is that of the Countess H., who has been under my observation for several years. The lady, who is somewhat over forty and very corpulent, shortly after her husband's death began to suffer from constant thirst. The polydipsia excited the attention of the servants, and the family physician found considerable quantities of sugar in the urine. Since then, this most conscientious patient has for several years constantly adhered to the same diet, with a considerable reduction of carbohydrates (100 grams of bread a day and some vegetables and animal food). Once or twice a year, at intervals of varying length, diabetic symptoms appear for some weeks, with the excretion of considerable amounts of sugar (from 20 to 25 grams daily), but these soon disappear, even if no change is made in the dietetic regimen. In the intervals the urine for twenty-four hours shows, with Nylander's and Fehling's solutions, just appreciable traces of sugar. At present the patient has just passed through a new diabetic period, which, unlike the previous attacks, continued for five months, until, when she appeared again in Carlsbad, I reduced for some time the carbohydrates to a minimum. The patient is now able to take eighty grams of bread daily, together with some vegetables, without showing more than traces of glucose in the urine, which will be examined more frequently in order to effect without delay any reduction in carbohydrates that may possibly be necessary. I consider it probable that the case will develop into a common, persistent, mild diabetes.

Very likely similar cases, complicated by gout, have been designated "*diabetes alternans*" ever since the time of Peter Franks. By this appellation is generally meant a state in which *alternately* sugar and uric acid in abundant quantities appear in the urine. Gouty patients often present either simple glycosuria or an especially mild diabetes. With the periodic increase in the power of assimilation, which may occur in such cases, the amount of sugar in the urine falls to a minimum. That a real alternation occurs, so that the quantity of uric acid increases as the quantity of sugar in the urine diminishes, and vice versâ,

is at any rate not proved, and among the large number of gouty and glycosuric patients that I have treated I have not been able to find a single case in which, as a result of the considerable analytic work necessary, the slightest evidence of such an alternation was detected. It is difficult to understand how the presence of uric acid in the urine should bear any fixed relation to the glycosuria.

A connection between glycosuria and the presence of oxalic acid in the urine—the molecular construction of the latter giving it a position between glucose on the one hand, and water and carbonic acid on the other—has a good theoretic basis, and I have seen cases of simple glycosuria that, when free from glucose, have presented marked oxaluria.

Though no exact dividing-line can be drawn between adjacent cases of the one and the other, a comparison between the typical forms of simple glycosuria and of true though mild diabetes will show several practically important differences :

Glycosuria.	Mild Diabetes.
Smaller quantity of glucose which, even after abundant and protracted ingestion of carbohydrates, seldom rises to any considerable fraction of one per cent. in the urine for twenty-four hours, and altogether only amounts to a very small number of grams.	Larger quantity of glucose which, after abundant and protracted ingestion of carbohydrates, always reaches large fractions of one per cent., and usually more than one per cent. in the urine for twenty-four hours, the whole excretion, under such circumstances, always amounting to several grams.
The excretion of glucose is in less definite relation to the amount of carbohydrate ingested. The patient may show some glycosuria after a hearty dinner, but may be capable of ingesting large quantities of cane-sugar or rice without glycosuria making its appearance, Emotions, alcohol, etc., have a very conspicuous influence in inducing glycosuria.	The excretion of glucose is in a more definite relation to the amount of carbohydrate ingested, though it may be increased by emotional and other influences.
The amount of glucose, therefore, under the same dietetic conditions, though always small, undergoes comparatively wide variations.	The amount of glucose under the same dietetic conditions usually varies less than in simple glycosuria.
Simple glycosuria gives rise to no distinct diabetic symptoms, except the pathologic amount of sugar in the urine.	True diabetes, though mild, generally upon a free, mixed diet gives rise to other symptoms than glycosuria, especially to polydipsia and polyuria.

GLYCOSURIA.—(*Continued.*)	MILD DIABETES.—(*Continued.*)
Simple glycosuria has a more stationary tendency, and is often attended for decades with the same power of assimilating carbohydrates.	True diabetes, even in its mild stage, has a more progressive tendency. The power of assimilating carbohydrates often gradually diminishes, and the mild stage not very rarely passes over into the severe stage.
After the ingestion of a large dose of some other saccharid than glucose, a certain amount of that saccharid appears in the urine, accompanied by no glucose or by a relatively small amount of it.	After a large dose of some other saccharid than glucose, a certain amount of glucose appears in the urine accompanied by no other saccharid or by a comparatively small amount of the ingested saccharid.

The late excellent Norwegian physiologist and specialist in diabetes, Worm-Müller, considered that he had discovered a distinct difference between glycosuria and diabetes in their different behavior after the ingestion of large amounts of other saccharids than glucose. In simple glycosuria, according to this observer, some part of a large amount of another saccharid ingested would pass unaltered in the urine, while in diabetes every trace of saccharid found in this secretion appears in the form of glucose. Thus, in a case presenting pathologic excretion of glucose after the ingestion of from 200 to 300 grams of cane-sugar, one of three different conditions of the urine would arise :

If cane-sugar only is found in the urine, the urine reducing Fehling's or Nylander's solution not previously, but only subsequently, to boiling with dilute sulphuric acid,	a diagnosis of glycosuria must be made.
If both cane-sugar and glucose are found in the urine, greater reduction taking place after than before boiling with dilute sulphuric acid,*	a diagnosis of glycosuria must be made.
If the urine contains only glucose, and the reduction is as marked before as after boiling with dilute sulphuric acid,	a diagnosis of diabetes must be made.

* I would remind the reader that in this experiment titration and not polarization must be used before and after boiling with dilute sulphuric acid. Before the boiling, the glucose alone reduces ; the cane-sugar does not. Both saccharids turn the polarized light to the right. By boiling, the cane-sugar is changed into "invert sugar," a mixture of levulose and glucose, of which the former turns the polarized ray of light to the left, while the latter turns it to the right, but both have about the same capacity for reduction (see below).

This mode of distinguishing between diabetes and simple glycosuria has, however, only relative value, and we find also in this respect only a gradual difference. In diabetes (except in some cases after long periods of abstinence from carbohydrates) glucose is far more easily made to appear in the urine after ingestion of cane-sugar than in simple glycosuria, and after certain amounts in the former only glucose may be found in the urine; but after large amounts of cane-sugar even the diabetic patient of the most aggravated type may pass, in addition to large quantities of glucose, small quantities of unaltered cane-sugar. Minkowski found this to be the case even in diabetic dogs after the extirpation of the pancreas, though the dog—judging from many experiments recorded in literature—is more prone than man to develop glycosuria after ingestion of cane-sugar. In several cases of slight simple glycosuria I have found the proportion between the amounts of cane-sugar and glucose excreted after the ingestion of large amounts of the former to vary greatly from one day to another in the same individual. In one case of simple glycosuria of long and stationary standing in a gouty and neurasthenic individual, the patient, to overcome his dread of diabetes, used once every year to take 300 grams of cane-sugar. The urine, which some time after every rich dinner contained, for a while, a small amount of glucose, after this enormous dose of cane-sugar yielded no distinct reaction with Nylander's solution, although it contained a few grams of unaltered cane-sugar. One day, however, just after taking the 300 grams of cane-sugar, the patient got into a violent passion, and an hour afterward a small amount of urine contained 1.3 per cent. of glucose, but only a small, doubtful amount of cane-sugar. The test being repeated some few days later, yielded the former usual result; the urine contained no definite amount of glucose, but a few grams of cane-sugar.

Simple glycosuria does not perceptibly alter the "patient's" state of nutrition, and generally shows a strong tendency to remain stationary, even under the influence of deleterious circumstances. The later in life it appears, and the longer it has remained unaltered, the smaller is the danger of its development into true diabetes. Whenever gout exists as a complication, the probability of the glycosuria

remaining unaltered is exceedingly great, and I consider such excretions of sugar in the urine in elderly, gouty persons to be of small clinical importance; but even an inconsiderable glycosuria, after having shown itself for a greater length of time, is most likely to continue through the patient's whole life, and a development into true diabetes is not with certainty excluded.

Hepatogenous Glycosuria.—The liver is the organ in which glycogen is stored as a reserve force, and the organ in which this glycogen is again converted into glucose and yielded up to the circulation for the purpose of generating energy by oxidation. It is evident, therefore, that certain disturbances in the activity of the liver may cause disturbances in the metabolism of the sugar of the blood, and occasion hyperglycemia and glycosuria. Though it involves some repetition, I consider it best, for the purpose of gaining a clear view of the subject, to make a summary of the different ways in which this may occur.

The supply of glucose to the liver through the portal vein may be so large and so sudden that even a normal capacity of the liver to convert the surplus into glycogen is overtaxed, and the glucose over and above that which can be stored in the muscles and elsewhere, or be consumed in the tissues, enters the circulation. This is evidently the case in what we call alimentary glycosuria after very large amounts of glucose have been taken. Another instance of a similar form of glycosuria—which with Claude Bernard, who first demonstrated it, we may call alimentary, as its origin is essentially the same—is that produced by the injection into the mesenteric veins or into the portal vein of glucose or glycogen (which is transformed into glucose in the blood).

When hyperemia of the liver occurs, hyperglycemia may result from an increased production of sugar, either in consequence of the diastatic ferment of the blood attacking the glycogen more vigorously or of the liver-cells becoming more pronounced in their specific activity, including the secretion of sugar. It is certain that Bernard's "piqûre," many kinds of poison, and most of those other conditions that induce glycosuria have been shown to be the cause also of hyperemia of the liver; and that which directly causes hyperemia of the liver, often causes also glycosuria. Arthaud and Butte

have recently shown that after ligation of the splenic artery and the right gastro-epiploic artery, which considerably increases the supply of arterial blood of the liver, glycosuria arises. The finding by Exner (1898) of glycosuria in each of forty cases of gall-stones leads me to believe that the glycosuria also in these cases is due to the congestion of the liver. Trauma of the liver sometimes causes glycosuria—if through congestion or through nervous influences is uncertain. Hyperglycemia and glycosuria also follow if arterial blood is injected into the hepatic artery (Pavy) or if the vaso-constrictor nerves of the liver are divided (Chauveau and Kaufmann). On the other hand, anemia of the liver seems to induce hypoglycemia. After ligation of the hepatic artery Arthaud and Butte found at first hyperglycemia, probably brought on by the struggles of the animal during the experiment or by the loss of 100 grams of blood taken before the application of the ligature for the sake of determining the quantity of sugar (see below); but after this transitory hyperglycemia, the ligation was followed by distinct hypoglycemia. Tangl and Harley also found hypoglycemia after ligation of the hepatic artery.

Furthermore, glycosuria may arise from such disorders of circulation as prevent the blood in the abdominal vessels from passing in the portal vein through the liver in normal quantities, so that a large part of this blood escapes the customary regulating influence of the liver by being made to pass through the other otherwise comparatively unimportant channels outside the liver. Claude Bernard thus caused glycosuria in the dog by ligation of the portal vein. Andral, as early as 1856, found sugar in the urine in a case of pyle-thrombosis, and Colrat and Couturier, in the seventies, confirmed this observation.

Finally, we may not unreasonably assume that such processes as directly decrease the power of the liver to store the glycogen may tend to produce glycosuria, and some facts seem to corroborate this. The retention of bile speedily empties the liver-cells of their glycogen (Dastre and Arthur, Hergenhahn), and Golowin found glycosuria after closure of biliary fistulæ, v. Wittisch after ligation of the bile-ducts. Tscherinow observed glycosuria in association with acute yellow atrophy of the liver, Schmitz with amyloid degeneration of the liver, Neusser with poisoning by phosphorus.

(This effect of phosphorus, however, seems, according to Bollinger, Huber, and Münzer, to be rather the exception than the rule.) Cirrhosis of the liver has been the subject of many investigations in this connection, but in default of an exact expression for the normal power of assimilation and of any considerable number of perfectly uniform researches, and on account of the frequency of excretion in the urine of small, pathologic amounts of glucose, apart from disease of the liver, it is difficult to arrive at definite conclusions. I have in this connection observed a large number of patients with simple atrophic cirrhosis and some with hypertrophic cirrhosis of the liver, and repeatedly have found glycosuria, and sometimes true diabetes. On the other hand, I have seen quite a considerable number of patients in a far-advanced state of cirrhosis of the liver that were able to take large amounts of carbohydrates without developing glycosuria, and I was for a long time unable to make up my mind as to the supposed intimate connections between cirrhosis of the liver and glycosuria. Even now I am able to accept such a connection rather on account of Naunyn's figures of about sixteen per cent. of cirrhosis of the liver among diabetic patients than from my own experience.

Naunyn's observations seem to confirm Claude Bernard's opinion as to the greater frequency of glycosuria in cases of incipient than in those of advanced cirrhosis. One sometimes, however, finds glycosuria in patients with most pronounced cirrhosis of the liver.

Toxic glycosuria arises from the ingestion of various substances, and many experiments that have recently been made seem to indicate that almost any poisonous substance may increase the amount of sugar in the blood and cause glycosuria, and that this may even result through substances that are normally present in the blood, if they be injected or ingested in abnormally large amounts.

Except in the cases in which phloridzin has been given, and in those of slow asphyxiation, the glycosuria that results from poisoning is always caused by hyperglycemia, which may be the result of a toxic influence exerted in various ways. Such an occurrence may be brought about by a direct effect on the nervous centers, and through them on the vasomotor nerves, with hyperemia of the liver and increased production of sugar; or by a paresis of the muscles, with

decreased consumption of the sugar of the blood, either in consequence of metabolic changes in the muscles themselves, or in consequence of disturbances of respiration and want of oxidation; or of an influence on the tissues and on cellular vitality, with deterioration of the general metabolism; or of some influence on the liver-cells, with a weakening of their power to store glycogen; or of a change in the epithelial elements of the kidneys, in consequence of which they permit the escape of the sugar of the blood with the urine (phloridzin). We have as yet on this subject only hypotheses that are analogous to the theories concerning diabetes. An enormous amount of experimental work will be required to put us in possession of all the knowledge that is to be gained from a study of the glycosuria due to various forms of poisoning.

In all of the glycosurias of this group, with the exception of that due to phloridzin, the amount of sugar in the urine keeps at a moderate level* and constitutes only an unimportant feature of the entire clinical picture. Having made its appearance with the other symptoms, the glycosuria generally persists for some time after the elimination of the poison. The glucose is often accompanied by other pathologic substances. One of these is lactic acid, which is considered to represent a station in the combustion of carbohydrates on their way to complete oxidation and to the formation of carbonic acid and water. After the ingestion of chloral† or chloralamid (Manchot), of nitrobenzol and nitrotoluol (Ewald, v. Mering, Magnus-Levy), of orthonitrophenyl-propionic acid (Hoppe-Seyler), side by side with the glucose we find the combined glycuronic acids, which reduce solutions of copper and bismuth and deflect the polarized light to the left, but do not undergo fermentation (see below).

Acids, both without and within the organism, seem to favor the

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* Araki has recently induced glycosuria by the administration of veratrin, morphin, cocain, strychnin, amyl nitrate, and carbon dioxid, the amount of sugar in the urine reaching four per cent. There was often albuminuria. The lactic acid in the urine reached two per cent.

† Ewald first saw reduction after ingestion of chloral, and attributed it to glucose. Von Mering, however, by the absence of fermentation, demonstrated the reducing substance to be something else than glucose. It was found to be a combined glycuronic acid (urochloralic acid). In some cases both substances are present.

molecular construction of sugar and to facilitate the transmutation of glycogen into glucose, just as alkalies seem to have the opposite effect.* If acids are introduced into the blood for some time and in sufficient quantities, they cause emaciation, anemia, lowering of temperature, neuralgia, paresis and paralysis, and, finally, a state that greatly resembles diabetic coma (Rolf, Walter, Hugonenq, Stadelmann, Külz, and others). Moreover, there may or may not be albuminuria. The glycosuria also is not constant, and when it follows, it is slight. It has been observed in cases of poisoning with sulphuric acid (Pavy), lactic acid (Golz, Naunyn), hydrochloric acid (Naunyn and others), salicylic acid (Pollatschek), prussic acid (Geppert), oxalic acid, orthonitrophenyl-propionic acid (Hoppe-Seyler), and the lower fatty acids (Mayer).

Frerichs reports some cases of poisoning with sulphuric acid, in which he found sugar in the urine only exceptionally, though reducing substances, which do not undergo fermentation (combined glycuronic acids), are not rarely present.

1. B. L., a healthy servant-girl of twenty-two, took a large quantity of concentrated sulphuric acid and excreted as much as 0.5 per cent. of glucose (reduction, rotation, fermentation). The specific gravity of the urine was 1.043, and no albumin was present.

2. M. S., in the fifth month of pregnancy, drank, on May 26th, concentrated sulphuric acid; was given calcined magnesia in milk, but vomited blood; had violent pains in the mouth and throat, hoarse voice, and pain in the epi-

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* Acids cause saccharification of glycogen and starch, while alkalies do not. Coignard watered radishes, Martin-Damourette a vine, with alkaline water, and thus obtained a much smaller amount of sugar in the roots of the former and in the fruits of the latter, than by using ordinary water. Ehrlich found that frogs living in a solution of glucose stored a good deal of glycogen in their livers when sodium bicarbonate was added to the solution of glucose, but a comparatively small amount when acetic acid was added. Pavy assumes that sulphuric acid injected into the blood favors the transmutation of glycogen in the liver into sugar, but that injections of sodium bicarbonate favor its transmutation into something else. His opinion that the latter-named injections decrease the hepatic glycogen was not borne out by the experiments of Külz, which yielded exactly opposite results. In cases of severe diabetes with large quantities of (diacetic and β-oxybutyric) acids in the blood the hepatic glycogen is distinctly diminished (Frerichs, v. Mering and Minkowski, Stadelmann). As a result of his experiments Külz reached the somewhat uncertain conclusion that dextronic acid, sugar acid, and mucous acid contribute to the formation of glycogen in the liver. This seemed certainly to be the case with the anhydrid of glycuronic acid, which is molecularly closely related to glucose. Even if all these weak acids should in some way contribute to the formation of glycogen in the liver, it can scarcely be doubted that stronger acids in the blood are decidedly antagonistic to such a result.

gastrium. She voided 700 cu. cm. urine of a specific gravity of 1.045 (!), free from albumin, sugar, and other reducing substances. On May 28th the specific gravity was 1.039, the next day 1.031, and free from abnormal substances. On June 1st the urine had a specific gravity of 1.034, was dark, smelt of acetone, and yielded a wine-red reaction with ferric chlorid (diacetic acid from inanition). There was no reduction, no rotation of the polarized light, no albumin. The sulphuric acid present in the urine equaled 1.68 grams, of which 1.43 were mineral sulphates and 0.25 aromatic sulphates. Thus, the latter were increased, although the whole amount was not abnormal. The vomiting and the pains continued, so that only small quantities of liquid food could be taken during the first few days. On June 3d the patient was able to take more food; on June 5th the wine-red reaction of the urine had disappeared, while the specific gravity was 1.010, and the sulphuric acid equaled 1.18 grams.

It has been proved that a large number of partly indifferent, partly poisonous, *metals and metallic salts*, when injected into the blood or taken by the mouth, are capable of causing glycosuria. This is the case with injections into the blood of ordinary sea-salt (Bock and Hoffmann, see below), sodium bicarbonate (Külz, Kessler), sodium acetate, sodium valerianate, sodium succinate, sodium phosphate, and sodium sulphate (Külz, Kuntzel), as well as with sodium salicylate taken by the mouth (Burton).

Phosphorus (Bollinger, Huber, v. Jaksch), arsenic (Bernard, Quinquaud, Saikowski, Masoin), mercury (Reynoso, Rosenbach, Bouchard, Cartier, v. Mering), lead (Brunelle, Strauss), uranium (Cartier), also cause glycosuria more or less constantly.

At least under some of the conditions named the hyperglycemia is induced through the agency of the nerves, as glycosuria does not follow the injection of sea-salt if the splanchnic nerves are divided (Külz).

Phosphorus causes glycosuria, lactaciduria, and peptonuria, but none of these is constant. Von Jaksch observed glycosuria in 15 of 43 cases of phosphorus-poisoning. Of Münzer's ten cases, of which several terminated fatally, it is in most cases especially stated that the urine contained no sugar, and in no single case is it mentioned that there was any. Laub in two cases noted 0.15–0.7 per cent. of glucose. Von Jaksch mentions that glycosuria is common in such cases when icterus is present.

Arsenic, which has the power of preventing glycosuria after Bernard's puncture, and is used therapeutically because of its property of diminishing the excretion of sugar in the urine, in toxic doses sometimes causes glycosuria. Whether this is a consequence of the glycogen being driven out of the liver and the muscles being unable to consume the increased sugar in the blood

(Zimmer), or the effect of the accumulation of arsenic in the brain (Scolozoboff), has not been decided.

Feilchenfeld has described a case of acute arsenical poisoning with an extensive, fully developed, multiple neuritis. The case, which first seemed to be one of true diabetes (4.7 per cent. of sugar), soon settled down to an insignificant glycosuria.

Both sugar and albumin are sometimes found in the urine of persons undergoing antisyphilitic mercurial treatment, but only when the mercurial poisoning is pronounced (Frerichs, Kussmaul, Lewin). Graf noticed in rabbits constant glycosuria after doses of mercuric chlorid.

Brunelle found from 0.2 to 1 per cent. of glucose in the urine after administration of 200 grams of syrup in more than half of a number of cases of lead-poisoning.

Uranium and its salts constantly cause glycosuria and albuminuria.* Those that, not very wisely, have introduced uranium nitrate into therapeutics for the purpose of diminishing glycosuria, should have first considered its poisonous properties. Cartier found subcutaneous injections of from ½ to 2 milligrams per kilo of body weight to be fatal, the animals (rabbits) manifesting thirst, diarrhea or constipation, loss of appetite, somnolence, torpor, paresis or paralysis, retarded respiration, emaciation, lowering of temperature, and death in coma, with or without convulsions. The glycosuria appeared about twenty minutes after the injection, reached its maximum in a day or two, seldom exceeded more than 1 per cent. of sugar, and then decreased. The urine first increased, then decreased, anuria finally setting in. Acetone was present, probably from inanition. The autopsy disclosed a severe congestion of the whole gastrointestinal tract, with ulcerations in the stomach and the duodenum. The liver was intensely hyperemic; large amounts of the drug caused cellular necrosis. The kidneys were also markedly congested, and the seat of diffuse parenchymatous inflammation, often with cellular necrosis. The heart presented subendocardial ecchymoses. Neither the nervous system nor the pancreas nor the lungs presented noticeable changes.

Alcohol, which in small amounts increases the power of assimilating carbohydrates, has in large amounts the opposite effect. Thus, the diabetic is, after generous indulgence in alcohol, found to excrete far more sugar than he does otherwise with the same allowance of carbohydrates in his diet. Simple glycosuria may, under the same influence, be attended with such quantities of sugar in the urine as are common in diabetes; while a normal individual may, after excesses "in Baccho," present glycosuria. This effect is more easily brought about in some persons than in others, but

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* Glycosuria following the ingestion of uranium was first observed by Leconte in the beginning of the fifties; then by Gmelin, Bernard, Blake, Rabuteau, Curée, Chittenden, Kowalewski, Whitehouse, Lambert, Woroschilski, and Cartier.

probably may be caused in any individual—a fact well worth knowing and remembering, to avoid false diagnoses of diabetes. Beverages that contain large quantities of both alcohol and carbohydrates are especially efficient in causing glycosuria, which is often observed after indulgence in champagne and beer and also in that disgusting mixture of arrack, sugar, and water, which is called Swedish punch, and often flows too freely in my native country. The glycosuria following the use of alcohol is generally moderate, and the sugar in the urine keeps within one per cent., but after excessive indulgence may continue for several days, especially appearing after meals.

In cases of chronic alcoholism one also sometimes finds a small amount of sugar in the urine. I have, however, seen a considerable number of such persons with a normal power of assimilating carbohydrates.

Ether, now and again, causes glycosuria, whether injected in the veins (especially the portal vein, Harley), inhaled, or taken by the mouth. There are, however, individuals that, in spite of long and great abuse of ether, exhibit no glycosuria (Frerichs). Andral observed diabetes in such a case, but the question whether *post* or *propter* remains undecided.

Chloroform often causes the excretion of small amounts of sugar (Eulenburg and others).

Chloral causes the appearance in the urine of urochloralic acid, belonging to the group of combined glycuronic acids (v. Mering); on account of its reducing properties this acid has often been mistaken for glucose. Chloral, however, now and again also causes true glycosuria (Telz, Ritter, Eckhard). Manchot observed slight glycosuria in about one-fourth of a number of cases in which *chloralamid* was being administered.

*Amyl nitrite** causes glycosuria more surely than alcohol, ether, chloroform, or chloral, the sugar in the urine rising at times above two per cent., and appearing for twenty-four hours after inhalation (Fr. A. Hoffmann). Bouchard thinks this due to the transmutation of the oxyhemoglobin into methemoglobin and to deficient oxidation; others lay stress on the vasoparalytic influence and the congestion of the liver.

Lactic acid is under these circumstances, as under others, sometimes found in the urine in association with glucose.

Ammonia, when injected into the portal vein, causes glycosuria, which also Bouchard ascribes to the decreased capacity of the blood to absorb oxygen.

Glycosuria from Asphyxia.—As early as 1868 Senator, in the course of his investigations on the effects of disturbed respiration,

* Siebold, "Ueber d. Amylnitrit-Diabetes," Diss., Marburg, 1874.

found glycosuria to be one of these effects, although it proved subsequently, after continued clinical observation, to be the exception rather than the rule.

Senff in 1869 observed that dogs, after inhaling carbonic acid, constantly exhibited glycosuria, sometimes accompanied by albuminuria. He found hyperglycemia, but a normal capacity on the part of the muscles to consume sugar, and he therefore attributed the hyperglycemia to an increased production of sugar in the liver.

Dastre in 1879, in his thesis "Sur la Glycæmie Asphyctique," made a distinction between slow and rapid asphyxiation : the former causing hypoglycemia, the latter hyperglycemia, and both, glycosuria. In slow asphyxiation, when the animals breathed in closed compartments or in rarefied air, the amount of sugar in the blood was distinctly diminished, and Dastre attributes the glycosuria under these conditions to the want of oxygen and the greatly reduced oxidation, in consequence of which even the decreased amount of sugar in the blood is not consumed.

In the nineties Hoppe-Seyler's pupils—Araki, Zillesen, and Irisawa—proved that different conditions and circumstances that induce dyspnea or are attended with a deficiency in the supply of oxygen (agony, severe anemia, etc.), often also cause glucose and lactic acid to appear in the urine, though neither the one nor the other is always present.

Hoppe-Seyler's pupils consider the glycosuria attending the collapse due to many poisons (curare, delphinin, strychnin, morphin, chloroform, ether, sulphonal, carbonic acid, hydrocyanic acid, etc.), as well as that appearing during tetanus, after epileptic attacks and other similar states, as being of asphyctic type. Schiff, Sauer, and others also insist that the glycosuria does not appear, or that it disappears, if asphyxia is prevented by proper artificial respiration. Still there are other plausible explanations : Dastre is of opinion that asphyctic blood excites the liver to increased production of sugar, and remarks that the glycosuria due to many poisons appears *before* any deficiency of oxidation could be effective.

Glycosuria due to carbon monoxid was mentioned by Bernard (1857), investigated by Senff (1869), and afterward studied by Richardson, Ollivier, Biefel and Pollek, Frerichs, Hasse, Kahler,

v. Jaksch, Araki, Garofalo, Rosenstein, Walter Straub, Vamossy, and others. It is caused by hyperglycemia; the sugar in the urine may reach 1.5 per cent. in man (Frerichs) and 4 per cent. in the dog (Senff). Lactic acid injected subcutaneously reappears almost entirely in the urine, but sugar injected does not. In fact, Walter Straub, Rosenstein, and Vamossy all have arrived at the conclusion that the amount of glucose in the urine in this most remarkable kind of glycosuria is not increased by the ingestion of sugar, and that the glucose is not derived from carbohydrates, but from proteids, especially fibrin (Vamossy).

Curare causes glycosuria, as was known to Bernard, and the condition has since been made the subject of many investigations.* The glycosuria appears quickly, and is associated not only with polyuria, but also with hypersecretion of the sudoriparous, salivary, lacrimal, and intestinal glands. The abdominal organs, especially the liver, are intensely hyperemic. Langendorff maintains that extirpation of the liver does not prevent the glycosuria due to curare, although starvation does. Unlike what takes place in the glycosuria due to strychnin, the liver afterward may contain a considerable amount of glycogen. Schiff, Penzoldt, Fleischer, Zuntz, and Sauer agree as to the freedom of the urine from sugar, if artificial respiration is properly maintained. As long as this is successful, the urine contains a reducing, but not a fermenting, substance (probably pyrocatechin, Sauer), but as soon as respiration begins to fail sugar appears.* The glycosuria due to *methyl delphinin* seems to be very like that due to curare.

Glycosuria due to *strychnin* was observed in the fifties by Claude Bernard and by Schiff; it was afterward studied by Langendorff and by Gürtler. It is most easily induced in frogs in the autumn, when their livers are well stored with glycogen. The sugar is somewhat slow to appear, and may not do so for a whole day. It may then persist for several days, although at a low figure. The liver is emptied of its glycogen (the "paraplasma" or substratum, for it is diminished), and the hepatic cells are reduced in size and become polygonal in shape (Langendorff). Extirpation of the liver prevents the development of the glycosuria, as does also destruction of the spinal cord, while severance of the head from the body does not (Claude Bernard). The glycosuria does not depend on the tetanus, as it appears also if the muscles are entirely paralyzed. There is some polyuria and lactaciduria.

Morphin gives rise to glycosuria, as is well known from Eckhard's work, and as can easily be demonstrated by injecting from three to five centigrams of the sulphate or hydrochlorate subcutaneously in a rabbit. The sugar appears in small quantities as early as the second hour after the injection, and often persists only for a few hours; the condition is the result of hyperglyce-

* Winogradoff, Casal, Lionville, Langendorff, Voisin, Saikowski, Schiff, Doch, Gaglio, Demant, Penzoldt and Fleischer, Zuntz, Sauer ("Pflüger's Archiv," 1891).

mia (Seegen). Like the glycosuria after Bernard's puncture, that due to morphin is prevented not by section of the pneumogastric, but by that of the splanchnic nerves or of the spinal cord above the roots of these nerves. After large doses the transitory polyuria is followed by a decreased secretion or even by anuria. An injection of glycerin prevents the glycosuria (Luchsinger), or at least has an effect in that direction (Eckhard).

Sugar is sometimes found in the urine of morphinists and sometimes not (Pichon). I have found only slight traces in a few cases of this kind. In these, as in other cases of poisoning, the acute state is attended with more pronounced glycosuria, and more frequently, than the chronic state.

Veratrin causes slight glycosuria and lactaciduria (Araki)—not in consequence of diminished "glycolytic power" on the part of the blood, but on account of an increased production of sugar, according to Lépine.

Von Noorden observed glycosuria after the use of *ergotin*.

Many diuretics cause glycosuria. This and some other facts have of late led some observers to the conclusion that there is a *glycosuria due to polyuria*. When Bock and Hoffmann injected a one per cent. solution of sodium chlorid into the veins of the rabbit, the animals first presented distinct polyuria and later glycosuria.* Jacoby (Strassburg) found that sulphocaffeinic acid, sodium caffein, benzoate, and theobromin-sodium salicylate ("diuretin"), all diuretics, caused glycosuria.†

Klemperer, who strongly maintains that glycosuria may result from polyuria, found sugar after administration of digitalis. We often find inosite accompanying polyuria—why not also glucose? There are also, at times, cases of diabetes insipidus with traces of glucose in the urine—though this does not at all seem to be a common occurrence. It is not easy to make up one's mind definitely as to the glycosuria resulting from polyuria. The facts already mentioned may be explained in different ways, and there is one important and well-known fact that denotes that polyuria does not always produce glycosuria. Cirrhosis of the kidneys is attended with polyuria, but not with glycosuria, and in case of diabetes it has a decided influence in decreasing the glycosuria.

Some *animal poisons* cause glycosuria. Ewald, and afterward Strauss, found as much as six per cent. of glucose in the urine after administration of *thyroidin*; when the thyroidin ceased, the glycosuria also ceased.

Teschemacher noted glycosuria after injections of Koch's *tuberculin*; Dufresne, after injections of *pancreatin*.

Toepfer and Freund observed glucose after injections of a dialysate of *feces*. The fact that the glycosuria reached a greater intensity and was of

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* This experiment, however, has many other effects than polyuria, and especially a decrease in the glycogen in the liver, and hyperglycemia. In some cases there was also albumin and even blood in the urine, denoting a condition of the kidneys that by some persons is considered conducive to glycosuria.

† Neumann administered "diuretin" in a case of insufficiency of the aortic valve, and observed polyuria and glycosuria, which he ascribes to the heart-disease. The glycosuria may as well have been caused by the "diuretin."

longer duration when feces from diabetics were used than when the feces were derived from healthy individuals, may, if not dependent on mere chance, be explained by the customary greater abundance of the products of the putrefaction of proteids in the intestines of diabetics. The theory advanced by Toepfer belongs, in my opinion, to what Punch calls "things one would rather have left unsaid."

As is well known, the liver is supposed, among other functions, to have that of retaining poisonous substances absorbed from the alimentary canal and of preventing their entrance into the blood. On the other hand, the toxicity of the urine is an index of the amount of such substances in the blood. Roger ("Action d. Foie sur les Poisons," Paris, 1887) observed that patients suffering from various hepatic disorders and secreting a highly poisonous urine readily developed glycosuria after the ingestion of considerable amounts of sugar; and he expresses the opinion that the liver has in those cases lost in part its capacity for retaining the poisons and for converting alimentary sugar into glycogen.

Phloridzin-glycosuria.—Scarcely had Koninck (1885) discovered phloridzin when v. Mering (1886) observed that this substance causes an exceedingly peculiar form of glycosuria.

Phloridzin is a glucosid obtained from the bark of the root of certain species of Pyrus and Prunus. It crystallizes in glistening silky crystals and is easily soluble in warm water, but requires 1000 parts of cold water for its solution. Phloridzin is levogyrate. It is decomposed by boiling with diluted acids:

$$C_{21}H_{24}O_{10} + H_2O = C_6H_{12}O_6 + C_{15}H_{14}O_5.$$
Phloridzin × Water = Phlorose + Phloretin.

Phlorose, as will be seen, is a hexose, has the same molecular construction as glucose, which it resembles greatly, is dextrogyrate, and reduces, though in less degree than glucose.

Phloretin, though less efficient in this respect than phloridzin, also causes abundant glycosuria. Treated with caustic alkali, it forms phloretic acid (an aromatic alcoholic acid) and phloroglucin (a triatomic aromatic alcohol), both of which are probably also formed in the organisms; they do not cause glycosuria, but increase the combined aromatic sulphatic acids in the urine (Moritz and Praussnitz). In the course of the intoxication, and as long as the glycosuria lasts, there appears in the urine a brownish-violet coloration on addition of ferric perchlorid (due to phloridzin). With phloretin a similar, but more deeply violet, reaction is obtained. The urine, especially if the animal has been kept fasting, becomes slightly albuminous.

The glycosuria commences after a couple of hours, after 0.01 gram per kilo of body weight has been given by subcutaneous injection, and after double that dose by the mouth in dogs. After large doses the amount of sugar may rise to more than thirteen per cent. (Moritz and Praussnitz), or even to more than eighteen per cent. (v. Mering) in dogs, and it may persist for several days or a week (Coolen). The quantity of urine is not increased, but the specific gravity may rise to 1.070. In rabbits the glycosuria is less marked and more transitory, but it appears regularly after subcutaneous injections; after injection of two grams it persists for from seven to twenty hours (Lusk). It is also observed in the hen, the goose, and the frog (Ritter and Cremer). It has been observed in the goose after extirpation of the liver (v. Mering, Thiel).

The organism, even under the influence of phloridzin, assimilates a considerable part of the ingested carbohydrates. The larger the dose of phloridzin, the greater the absolute value of the sugar in the urine, but the smaller its value in relation to the dose.

Klemperer, and recently (1899) Achard and Delamare, have found phloridzin to give rise to much less marked glycosuria in cases of chronic nephritis than otherwise.

Phloridzin, as may be understood from the relation between the quantity ingested and the amount of sugar in the urine, acts in a "specific" manner, and not by reason of being a glucosid, as other glucosids do not cause glycosuria (v. Mering, Gley, Germain Sée). Thus, 6 grams of phloridzin, containing 2.5 grams of phlorose, may cause glycosuria with 41.7 grams of sugar in the urine.

An abundant mixed diet, including a great deal of sugar and starch, causes the glycosuria to reach its maximum; but it continues during starvation and even after extirpation of the liver. Von Mering found glycosuria in the dog when the liver and the muscles were almost, but, as Külz remarks, not completely, emptied of glycogen.

When the food is made up exclusively of fat, the glycosuria falls as low as in starvation (v. Mering, Moritz, and Praussnitz)—a most remarkable circumstance, which speaks against the opinion of those who think that fat may, with a deficiency of carbohydrates and of albumin, form glucose in the organism.

As long as the food is abundant enough to cover the heat-wants

of the organism *and* the loss of sugar in the urine, even large doses of phloridzin do not cause any general disturbances; but during starvation and poisoning with phloridzin inanition speedily develops; the animals quickly lose weight; the proteids of the organism are decomposed; acetone, diacetic acid, and β-oxybutyric acid show themselves in the urine, while the ammonia increases, and weakness and somnolence become manifest. If the animals are then killed, the liver and the muscles are found in a state of fatty degeneration. [Rosenfeld is of the opinion that the fat in the liver in these cases is derived from an infiltration of fat from other parts than the liver, and not from fatty degeneration of proteids in the liver-cells.] If the animals are given food and the phloridzin is withheld, they speedily return to health. The liver is said to store more glycogen from meat under the influence of phloridzin than if the animals receive only sugar.

The most peculiar feature of the phloridzin glycosuria, however, is the presence of a *decreased* percentage of sugar in the blood. Von Mering and almost all other observers agree on this point.*

Von Mering found from 0.075 to 0.09 per cent. of sugar in the blood with from 6.5 to 9.2 per cent. of sugar in the urine of the dog, the blood normally containing about 0.10 per cent. Gabritschewski found that, while the white corpuscles of hyperglycemic (diabetic) blood contain an abnormally large quantity of glycogen, they contain an unusually small amount thereof in phloridzin cases.

There are only two ways of explaining phloridzin-glycosuria—it may arise in consequence of some alteration in the epithelial elements of the kidneys (v. Mering), or it may be the result of some combination of phloridzin or one of its derivatives with glucose (Graham, Lusk). In either case the passage of the latter into the urine is facilitated, and the blood, the liver, the muscles, and the whole organism are thus deprived of both sugar and glycogen, which are constantly renewed, though not at the same rate as they are lost.

After extirpation of the kidneys the hypoglycemia ceases, but

* Pavy, whose researches on blood-sugar have led him to such curious conclusions, has not found any hypoglycemia during phloridzin-glycosuria ("Journ. of Physiol.," London, 1894). Coolen also found no decrease of blood-sugar, and Levene found a somewhat higher figure for the sugar in the renal vein than in the arterial system.

hyperglycemia does not arise. Zuntz took the urine from both ureters of the dog immediately after an injection of phloridzin into one of the renal arteries, and found that the urine on this side immediately became saccharifierous, while that on the other side became so only when the phloridzin had reached the kidney on this latter side through the entire circulatory system.

According to Cornevin, phloridzin has an analogous influence on the lactogenous glands and increases the lactose in the milk.

Antipyrin (Sée and Gley) and syzygium jambolanum (Gräser) act in a manner opposite to phloridzin, and diminish the glycosuria.

Phloridzin and phloretin are sometimes used for the purpose of simulating diabetes.

The glycosuria due to infectious diseases is generally attended with the presence of insignificant quantities of sugar in the urine, and occurs very inconstantly in the course of acute exanthematous and other infections. It is not yet known under what conditions and during which period the sugar appears. On the one hand, we know positively that the sugar in the urine in diabetes or glycosuria decreases and sometimes disappears during the febrile state, while, on the other hand, the infectious diseases attended with fever often induce glycosuria. Poli recently, after the administration of glucose in cases of scarlet fever, diphtheria, septicemia, tonsillitis, and pneumonia, found a decreased power of assimilation and a much greater portion of the ingested glucose in the urine than would have appeared in normal individuals. In cases of malignant pustule Roger found the sugar in the blood in the beginning of the disease normal, or even somewhat below the customary amount; then a moderate hyperglycemia, with from 0.22 to 0.30 per cent. of sugar in the blood appeared, and after death the liver contained no glycogen. In other cases of febrile disease the glycosuria appears during the period of defervescence and the beginning of the convalescence. I have also seen it during the prodromal stage, and it does not seem to be excluded from any stage of febrile infections.

Glycosuria is often found in the course of, and after, influenza and malaria; and it is also observed in the course of typhoid fever (Seyfert, Bordier), diphtheria (Frerichs), scarlet fever (Redon, Zinn), measles (Fischer, Bouchut, Bordier, Barlow, Gelmo), dysen-

tery (Anstoots), cholera (Heintz, Samojé, Huppert, Gubler, v. Terray, Vas, and Gara), croup, pertussis, pneumonia (Bordier, Semmola, Stern, Beale, Reynoso), erythema nodosum (Bordier), variola, and vaccinia (during the florid stage, Guéneau, Prevost), anthrax (Proust, Philipeaux, Vulpian, Charcot, Frerichs, Goolden), lyssa (Eichhorst), lymphangitis, and erysipelas (Redard), and septic processes (Poli).

It would seem as if all suppurative processes might induce glycosuria, which has several times been observed in association with gangrene, phlegmon, noma, and especially with furunculosis and carbuncle. Wagner was, I believe, the first to mention glycosuria as complicating these two latter skin diseases. Still, as is well known, furuncles and carbuncles are common manifestations of diabetes. Furuncles especially appear at an early stage of the dystrophy, and there still remains some doubt if, in the cases in which they have been considered to be the cause of glycosuria, they have not really been the effect of a mild diabetes.

In rare cases syphilis causes glycosuria or real diabetes by attacking either of the organs that preside over the metabolism of carbohydrates. In most such cases arteriosclerosis, cerebral softening, hemorrhage, or gummata in the brain precede the appearance of the glycosuria. The few cases that I have seen were examples of glycosuria or mild diabetes. Sometimes their syphilitic nature becomes apparent *e juvantibus*, and quite a number are recorded of cure by antisyphilitic treatment. Decker has reported such a case in which the sugar appeared a little more than a year after the infection. Whether syphilis can cause glycosuria in any other way than through lesions of the brain, the liver, or the pancreas, is not known.*

The prognosis of glycosuria (or diabetes) due to infectious disease is decidedly more favorable than that due to any other cause—the sugar generally disappearing from the urine after or during convalescence. On the other hand, some infections undoubtedly may lead to true diabetes; but even in such cases one may sometimes

* One writer has affirmed—in a book and in advertisements on the walls in Carlsbad—that he *cures* diabetes, which he considers almost always to be an effect of syphilitic infection, either acquired or inherited, perhaps from some ancestor of the dark ages. Such a statement must not be taken too seriously—*quid verbis affirmat satis est verbis negare.*

observe instances of perfect recovery. I have seen this take place after typhoid fever and after influenza, and Zinn mentions a similar occurrence after scarlet fever, and Burdel in three cases after malarial fever.

In cases of *cholera* the sugar appears chiefly in the abundant urine following the anuria; it is often accompanied by indoxyl and albumin; the sugar rarely amounts to one per cent. and disappears during the first days of convalescence. Cases of true and even of severe diabetes are also observed in connection with cholera (Frerichs); but sugar is far from being found in all cases. Von Terray, Vas, and Gara found it only in one case of sixteen; the glycosuria began twelve days after the end of the anuria; the sugar rose to 0.5 per cent. and persisted for three days. The urine of several other patients strongly reduced copper, but did not deflect the ray of polarized light, and did not undergo fermentation.

In cases of *typhoid fever* it seems that sugar may appear in the urine as early as during the prodromal period. A clergyman came to Carlsbad for some dyspeptic trouble, and presented slight evening elevation of temperature and felt generally ill. A dull note on percussion over the apex of the left lung led me to suspect an incipient tuberculosis. A large specimen of urine was found to contain 1.1 per cent. of glucose. I quickly sent the patient to his home, where the typical temperature-curve of typhoid fever developed. After the end of the typhoid (or before) the glycosuria disappeared.

Malaria is not rarely accompanied by transitory glycosuria, which comes on after every paroxysm and sometimes, though rarely, may develop into true diabetes.* The glycosuria diminishes or disappears under the influence of quinin. Burdel found sugar in 14 per cent. of cases of quartan or tertian type, in 22 per cent. of cases of quotidian type, in 28 per cent. of cases of pernicious malaria, and in 80 per cent. of cases of malarial cachexia. He has recorded three cases of a distinctly diabetic nature, in which perfect recovery ensued after the use of quinin.

Since *influenza*, in the beginning of the nineties, again invaded the civilized world there have been published many observations of glycosuria or diabetes arising in the course of this disease, really much more dreadful than dreaded. I have myself seen all forms of defective power of assimilating carbohydrates during and after an attack of influenza, most of the cases presenting slight degrees of glycosuria. In other cases of simple glycosuria that I have had under observation for many years, repeated and severe attacks of influenza have been without any effect whatever on the glycosuria. I have seen several cases of diabetes following influenza improve greatly after convalescence from

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*Peter Frank and Sydenham, more than a century ago, mentioned diabetes in connection with malaria. Burdel, in 1859, directed the attention of the profession to the small quantities of sugar in the urine of patients suffering from malaria. Several French physicians in North Africa (Calmette, Rangé, Duponchet) have contributed to the literature on this subject. In "Malaria and Diabetes," Diss., Rostock, 1896, Otto Jacobson gives the bibliography.

the causal disease, and I have seen at least one case in which perfect recovery ensued.

Mr. X., a Finlander, some thirty years old, came in June, 1890, to Carlsbad, having had his first attack of influenza half a year before. In February he had had another severe attack, with high fever, violent pains in the back and legs, and great prostration. Early during convalescence the patient began all at once, on a certain day, to drink and to urinate freely, and an apothecary found in the urine a large amount of glucose, which by a specialist was estimated at 8.8 per cent. Unfortunately, I could obtain no information as to whether any diacetic acid had been present. The patient consulted Prof. Holsti, who affirmed the existence of diabetes mellitus, prescribed a strict diet, and after some time sent the patient to me in Carlsbad. The general state of health was then much improved, and there were no diabetic symptoms. A generous amount of carbohydrates was allowed and, no glycosuria appearing, the amount was slowly increased until it reached at least 300 grams a day. The urine remained free from glucose, nor could that substance be found after administration of 200 grams of cane-sugar. For some time after the patient's arrival at home he continued to be free from glycosuria upon ordinary diet, but I know nothing of his subsequent fate.

In this, as in some other cases, I have no doubt the glycosuria was due to the influenza.

Blot, in 1850, found in the urine of pregnant women a variety of sugar that Hofmeister afterward proved to be lactose. This *puerperal lactosuria* begins during the last months of pregnancy and persists throughout the whole period of lactation, during the beginning of which it seems to be most pronounced, so that it may reach two per cent. Abeles found lactose in every one of 30 cases; Ney observed it exceptionally before parturition, but in 80 per cent. of the cases he detected it from two to four days after parturition.* Lemaire found in the urine quite small quantities of glucose and isomaltose before parturition, and lactose only after parturition, but in large quantities.

There is no doubt that pregnancy and childbirth sometimes give rise to true glycosuria. *Puerperal glycosuria* is much rarer than puerperal lactosuria. I have seen one patient who, after some months following parturition, was sent to Carlsbad with a diagnosis of diabetes. The urine contained small quantities of a dextrogyrate-reducing substance, which readily underwent fermentation and disappeared in the presence of common yeast. I am unable to

* See, besides, the treatises of Sinety, Kirsten, Spiegelberg, Johannowski, Hofmeister, Kaltenbach, and others.

state how long this glycosuria lasted, but after two years the urine, with an ordinary free diet, contained no glucose. Marcus mentions glycosuria up to 0.7 per cent. during pregnancy; Rossa found glucose during the seventh month, and Lang found that pregnancy is quite often attended with some loss of the power of assimilating carbohydrates.

Sometimes parturition is followed by true diabetes.

The saccharid often found in the urine of nursing infants is lactose (Pollak, Eichhorst), which passes into the urine more easily than other kinds of sugar.

Cl. Bernard found sugar in the amniotic liquor in animals, observed later also by Moriggia and by Cramer. The amniotic fluid contains the urine of the fetus, and this *fetal glycosuria*, like the glycosuria of hibernating animals, constitutes one of the best arguments of those who see in hyperglycemia and glycosuria the effect of deficient combustion in the muscles; but sugar in the amniotic liquor does not seem to be at all a constant phenomenon in normal women, and it is sometimes absent even when diabetes exists in the mother (Williams, Naunyn), though, like other liquids of the organism, it may in other cases of diabetes contain quite considerable (up to 0.7 per cent.) quantities of glucose (Husband). Fetal glycosuria and the glycosuria of hibernates deserve further investigation.

Obesity and Glycosuria.—About one-third of all diabetic patients are corpulent; and very fat persons, according to several observers, present more frequently than others pathologic traces of sugar in their urine. I have, in several instances, found that persons who in early middle age suddenly grew corpulent at the same time began to exhibit distinct traces of sugar for a short while after meals, the urine having previously, under similar circumstances and with the same tests, proved to be normal. Almost all fat people with glycosuria present also neurasthenic symptoms. Some of these patients eventually develop true diabetes, but generally remain in the mild stage. Still, obesity is no safeguard against severe diabetes even exclusive of pancreatic cases; the severe dystrophy, however, within a short time puts an end to the obesity. Kisch believes that in about fifty per cent. of cases of hereditary, and in about fifteen per cent. of acquired, obesity pathologic excretion of sugar takes place sooner or later. The first of these figures appears to me somewhat too high.

Gout and Glycosuria.—Gout is more often than any other disease associated with glycosuria or diabetes. Any physician with many gouty patients under his care will, if he adopt the practice of testing at least once the after-dinner urine of every patient for sugar, find that a large percentage of gouty individuals excrete for some time every day distinctly pathologic quantities of glucose. This glycosuria may set in before the appearance of gouty symptoms, which when mild are often for years overlooked both by patient and physician; in other cases the urine remains normal for some time after the appearance of distinct gouty symptoms. In all such cases neurasthenic symptoms seem to be present. Whether gout or glycosuria has been first to make its appearance, no fact is of better prognostic import in a case of glycosuria than its association with gout. In almost all of the many cases of this kind that I have seen the glycosuric dystrophy has shown a strong tendency to remain stationary, and often, for the important purpose of encouragement, I tell such patients that they will never die until somebody clubs them, which rarely fails to make their faces brighten with the most intense satisfaction.

Diabetes Insipidus and Glycosuria.—Over and above polydipsia and polyuria as effects of hyperglycemia, we may explain a connection between diabetes mellitus and diabetes insipidus by the close proximity of the centers for glycosuria and polyuria on the floor of the fourth ventricle. The existence of a separate center for polyuria (and polydipsia)—*i. e.*, diabetes insipidus—also explains why neither the intensity nor the degree of the glycosuria has any fixed relation to the degree of the polyuria. One patient may pass in the twenty-four hours 1.5 liters of urine containing forty grams of glucose, while another may with the same amount of carbohydrates and other food pass in the same time three liters of urine with twenty grams of glucose. Many think, with Klemperer, that polyuria *per se*, by its influence on the kidneys, favors the elimination of glucose with the urine, as it favors the elimination of inosite. Sometimes, though rarely, one therefore finds small quantities of sugar, which are too insignificant to constitute diabetes mellitus in a case of distinct diabetes insipidus (Mannkopff, Senator).

Starvation and Glycosuria.—Claude Bernard observed that dogs, after having been subjected to starvation, on again receiving carbohydrates presented glycosuria. Lehman (1873) and Hofmeister ("Arch. f. exp. Path.," 1887) have made investigations in this field. A dog, weighing two kilos, showed, after some days of abstinence

from food, distinct glycosuria after the ingestion of as little as ten grams of starch. The sugar under such conditions appeared one to two hours after meals, and generally persisted for only a few hours in small quantities, although sometimes it reached nearly four per cent. In their normal state the animals generally were able to receive about five grams of glucose per kilo of body weight without presenting glycosuria; after starvation the sugar appeared in the urine after less than two grams per kilo of body weight, the rapidity of absorption from the alimentary canal being, in the latter case, rather diminished than increased. It is to be remembered that starvation undoubtedly plays some part in the etiology of true diabetes.

Fatigue and Glycosuria.—Zimmer and others have observed that muscular exercises up to a certain point, in addition to their customary healthful influence on diabetic patients, also have a tendency to diminish existing glycosuria; but too long walks, too much physical effort of any kind has a contrary effect; and sometimes severe fatigue is followed by a considerable increase in the amount of sugar in the urine. The same influences will sometimes show themselves in normal persons, so that after muscular excesses glycosuria may appear for a short while and quickly disappear after rest.

Cold and Glycosuria.—Böhm was, I think, the first to mention the slight glycosuria that may come on after exposure to cold; it has since been observed by Araki and others in rabbits and dogs after application of ice around the body. Exposure to severe cold is not rarely mentioned by diabetic patients themselves as a probable cause of their dystrophy.

Senility and Glycosuria.—Small quantities of sugar often appear in the urine of old persons. This senile glycosuria is of no clinical importance, and entails upon the physician no other duty than to withhold the fact from the "patient," who might be unnecessarily alarmed by such an information.

Cachexia or Marasmus and Glycosuria.—In cases of carcinoma, tuberculosis, Addison's disease (Burghardt), leukemia (Rebitzer), and in other diseases that are accompanied by marked cachexia or maras-

mus, slight traces of glucose are often found in the urine (Zimmer and others). On the other hand, it is often observed that the glycosuria perceptibly diminishes in cases of diabetes as a cachectic or marantic state develops (Naunyn and others).

The Kidneys and Glycosuria.—It is well known that the same amount of hyperglycemia may cause in different persons a widely different degree of glycosuria (see Seegen's figures), and there is a wide-spread opinion that the kidneys have an influence on the latter (Lépine and others). This opinion seems corroborated by several recently acquired facts, which I recapitulate here.

The glycosuria due to phloridzin seems to depend upon changes in the kidneys. We know that after extirpation of the pancreas in birds, whose normal glycemia is about 0.14 or 0.15 per cent. (Kausch), the hyperglycemia reaches a higher figure than in mammals before glycosuria sets in; or, in other terms, that the kidneys of birds have a greater power of preventing the sugar of the blood from passing over into the urine (Kausch). Klemperer found, in nephritis, glycosuria (of 0.35 per cent.) with a normal quantity of sugar in the blood. Other changes in the kidneys seem also to bring about a diminished power of retaining the sugar of the blood. Frerichs, Morison, Habershon, and Pavy (cited by Naunyn) saw chyluria associated with glycosuria. Naunyn found sugar in conjunction with hemorrhages from the kidneys. Jacobi found that diuretics (theobromin, sulphocaffeinic acid, "diuretin") cause glycosuria, which seems easily brought about in traces when polyuria exists from any cause whatever—*e. g.*, diabetes insipidus. Most of these facts, however, may be explained in other ways, and "renal glycosuria" at the present moment represents scarcely more than a hypothesis.

CHAPTER IV.—SYMPTOMS AND COMPLICATIONS OF MILD AND SEVERE DIABETES.

Diabetes mellitus is, as already mentioned, not a disease or a clinical entity, but a syndrome that may arise from a number of quite different processes in the organism. The glycosuria is not necessarily the first in the series of manifestations that mark the change in the patient's state of health.

In the great majority of cases the precursory signs that are not rarely observed are referable to the nervous system and belong to the neurasthenic group. When a patient, with a urine still free from sugar and with nothing more abnormal than perhaps the presence of a rather large quantity of crystals of calcium oxalate, has for some time complained of insomnia, irritability, enfeebled sexual power, neuralgia, etc., glycosuria may appear and slowly progress. In other less frequent cases changes in the vessels, new-growths, cerebral softening, hemorrhages, parasites, or traumatic influences may cause cerebral symptoms before glycosuria makes itself manifest.

In still other cases, and especially in persons that are approaching middle age, I have several times found that the first appearance of sugar in the urine was preceded by a tendency to corpulence, whereupon a simple glycosuria or a mild diabetes has set in.

In rare cases it is possible, before glycosuria begins, to diagnosticate disease of the pancreas, then generally of carcinomatous nature.

Upon the whole, a rule prevails—though one with many exceptions—that a diabetes that afterward pursues a mild course quite imperceptibly invades the patient, and years may pass after the first appearance of sugar in the urine before an accidental analysis, a slowly increasing polydipsia, a poor and complicated healing-process, or some local complication direct the patient's or the physician's suspicions on the right track. Many physicians omit the important investigation of the urine, and it often happens that the specialist—*e. g.*, the ophthalmologist or the dermatologist—forestalls the family physician in discovering the existence of diabetes.

In other cases, especially in such as prove to be of a severe kind, diabetes sets in suddenly with marked glycosuria and specific diabetic symptoms, without any prodromal manifestations.

Mild, slowly developing diabetes is much more common than severe diabetes.

When the secondary dystrophy, the general disturbance of nutrition, has developed in consequence of the primary lesion of the nervous system, or the pancreas, etc., the effects may be induced in any organ as a result of either the deficiency on the part of the organism to fully utilize its carbohydrates and its consequent inanition, or of the action of certain toxins, or from defective central or peripheral nervous influences.

Among the toxins in the blood we include the *superfluous* amount of sugar contained therein. In mild cases this probably is the only toxin, and one whose deleterious influence has been enormously overrated. A glycemia of 0.15 per cent. may still be considered not in excess of the normal; above 0.4 per cent. is found only in a small minority of cases of diabetes (Seegen, Naunyn, and others). Persons suffering from true diabetes, who can not be persuaded to adhere strictly to a proper diet and who constantly present glycosuria (and hyperglycemia) *may* live in fairly good health for more than twenty years. This single fact *proves* that hyperglycemia *per se* can not possibly be a very powerful *nocens*. Its worst effect is probably the retaining firmer than is the normal the water in the blood-vessels, and thus, to a certain extent, desiccating the tissues. This causes some disturbance in the nutritive state and the functional power of the organs; it may, *e. g.*, bring about cataract and contribute to the development of gangrene, suppuration, and other disintegrating processes, or of neuritis and other "parenchymatous" changes. The hyperglycemia may also be in part responsible for the diabetic endarteritis and the arteriosclerosis. The hyperglycemia, however, which in most cases is quite moderate, generally takes a very long time to bring about these changes.

A much more deleterious effect is attributable to the acid toxins, the free fatty acids, the diacetic acid, and the β-oxybutyric acid. When the physician sees for the first time a diabetic patient, the quickest and best way of determining approximately the stage of the diabetic dystrophy is to make use of Gerhardt's test, which

consists in pouring a few drops of ferric chlorid in a tube nearly filled with the patient's urine. The appearance of a beautiful wine-purple color denotes directly the presence in the urine of diacetic acid, and indirectly often the presence of that most ominous substance, β-oxybutyric acid (see below). It may then be concluded that the patient is in the severe stage of diabetes, that he has at the utmost only a few years of life left, which will pass in a struggle with the autophagy and the acid diathesis ("acidosis"), with all its manifold dangers, and that death will probably be caused by the blood-toxins.

What rôle each of the different pathologic factors—the toxins and the deficient nervous influences, etc.—play in the production of anatomic lesions is only imperfectly known. A good deal of mystery surrounds especially the purely nervous "trophic" influence and its anomalies in diabetes as in other dystrophies.

In this chapter will be considered dystrophic general changes and those that occur in each of the different organs. However wide a clinical difference may exist between a diabetic patient in the mild and one in the severe stage, there is no distinct scientific demarcation separating these two stages, and it is injudicious to contribute to the idea prevailing in some quarters of two entirely different "forms" of diabetes. I give, therefore, no separate description of mild and severe diabetes, but only point out the toxic and cachectic nature, and the autophagy of the latter, and describe its usual final scene—diabetic coma.

In connection with the clinical symptoms, we must consider the pathologic anatomic lesions of diabetes. These are often but little marked, both macroscopically and microscopically. After the existence of mild diabetes, which is not *per se* fatal, changes of a purely diabetic character are generally overshadowed at the autopsy by alterations due to the intercurrent or complicating disease. After diabetes in the severe stage or of long standing, the autopsy is certainly very likely to reveal characteristic changes. These, however, even when found in those organs that play a rôle in the pathogenesis of diabetes,—the nervous system, the pancreas, and the liver,—are far more frequently an effect than a cause of the diabetes, and represent retrogressive and degenerative processes due to the marasmus and the cachexia. The alterations in the

kidneys, the most frequent of all, have no connection with the origin of the dystrophy, but are the results of its effects on the renal functions.

SPECIFIC DIABETIC AND DYSTROPHIC SYMPTOMS.

The *sugar that appears in the urine* in cases of simple glycosuria is present in determinable quantities only for some time after meals, while in cases of true diabetes, however mild, it is present under continued ordinary diet throughout the whole or, at least, the greater part of the twenty-four hours, being absent only when the patient's stomach is empty just before meals, and especially in the morning before breakfast. With restriction of the carbohydrates to a quantity below the patient's power of assimilation, the sugar in the mild stage of the dystrophy disappears from the urine. In the severe stage, when glycosuria is derived at least partly from proteids, the urine constantly contains glucose—except, perhaps, just before death, when the entire metabolism fails.

After carbohydrates have been taken glycosuria begins in about half an hour, and so quickly reaches its maximum that the greater part of the sugar in the urine may have been excreted during the first hour. The whole excretion generally does not last more than five or six hours, and often a shorter time. In rare cases one sometimes finds a distinct postponement of the whole excretion.

The glycosuria following proteids in the severe stage of the dystrophy is attended with the excretion of less sugar, and reaches its maximum later than after ingestion of carbohydrates; or, in other words, the glycosuric curve due to proteids shows a lower wave.

The intensity of the glycosuria—*i. e.*, the amount of glucose excreted in twenty-four hours—varies greatly, and depends on the power of assimilation and on the quality and quantity of the food ingested. In cases of true diabetes, however, after prolonged free diet it generally reaches a considerable degree and always some number of grams. Anything below one, or even two, grams under such circumstances is properly considered simple glycosuria. Sometimes the glycosuria reaches quite extraordinary figures, and it may reach one kilo. in twenty-four hours. Dickinson found in

one case 1500 grams, and some French observers have noted still higher figures.

The *intensity of the glycosuria—i. e., the percentage of glucose*—varies exceedingly during the twenty-four hours. The minimum is always found in the morning before the patient's first meal, and a large number of diabetics present at this time of day no glycosuria that is discoverable with our ordinary tests. The maximum is generally reached between one and two hours after meals, and there are usually three distinct waves during the twenty-four hours, their height depending on the nature of the food. With a strict diet no reaction may be observed in mild cases or only a slight one. In advanced cases, with a liberal supply of carbohydrates we sometimes find ten per cent. of sugar. Naunyn noted eleven per cent. Higgins and Ogden speak of twenty per cent. (?) Urine containing more than six per cent. of sugar is rare. In the course of an enormous number of analyses I have found some few show more than nine per cent., but only one reaching ten per cent. The percentage of glucose, depending under all circumstances largely on the quantity and quality of the food, forms in itself only a vague expression of the intensity of the diabetic dystrophy.*

A patient living exclusively on meat and fat (water and salts), with 0.3 per cent. of glucose in his urine, is much worse off than another living on an abundant ordinary mixed diet, with three per cent. of glucose in his urine. The same patient who, one or two hours after dinner, exhibits three per cent. of sugar in his urine, may early the next morning exhibit only 0.05 per cent. When I hear of any one whose urine contains from three to five or seven per cent. of glucose, I conclude that he is diabetic—nothing more; but if I hear of some one whose urine contains 0.5 per cent. of glucose, I gain scarcely any information at all about his case—it may be one of simple glycosuria, or of mild or severe diabetes. When I hear of any one whose urine contains 0.5 per cent. of glucose,

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* Bouchard unconditionally and *sans phrase* proposes to designate as severe every case of diabetes with an excretion of over fifty grams of glucose in the twenty-four hours; and as mild, every case with less than this amount. This is for me a most striking illustration of the possibility of complete *absences intellectuelles*, even in men of genius. Many a diabetic patient may, according to this most extraordinary classification, repeatedly be a severe case on Mondays and a mild one on Tuesdays, and vice versa.

with strict diet, this at once tells me that he is in the severe stage. It is useless to give figures of the glycosuria without some information as to the diet.

With an exclusive diet of meat and fat, glycosuria, which disappears entirely in the mild diabetic stage, rarely reaches above two or three per cent. in the severe stage.

In severe cases the patient often passes a clear, pale, greenish-yellow urine with a specific gravity that often is nearer 1.040 than 1.030, and that sometimes may reach far above the first figure. Several observers mention 1.070; Proust and Bouchard, 1.074. Diabetic urine, however, especially in mild cases, varies enormously in appearance, specific gravity, and other qualities. A diabetic in the mild stage, when he has not received carbohydrates beyond his limit of assimilation, passes urine that, besides being free from glucose, is otherwise scarcely different from that which a healthy person passes under the same dietetic conditions. We quite frequently find, even in severe cases, a urine of perfectly normal, sometimes even a somewhat high, yellow color, and in mild cases not rarely a strong sediment of uric acid. Under the microscope the conditions often are normal, although sometimes there may be a rather large amount of the small crystals of calcium oxalate and sometimes also occasionally hyaline and more rarely granular casts. The nitric-acid test not uncommonly discloses the presence of albumin, and the colored zone above the acid is frequently pronounced. By reason of the abundance of animal food the urea and other derivatives of proteids are generally present in rather large quantities, and the specific gravity, therefore, is often high, even when no sugar is present. In many cases in the mild stage, however, the specific gravity is below 1.030, and not only within normal but within very common limits.* One may find urines of a specific gravity of 1.020 that contain quite a considerable amount (above one per cent.) of glucose. Sometimes one may even find distinctly pathologic, though small, quantities of glucose in urine of an exceptionally low specific gravity. Some

* A normal middle-aged man, who eats much meat, often passes urine of a specific gravity nearer 1.030 than 1.020. One may sometimes, apart from diabetes, even find the urine of comparatively normal persons with quite a high specific gravity. Only recently I encountered a specific gravity of 1.034 in such a case.

time ago I saw a urine of 1.005 specific gravity undergo a beautiful reduction with Nylander's and Fehling's solutions before, but not after, fermentation. It came from a gouty patient with simple glycosuria, who had been on a spree and had drunk two quarts of beer. True, though mild, diabetes may give rise to exactly such a urine either after prolonged abstinence from carbohydrates or during one of those periods, sometimes observed in mild cases, when the power of assimilation becomes very high or, finally, when some care in diet has been observed, but much water has been drunk.

It is interesting to note the differences in view as to the frequency of albuminuria in association with diabetes. Schmitz noted albuminuria in 68.6 per cent. (!?),* Bouchard in 43 per cent., v. Dusch in 25 per cent., Garrod in 10 per cent. of their cases of diabetes. Grube (1878) states that he found albumin in the urine in 191 of 473 cases of diabetes, or in 40 per cent. In the severe stage of the disease albuminuria is much more frequent than in the mild stage. Including all cases of *true* diabetes in private practice, it will be found that Grube's figures, which certainly are rather too high than too low, best represent the truth, while in hospitals, where chiefly severe cases are found, the figures will be considerably higher (see below).

In some cases the solution of ferric chlorid shows the presence of *diacetic acid* (Gerhardt's most important reaction), which, except with inanition, is absent in mild cases.

For the other changes in diabetic urine I refer the reader to the chapter on Metabolism.

Increased thirst, *polydipsia*, and *polyuria* are, as is well known, frequent symptoms of diabetes, and hold a causal relation with each other, which is still far from perfectly understood. Thirst and polydipsia are certainly causes of polyuria, and any one, whether diabetic or not, who drinks much, will pass a large quantity of urine. The increased thirst of diabetes must arise from the increased amount of sugar in the blood, which keeps the water in the vessels firmer than normal, and dries the tissues, which still are thirsting when a normal quantity of water is ingested, just as they

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* These figures can scarcely be explained in any other way than by the zone of urates (with Heller's test) having been mistaken for one of albumin.

may hunger from the loss of glucose and from the protoplasmic disintegration (see below) with a normal supply of food. Hyperglycemia in itself acts on the kidneys as a diuretic. When enormous doses of saccharids are given, the urine always suddenly increases.* To some extent an increased want of water arises within the organism merely in consequence of the carbohydrates passing off as glucose instead of being oxidized into water and carbonic acid. If the supply of carbohydrates in the food is restricted and hyperglycemia and glycosuria cease, polydipsia and polyuria often also cease.

Polyuria may, however, arise also in consequence of direct vasomotor influences, and not be the effect but the cause of increased thirst and polydipsia. Thus, lesion of the "lobus hydruricus" in the vermis, near the seat for Bernard's puncture, causes diabetes insipidus, as does also lesion of Kahler's centers. Further, the increased excretion of urine is observed in progressive paralysis. These facts suffice to explain, easily, cases of diabetes mellitus with slight glycosuria and marked polyuria, and cases of diabetes insipidus with slight traces of sugar, and the circumstance that the polyuria sometimes remains after the disappearance of the glycosuria in the rare cases of incomplete recovery from diabetes mellitus.

Sometimes cirrhosis of the kidneys contributes to the polyuria and polydipsia of diabetes mellitus; in these cases, often of a gouty nature, the sugar in the urine, from some unknown cause, usually decreases as the cirrhosis advances.

Pick mentions that ingested water passes through the kidneys in a shorter time in diabetics than in normal persons.

The *quantity* of urine is generally increased only moderately—to two or three liters. More than five liters is rare, except in hospital practice with almost exclusively severe cases. Sometimes enormous quantities are observed. Dobson noted 14, Cantani also 14, Fürbringer 17 liters; Schindler mentions 16 liters in a child, etc. Such quantities always belong to the most severe cases.

Increased thirst, polydipsia and polyuria do not, however, constitute such constant symptoms as many members of the medical pro-

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* The frequency of the pulse decreases, but the systolic and diastolic excursions of the heart become greater (Vespa).

fession seem to think. In the severe stage, especially regardless of diet, this group of symptoms is certainly, as a general thing, quite pronounced. In the mild stage, even apart from diet, the quantity of urine often keeps within the normal, and the condition corresponds with what already Peter Frank has called *diabetes decipiens*. Even a moderate restriction of carbohydrates will in this stage keep the quantity of urine within normal limits in about fifty per cent. of the cases. Sometimes diabetic patients may pass even an exceptionally small quantity of urine in the twenty-four hours. I have observed cases in which only 900, 800, and 700 cu. cm. were passed.

I have records of 65 diabetic patients, whose urine has been measured for the twenty-four hours during a somewhat considerable time, and find that of 27 in the severe stage, 22 have generally passed more, and 5 less, than 1600 cu. cm.; and that of 38 mild cases, half the number have passed less, the other half more, than this quantity. All of these patients were of high stature, and include Scandinavians, Britons, Germans, and Americans. On the other hand, it may be conceded that almost all the possible errors in measuring have contributed to make the figures too low; and that in many cases the diet has corrected a preexisting polyuria.

As the quantity of glucose, so also the quantity of urine, is generally larger during the day than during the night; but the rule has many exceptions, both glycosuria and polyuria depending on the character of the food. Thus, when the largest meal, dinner, is taken late in the evening, the urine and the glucose often reach higher figures during the night than during the day. Increased intensity of glycosuria is, as a rule, accompanied by increased intensity of polyuria.

Pollakiuria, or abnormally frequent passing of urine, is a common symptom, but stands in no distinct relation with the intensity of either the glycosuria or the polyuria. Sometimes there is distinct pollakiuria without any polyuria, and the patient passes urine a dozen times a day, although the whole quantity may not exceed the normal. In other cases, sometimes even in severe cases, there is no pollakiuria, but a decided polyuria. One of my patients, who died in coma, used, with great regularity, to pass urine only four times in twenty-four hours, but each time the quantity approached a liter.

Among symptoms of diabetes may be mentioned the *diminution in the secretions* and excretions other than the urine, although exact investigations are still scanty. Of the saliva this has been long known, and *dryness of mouth* is one of the most common complaints of diabetics. In mild cases one often finds perspiration normal, sometimes abundant, even to hyperidrosis; but in advanced cases a decrease in the secretion of the glands of the skin is generally manifest, with *asteatosis* and *anhidrosis* and an extreme dryness of the skin. Gall-stones are more common among diabetics than among other persons, and this I consider probably the result of a decrease in the secretion of bile, and chiefly the water thereof.* Young diabetic men with undiminished sexual vigor sometimes mention symptoms indicative of a diminished secretion of spermatic fluid. The decrease in the secretions is doubtless due in part to the desiccating influence of the hyperglycemia on the glands as well as on other tissues. In severe cases, however, with marasmus, atrophic and degenerative changes of the different glandular elements surely contribute largely to this result.

Excessive hunger—bulimia—is a common symptom in the severe stage of diabetes. In the mild stage it appears only in comparatively advanced cases with a low power of assimilation and a diet too rich in carbohydrates, when a considerable part of the food passes off in the urine as glucose.

In the severe stage the increased hunger is so far a favorable manifestation, as it alone enables the patient to make good the loss of glucose and to mitigate the consequences of the protoplasmic disintegration taking place in the tissues. The ingested proteids under such circumstances sometimes develop enormous values, and I have more than once seen patients who for a short time, in addition to large quantities of butter and moderate portions of carbohydrates, were able to take considerably over one kilogram of cooked beef a day. In far advanced cases the patient may even, with such food and with an excellent digestion, present a clinical picture that

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* Bouchard states that ten per cent. of all diabetics suffer from gall-stones. Even if this figure should be somewhat exaggerated, there can scarcely be any doubt about the increased frequency of gall-stones in diabetics. All other explanations than the one given here of the connection between diabetes and gall-stones (by I. Kraus) seem to me to lack any rational basis.

strongly resembles that presented by starvation. In both instances there are observed constant loss of weight, utter prostration, low bodily temperature, decrease in the secretions, and the presence in the urine of acetone, diacetic acid, β-oxybutyric acid, and increased ammonia. The final scene increases the similarity, for death from starvation is partly due to the acid toxins in the blood already mentioned, and is, so far, death from poisoning, with a clinical picture that strongly resembles diabetic coma.

Instead of bulimia, *anorexia* is sometimes observed in cases of diabetes of all stages. This is a most ominous manifestation in the severe stage of the dystrophy, and I shall return later on to this subject.

Loss of weight belongs essentially to the severe stage, but it may occur under varying circumstances, and it can as little as the glycosuria or other manifestations of derangement of metabolism be rightly considered clinically without reference to the food.

During periods of great restriction or even exclusion of carbohydrates every one, whether diabetic or not, is likely to lose in weight, because it is generally difficult without carbohydrates to supply the organism with the necessary amount of heat-units. Loss of flesh of this purely "alimentary" kind is of no clinical importance at all, and does not constitute a contraindication against a rational, periodic, rigid restriction of carbohydrates. The patient will afterward, under a somewhat freer diet, easily recover his loss.

Then we sometimes find loss of weight, even in the mild stage, *before* the patient has been put upon a restricted diet, and before his dystrophy has been discovered. Such a loss of flesh is of greater importance, and generally takes place when the power of assimilating carbohydrates is considerably impaired and they constitute a large part of the food. Still, it is usually no very difficult task in the milder stage to check the loss of weight, or even to make it good, by increasing the proteids and fat of the food (and duly reducing the carbohydrates).

Finally, the most marked and the most important loss of weight takes place in the severe stage. When the patient's power of assimilating carbohydrates has reached a very low point; when he loses in the form of glucose even a considerable part of the ingested proteids; when the toxic protoplasmic disintegration of tissues

entails a greater nitrogenous expenditure than income, and a daily deficit under any dietetic conditions; when the tissues are still insufficiently supplied, although the digestive apparatus has been satiated, then appears the terrible *diabetic autophagia*. The loss of weight under these circumstances is, in spite of all dietetic measures, often exceedingly rapid, and affects not only the fat and the carbohydrates of the organism, but also the proteids, and probably often the bones, and a fatal issue may be looked for in the immediate future.

The great *vulnerability* and *diminished recuperative power* of the diabetic have been long known. They are due to the hyperglycemia and the toxins in the blood and to the dryness of the tissues, probably also to defective nervous influences. The changes in the vessels, especially the diabetic endarteritis in the smaller vessels, must also have a marked influence in this direction. This weakness is found not only in the severe stage, but it is often quite extreme in patients who, with restricted diet, are free from glycosuria, but who have suffered from diabetes during many years. In such persons wounds remain open for a long time, heal less often without suppuration, and have pigmented cicatrices. The impaired healing power in cases of diabetes has restrained surgeons from many a necessary operation, and does so sometimes even yet, although the diabetic patient has profited still more than others by aseptic and antiseptic prophylaxis. Inflammatory and suppurative processes, especially in inveterate cases of diabetes, are much to be dreaded, and a carbuncle is a far more serious matter in a diabetic than in a nondiabetic person.

The dry tissues, the hyperglycemia, the toxins, the defective nervous influences, the arteriosclerosis, and the peculiar changes in the small vessels of the diabetic render him more susceptible to gangrene than others.

Diabetic gangrene,* which sometimes develops in the sequence of traumatism or other accidental agency, and sometimes appears spontaneously, is comparable to senile gangrene; in fact, it is usually the

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* Marechal de Calvi and Hodgkin (1864) were the first to point out a causal connection between diabetes and gangrene. Peyrot (1878), Giron (1881), W. Hunt (1888), Heidenhain (1891), N. S. Davis (1898), and others, have since treated of the subject.

expression of both diabetes and senility. Of 38 cases of diabetic gangrene in the city of Philadelphia, the age in 1 case was between thirty and forty; in 2 cases, between forty and fifty; in 11 cases, between fifty and sixty; in 12 cases, between sixty and seventy; in 10 cases, between seventy and eighty; and in 2 cases, between eighty and ninety years (Hunt). It is thus seen that the cases are rare before fifty, begin to be more frequent with advancing years, and are relatively more frequent late in life. Diabetic gangrene is almost always of the moist variety, and is generally without a sharp line of demarcation. It usually attacks the lower extremities, especially the feet, but it may occur almost anywhere—on the body, in the lungs, on the arms, the nose, the penis, etc. Sometimes the gangrene develops in several places simultaneously in smaller or larger patches. Settenbom has recently described a case presenting such patches with a circumference of from 10 to 15 cm., distributed over the whole body except the head. Kaposi mentions a case with "gangrena bullosa serpiginosa"; and Pitres, Rosenblath, Blau, and others have also described cases with multiple gangrene of the skin. Diabetic gangrene, chiefly a manifestation of old age, does not usually occur in the severe stage, which is rare late in life and of comparatively short duration, but in cases in which the exclusion of carbohydrates leads to disappearance of the glycosuria, though many years of diabetes have had time, in combination with senility, to bring about the changes already mentioned. I have myself seen several cases in which the power of assimilation was comparatively quite considerable, although the dystrophy had existed for between fifteen and eighteen years. In one of the cases there was marked arteriosclerosis and atrophy of the kidneys.

The prognosis of diabetic gangrene is always dubious, but even pulmonary gangrene is not necessarily fatal. One of my patients has successfully passed through this complication. In the lower extremities gangrene may often, under rational treatment, general and local, result in recovery. I have seen one case in which an enormous scar on the calf of the left leg reminded the patient during the last three years of his life that he had undergone such a process.

The variety of gangrene due to pressure, and usually designated

decubitus (bed-sore), is more easily acquired in diabetes than in other conditions, and one has to be especially on his guard against such a complication in the course of intercurrent diseases or other states that are likely to cause it.

Among complications of diabetes with gangrene, suppuration, and disintegration of tissues, must be mentioned the common *furuncle* and the *carbuncle*, and the two rare disorders, "*le mal perforant*" and "*Raynaud's disease.*"

The *furuncle* is exceedingly common, and is especially to be found in the mild stage in fat patients ; the thin, severely ill diabetic usually have had no furuncle. The complication is generally not a dangerous one.

The *carbuncle*, which generally appears on the neck or on the back, belongs to advanced cases, is, when associated with diabetes, quite a formidable disorder, and manifests a marked tendency to spread and to give rise to general septic infection. It causes death in a not inconsiderable number of cases of diabetes. "*Le mal perforant*" (Kirmisson, Gascuel) is, as is well known, generally a symptom of tabes dorsalis ; if it is found in other cases one must suspect diabetes mellitus. It is sometimes found together with diabetic gangrene of the ordinary form. I have seen it several times, and I suppose that it occurs in at least two or three per cent. of all cases. The small, sharp-edged, perfectly round, torpid ulcers may occur on one or both sides, generally on the hands or feet, and mostly over a joint. The innocent-looking ulcer then advances into the joint, and may cause extensive destruction of both the soft tissues and the bones and necessitate amputation. It sometimes leads to death. The cases of "mal perforant" that I have seen have presented typical symptoms of neuritis in the affected area, and neuritis has been repeatedly found postmortem.

That most interesting of all forms of gangrene, *Raynaud's disease*, is rare both in association with and independently of diabetes ; but the considerable number of cases of diabetes thus complicated leave no doubt that diabetes is a predisposing cause. "Raynaud's disease" is a vasomotor disorder, and neuritis has several times been demonstrated postmortem. As is well known, the disease often attacks peripheral parts symmetrically, as the feet, the hands, or the ears. It begins with strong vasomotor spasm, giving rise to

ischemia, pallor, coldness, and some loss of sensibility in the affected region. I presume it is this "local syncope" that under some conditions may lead to scleroderma. After some time, however,—hours or days or weeks,—dilatation of the vessels usually follows, with hyperemia, cyanosis, and excruciating pains,—whether from active vasodilator influence or from vasoconstrictor paralysis, has not yet been agreed upon. We have then the "local asphyxia," which some consider identical with erythromelalgia as described by Weir Mitchell. After this, gangrene may set in.

Lymphangitis and *erysipelatous* and *phlegmonous processes* threaten the diabetic much more frequently than healthy persons, probably on account of the better conditions for vegetation that he presents to microorganisms. Senator and Rovere have described cases of suppurative polymyositis with multiple abscesses in the muscles. I am unable to understand in what respect such a process differs essentially from some cases of pyemia.

The cavity of the mouth often presents characteristic changes, which are of serious import to the patient and of practical significance to the physician, because they stand in a certain relation to the duration and the intensity of the glycosuric dystrophy. The *breath* gives at once important information, its strong *odor of acetone*, which is much like that of chloroform, denoting the severe stage of the dystrophy. This odor may diffuse itself throughout the patient's room, often suggesting the diagnosis immediately, and sometimes revealing to a physician the state and the impending fate of some stranger passing on the street. One may sometimes perceive a slight uncertain odor of acetone from the mouth of a person in the mild stage of diabetes, as one always does from the mouth of anybody in a state of severe inanition and sometimes does from the mouths of quite healthy children. If there is no odor of acetone from the mouth of a diabetic patient, he is pretty certain to be in the mild stage. Inspection of the mouth also very often affords valuable information. The *tongue* is often somewhat dry in mild cases of diabetes, but otherwise it is usually little changed. In severe or advanced cases it is dry and marked off into rectangular areas by deep furrows, like the hide of an alligator; the base is often covered by a brown, sometimes almost black, coating, while the apex is abnormally red, with hyperemic papillæ.

Here and there one sometimes finds glossy, fleshy looking patches, where the mucous membrane has undergone atrophic changes. *The teeth* also undergo changes after true diabetes has existed for any great length of time. If I find a complete and normal set of teeth, I know at once that the glycosuria (and hyperglycemia) is either of recent date or does not amount to a true diabetes. In diabetics, even in the mild stage, the teeth are, as a rule, *carious;* a smaller or greater number of them, besides, have fallen out. Inspection of the *gums* often leads to discovery of the causes of loss of teeth. A distinct *gingivitis* is often present, exhibiting tender, swollen, red areas. Here and there a drop of pus may be made to appear on pressure; the bistoury may empty a little pocket of pus; and the probe may, through a fistula, reach bone. These features belong to the common condition of *alveolar pyorrhea.* Sometimes the patient presents the ordinary symptoms arising from a more or less pronounced *periostitis*, or a *pericementitis*, as, I believe, the dentists call the process when it affects the periosteum surrounding the roots of the teeth. In some cases, even independently of senility, teeth are missing without any evidence of an inflammatory process and without the patient ever having suffered from symptoms of that condition. This is in great probability the result of retrogression and atrophic changes in the periosteum and in the maxillary bones. The latter process leads to *osteoporosis*, which, there is good reason to believe, occurs in severe marantic cases of diabetes (see below), and which is known to occur in other disorders of the central nervous system (*e. g.*, progressive paralysis).

Diabetes mellitus does not *per se* cause any elevation of temperature. Whenever fever takes place we have to do with some complication and must make a careful investigation for it, especially in the lungs. In mild cases without complications the temperature is normal. In severe marantic cases the temperature is below the normal; but, apart from coma, it is rarely below 36° C. (96.8° F.). In the presence of coma it sometimes sinks several hours, or even several days, before death to between 25° and 30° C. (77° and 86° F.).

The Nervous System.

The diabetic patient is, as I have mentioned, often a member of a nervous or even of a neurotic family in which, according to the two laws of heredity and transmutation, may be found most of the diseases that thrive on neurotic soil. We may thus find in different generations of the same family slight mental disturbances, developed psychoses, diseases of the brain and spinal cord alternating with exophthalmic goiter, diabetes, gout, and other morbid processes, whose dependence upon the nervous system, though not perfectly established, is yet beyond doubt.

Then it has been ascertained that certain lesions of the nervous system directly cause diabetes, the symptoms of which develop simultaneously with the nervous symptoms.

Finally, it has been learned in the last few decades that diabetes *per se* may cause changes in the nervous elements, partly directly, partly through some of its complications, and especially through its influence on the vessels of the brain and consequent hemorrhage, as well as other circulatory disturbances.

Thus, nervous disorders—central and peripheral, acute and chronic—are exceedingly common in conjunction with diabetes. Among these disorders, however, neither the severe neuroses nor the systematic diseases of the brain and spinal cord are at all frequent. Jacoby, of New York, observed three cases of epilepsy complicated by diabetes mellitus, and admits the possibility of a connection between the epileptic attacks and the diabetic toxins in the blood. Finlayson, Ebstein, and others also mention such cases; but among nearly 200 diabetics seen in the course of the last few years I have not encountered one complicated by epilepsy.* Tabes dorsalis and diabetes mellitus have been observed in the same person in a number of instances; but these and other cases of diabetes occurring in conjunction with organic, systematic, central nervous diseases constitute but a small proportion among the large number of diabetics, even if such complications are found somewhat more frequently in association with than independently of the glycosuric dystrophy.

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* In a male child and in some few cases in women I have seen general convulsions, with complete preservation of consciousness; these I considered to be hysteric.

A far less rare, but still not very common, expression of the neurotic tendency and of a depraved state of nutrition is a more or less well developed psychoneurosis. In Europeans and their descendants * this generally goes no further than hypochondriasis. Sometimes, however, the patient presents a somewhat more profound mental change, and the clinical picture of simple melancholia appears. We then generally find only the mild, active form of the disease, with only moderate impairment of intellectual activity, though a certain degree of lack of energy is found in these as in all cases of melancholia. Pronounced apathy, hebetude, or even stupor is exceedingly rare, and the same may be said of hallucinations. The false ideas are rarely without some real objective cause, and generally only represent the hypochondriacal state already mentioned. Sometimes, however, one finds entirely unfounded fixed ideas, such as are observed in developed melancholia—*e. g.*, a delusion of poverty in the face of excellent material circumstances, etc. I have also seen instances of fully developed melancholy raptus with strong terror and violent tendencies. Suicide is rare, even among diabetics, although somewhat more frequent than among other persons.

The nervous centers that preside over the metabolism of carbohydrates are not the same as those that perform the highest mental functions, and the connection between diabetes and the disturbances of these functions is most vague. Mild diabetes may be complicated by a true psychosis, and severe diabetes may leave the mental state almost intact. On the other hand, an influence on the mind by the diathesis can not be denied, and in diabetics of a psychopathic constitution hyperglycemia may contribute to the development of mental disease. An analogous influence is exerted by gout (Berthier, Raynor, Savage, Chrichton-Browne). In a mild but fully developed case of melancholia I discovered also mild diabetes, with 1.3 per cent. of glucose in the twenty-four hours' urine under ordinary diet. A moderate restriction of the carbohydrates stopped the glycosuria and was followed by immediate improvement in the mental state, obvious to the patient's family. In another case of melancholia associated with diabetes restriction of the carbohydrates, with diminished hyperglycemia, did not seem to influence the melancholia at all, the patient eventually committing suicide.

Other pure neuroses than hypochondriasis and melancholia are

* In the East Indian medical literature we find statements from which we may conclude that severe mental diseases are more frequent among diabetic Hindoos than among diabetic Europeans.

rare in association with diabetes. Hysteria—if properly distinguished from purely neurasthenic neuroses—is sometimes, but not often, found in cases of diabetes (Gumpertz, Toralbi, Kleen, and others).

Neurasthenic symptoms, both cerebral and spinal, are exceedingly common in diabetics, and it is rare to find such a patient entirely free from them. The diabetic is almost always a wretched sleeper, even if polyuria does not disturb him. During the day he suffers from another neurasthenic symptom—namely, drowsiness, which prevents intellectual activity without inducing sleep.* The slight neurasthenic headache, almost continuous, sometimes only felt as a sense of "emptiness" or of pressure, is frequent. The capacity for assiduous intellectual work is almost always diminished and memory is often distinctly impaired. Irritability is increased, as any physician having much to do with diabetes has learned at his own expense. In cases on the psychoneurotic border-line this may amount to a true "iracundia morbosa," with an unbearable temper and impulsive, violent acts. Spontaneous vertigo is not common, but vertigo at heights is present in about two-thirds of all cases with diminished power of assimilating carbohydrates. I have also, though rarely, observed agoraphobia. A host of less important neurasthenic sensory disturbances, in the form of hyperesthesia, paresthesia, and vague pains, annoy the diabetic patient. Feelings of cold or of heat, of the hair standing on end or being absent, of a more or less distinct "casque neurasthenique," of pressure, of creeping, of "plaque sacrée" or other rhachialgic manifestations, of shooting-pains in the limbs, etc., add to the patient's distress. Pains in the epigastrium are not uncommon in diabetes, and have been compared to the "crises gastriques" of tabes dorsalis, but they seem hardly to be distinguishable from analogous complaints often made by neurasthenic patients that are not diabetic.

Among *neuralgias* in diabetes, *sciatica* is the most common. Next in frequency come neuralgias of the fifth pair of nerves (trigeminus), especially of the inferior maxillary division. Supra-orbital neuralgia, as in other conditions, is sometimes accompanied

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* An American neurasthenic (nondiabetic) lady aptly described this condition by saying: "I suffer from insomnia all night and from somnia all day."

by the vasomotor disturbances that constitute migraine.* All of these neuralgias, while generally not very intense, are quite obstinate, and are often bilateral.

In 1887 I treated at Carlsbad a case of one of those curious forms of aberrant vasomotor neurosis that are called equivalents of migraine. The patient, fifty-three years old, was the principal of a school. His father, an uncle, and at least one cousin had suffered from diabetes. The patient himself had suffered from the glycosuric dystrophy for at least fifteen, probably for nineteen, years, and he had reached the boundary between the mild and the severe stage. He had not had syphilis, presented no distinct rigidity of the arteries, and no other ocular disorder than moderate myopia. From time to time he felt a sense of rigidity in the left side of the face, and at the same time paresis in the left arm. I saw the man during one of these attacks, which had begun at 2 P. M. He presented marked paresis of the left facial nerve and of the whole left arm; at 5 P. M. his condition again was perfectly normal. Some months afterward the patient suddenly suffered a cerebral hemorrhage and in one of these attacks died "apoplectico modo." I presume that vasomotor neurosis in a case of long-standing diabetes, with brittleness in the vessels from diabetic endarteritis, is rather likely to end this way.

Sometimes there occur functional disturbances of the secretory nerves, and instead of the customary decrease of secretion there may be an abundance, as manifested by local sialorrhea, hyperidrosis, etc.

The muscular neurasthenia—not to be confused with the functional disturbances resulting from marantic and other changes in the muscles in the severe cases—is often marked, and even in a mild case the patient has often much less muscular endurance than his general robust appearance would seem to indicate. Among other muscular neurasthenic symptoms there have also been observed, generally at night, *cramp* in the calves of the legs, which sometimes, however, is not merely functional, but a symptom of beginning inflammation of the posterior tibial nerve. The fine, fibrillary, clonic spasm is not uncommon, especially in the orbicularis.

Sexual potency is generally weakened, but the degree of failure varies greatly and has no fixed relation to the intensity of the diabetes. This symptom often is but little influenced by hyperglycemia, and is often found, together with other neurasthenic disturbances, in mild cases, as in cases of simple glycosuria or of

* That terrible cousin of the comparatively innocent migraine—epilepsy—is, in spite of their angioneurotic tendencies, rare among diabetics.

neurasthenia without glycosuria. In some cases, on the other hand, the patient is conscious of a decided improvement after restriction of carbohydrates and the disappearance of glycosuria. In mild cases of diabetes the potency sometimes remains normal or nearly normal for many years; in a small number of cases apparently trustworthy patients make statements of virile power that painfully strain credulity. Sterility in diabetes will be considered later.

Diabetic neuritis and polyneuritis * are often detected, but still more often exist and escape detection. They certainly do not depend exclusively on the acetone and the acid toxins in the blood,—the "acidosis," as Naunyn terms the condition,—as they are much more common in mild cases (without acidosis) of long standing than among cases in the severe stage (with acidosis), which generally are severe from an early period of their existence and rarely last many years. In fact, the one feature common to all cases of diabetes with neuritis I have found to be the long duration of the dystrophy. If an accessory influence is present, one may find distinct neuritis in cases with an only slightly impaired power of assimilating carbohydrates. The most frequent of these accessory influences are gout and alcoholism. Even in cases of purely diabetic neuritis (without gout or alcohol) the symptoms are closely similar to those of gouty neuritis. By this I mean that diabetic neuritis, though sometimes isolated and circumscribed and sometimes unilateral, is far more often multiple and bilateral; that it involves especially the lower extremities, though I presume it may attack any nerve; and, finally, that it is of a pronounced torpid character. Only rarely does the process set in with active symptoms, acute pains, and sensations of "tingling." Usually its onset is so insidious that the patient is virtually unconscious of his sensory disturbance until it is disclosed by the physician's investigation. Sometimes, however, the patient complains of a feeling of burning or of prickling, and hyperesthetic areas may be found upon the skin. One must not expect often to find distinct tenderness of the nerves on pressure. Diffuse muscular sensitiveness, like that due to rheumatic infiltration, is much more

* Von Ziemssen was, so far as I know, the first to point out the occurrence of diabetic neuritis (1885). Thomas, Leyden, Althans, v. Strümpell, Buzzard, Charcot, Bury and Ross, and many others have since contributed to our knowledge of this subject.

common. Diminished sensibility to pin-prick, or the esthesimeter, or to a tube filled with hot water is frequently present. Complete analgesia and anesthesia are exceedingly rare; I have not seen a single instance of either, though cases so complicated are recorded in literature. In rare instances I have observed retarded sensibility.

Apart from the frequent spasm of the muscles of the calf, which probably is caused by neuritis only in rare cases, motor disturbances are much rarer than sensory. If the neuritis is intense, and there is also general debility and marasmus, marked reaction of degeneration to the electric current is sometimes present, and in rare cases profound functional disturbance. Foot-drop and complete paraplegia have been observed in some cases, and many instances of paresis or paralysis of single muscles or of groups of muscles are recorded (Charcot, Buzzard, and others).

The neuritis often causes trophic changes within the distribution of the nerve or nerves affected. Among such manifestations are local hyperidrosis or anhidrosis; atrophic, thin, "glossy" skin; cutaneous eruptions, as urticaria, eczema, herpes zoster, etc. (see below); discolored, thick, brittle nails, which readily fall out, etc. The "mal perforant" and "Raynaud's disease" are undoubtedly manifestations of neuritis, which probably also contribute to the development of other gangrenous processes, whether occurring as a single area of sphacelus or disseminated in patches.

Absence or weakening of the *knee-jerk* (and other tendinous and cutaneous reflexes) is a frequent symptom of diabetes.* The explanation for the disappearance of the tendinous and other reflexes is to be sought in changes in both peripheral and central nervous elements (see below). Inflammation of the crural nerve has been found in cases with absence of knee-jerk. According to Erlenmeyer, the cause is generally to be found in changes in the "bandelettes externes" of Burdach's tracts in the posterior columns of the spinal cord. In other cases postmortem investigation has failed to disclose any nervous change whatever (Nonne, Rosenstein), and

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* Absence of the knee-jerk was noted by Marinian and by Bouchard in 1884. It occurs also in tabes dorsalis and sometimes in apparently normal individuals. This latter occurrence seems to be much more frequent in some races than in others. Prof. H. C. Wood, of Philadelphia, has told me that he has found it strikingly often in South Americans.

it seems possible that the absence of the knee-jerk may sometimes be the result of a purely functional disorder, *i. e.*, a change without discernible anatomic basis.

The knee-jerk is found absent in both the mild and the severe stage, but much more frequently in the latter than in the former. Apart from this fact, absence of the knee-jerk has no distinct prognostic significance, and it is sometimes found in cases in which the diabetic syndrome has remained stationary in a mild form for many years. Often the knee-jerk is weakened. Sometimes it remains distinct for a long time on one side after having disappeared from the other. In some few cases I have observed that one or both knee-jerks have reappeared after having been absent for some time.*

Statistics show that the knee-jerk is absent in from 7.6 to 50 per cent. of all cases of diabetes. The former figure is much nearer the truth than the latter. Tests even of the almost exclusively severe cases seen in hospitals will show that the knee-jerk, at least among Anglo-Saxon or Teutonic diabetics, though often weakened, is still distinct in the majority of cases. As I write this, an analysis of 100 cases of diminished power of assimilating carbohydrates, taken at random from my records of private practice, shows that the knee-jerk was absent in 7 of 39 severe cases, in 7 of 51 cases of true though mild diabetes, and in 1 case of simple glycosuria of many years' standing from among 10 similar cases. Of the 85 cases in which the knee-jerk remained distinctly, it was weakened in many and in several it was absent on one side. When the result of the investigation was at all uncertain, the knee-jerk has always been recorded as absent.

The other tendinous reflexes and the cutaneous reflexes may also be weakened or lost. It is important, however, to remember that the reflex contraction of the pupil on exposure to light is not lost in uncomplicated cases of diabetes, and the Argyll-Robertson pupil (contracting in accommodation, but not on exposure to light) points to a complication with central nervous diseases of organic origin.

In causing changes not only in the peripheral nerves, but also in the spinal cord, especially its posterior columns, diabetes mellitus sometimes presents an anatomic similarity to tabes. Diabetes also

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* This may or may not be a favorable sign. We know that removal of the influence of higher centers is capable of heightening a reflex dependent on lower centers. In a case of diabetes it may happen that an absent knee-jerk reappears after acute cerebral disturbances of paralytic character.

is almost always associated with more or less pronounced neurasthenia or a group of symptoms sometimes attended with functional disturbances similar to those that occur in tabes. It is, therefore, not astonishing to encounter cases of diabetes presenting a clinical picture that resembles more or less closely that of true tabes. This "*pseudotabes diabetica*," like all other forms of pseudotabes, may be attended with more or less hyperesthesia, paralysis, or ataxia. The individual case, however, rarely comports with the somewhat artificial division of Leyden, but presents symptoms of each kind. Sometimes, apart from true tabes, diabetic patients present hyperesthetic or anesthetic areas, with peripheral neurasthenic pains, which, though less violent, may resemble the lancinating pains of tabes, and be associated with epigastric pains that may be mistaken for "crises gastriques"; we further find absence of tendinous reflexes, sexual impotence, a neurasthenic, tired, gait, or—if the multiple neuritis is pronounced in the lower extremities—high-stepping, uncertain, ataxic movements of the legs in walking and an unsteadiness in standing with closed eyes, much like Romberg's symptom, etc. In short, diabetic cases of long standing may exhibit sensory, motor, secretory, and trophic changes of various kinds, that cause difficulty in distinguishing this "pseudotabes peripherica diabetica" from true tabes, especially from "neurotabes peripherica." The absence or the presence of tabetic ocular symptoms, which usually appear early in true tabes, especially reflex immobility of the pupils, may sometimes govern the decision, while in other cases it may be necessary to reserve the diagnosis for a time.

A combination of diabetes mellitus and true tabes is rare, but, apart from being merely accidental, it may be brought about by the sclerotic process of tabes attacking the diabetic center in the floor of the fourth ventricle of the brain. Under such circumstances there will (always?), according to Guinon and Souques, be found: (1) anesthesia within the distribution of the trigeminus, in consequence of destruction of the center for that nerve, and (2) increased frequency of the pulse, in consequence of destruction of the center for the pneumogastric nerve.

The question of a connection between tabes dorsalis and diabetes has been most elaborately discussed in recent years. Frerichs, in 1863, reported a case of tabes associated with diabetes; Smith, in 1883, had a patient with tabes associated with glycosuria; and Oppenheim, in 1885, presented a similar case to the Society of Physicians of Berlin. Absence of knee-jerk, one of the earliest

symptoms of tabes, has since 1884 been noted in many cases of diabetes, while from the eighties the expression "pseudotabes" of Leval-Piquechef became current, and our knowledge of the polyneuritis of diabetes and of "pseudotabes peripherica diabetica" on the one hand, and of "neurotabes peripherica" in true tabes on the other hand, developed. A vast literature has grown, from which I select especially the names of v. Ziemssen, Rosenstein, Lecorché, Eichhorst, Marie and Guinon, v. Hoesslin, Price, Auerbach, Buzzard, Leyden, Althans, Charcot, Auché, Burns, Vergely, Ross and Bury, Naunyn.

In true tabes one rarely finds glycosuria. Eulenburg observed one such instance among 125 cases of tabes, and Gilles de la Tourette, 3 among 100 cases, while Marie and Guinon found no case of glycosuria among 50 of tabes. These figures illustrate the superficial character of the investigations, and it is certain that one would find pathologic quantities of glucose in the urine in a much larger percentage of average individuals; but, on the other hand, these figures permit us to draw the conclusion that the combination of tabes and diabetes mellitus is a rare one.

I have seen a number of, in part merely neurasthenic, in part really neuritic, cases of "pseudotabes," but only one case of true tabes complicating diabetes. This case occurred in a clergyman, sixty-two years of age, who somewhat feebly denied a history of syphilis, but who was well known in his younger days to have sinned much and indiscriminately against sexual morality. This somewhat unfaithful servant of the Church later in life, after marriage, —and especially after becoming completely impotent,—turned his iniquitous ways from the temple of Venus to that of Bacchus, and sometimes shocked his flock by being terribly drunk. Still, these triumphs of the flesh, thanks to the careful control of his strong-minded wife, caused such rare interruptions in an otherwise exceedingly moderate mode of life, that an alcoholic basis for neuritis could be excluded. But there was distinct, though not pronounced, locomotor ataxia, with Romberg's symptom, a feeling as if cotton were under the feet, lancinating pains in the upper part of the legs, absence of tendinous reflexes, Argyll-Robertson pupil, an unreliable sphincter ani, and a quick pulse. The urine, of normal quantity, generally contained, with a free diet, somewhat more than 1 per cent. of glucose. Not then having in view the publication of any article on diabetes, I made no more careful investigation than that indicated by the facts recorded.

In advanced stages of diabetes, or, rather, in cases of long standing, when diabetic endarteritis has had time to render the vessels brittle, accidents from *intracranial hemorrhage* are not uncommon. I believe that small hemorrhages often take place under such conditions without causing symptoms sufficiently pronounced to attract the notice of either the patient or the physician, and especially that a number of such hemorrhages may take place simultaneously with similar small ecchymoses that occur in conjunction with hemorrhagic diabetic retinitis. In some cases the patient may com-

plain of deep-seated pains in the head, nausea, ocular disturbance, etc., but the condition often remains so vague and indistinct that the physician is easily misled to consider it an insignificant vasomotor disorder, until some serious accident directs attention to the warnings. The patient may suddenly exhibit apoplectic symptoms, and subsequently become monoplegic or hemiplegic, with hemianopsia, diplopia, amblyopia, strabismus, ptosis, etc. The nervous symptoms included in Weber's syndrome have several times been observed in cases of diabetes. The oculomotor nerve of one side is paralyzed, with resulting divergent strabismus, crossed diplopia, dilatation of the pupils, paresis of accommodation, and ptosis; while on the other side the lower branch of the facial nerve, the arm, and the tongue are paretic or paralytic. In other cases the abducens or trochlear nerve is paralyzed. The paralysis of the facial nerve in diabetes is often central, but not rarely is it peripheral.

There is one thing to be said about these diabetic hemorrhages —they indicate a more favorable prognosis than any other kind of cerebral hemorrhage, except, perhaps, the syphilitic; I presume because the bleeding often takes place from quite small vessels. Even when the hemorrhage has left the patient unconscious, the symptoms sometimes quickly disappear. The patient, however, is in constant danger, and a new attack may bring life to an end.

In some cases, when a chronic nephritis is present, intracranial hemorrhage may have to be diagnosticated from uremia.

In autopsies after diabetes, whether of the mild or the severe stage, it often happens that both the naked-eye and microscopic examination fail to disclose any change in the nervous system. This may be so even when neither the liver nor the pancreas is materially altered, and when clinical observation has given reason to believe that the glycosuric dystrophy has, as usual, been dependent upon nervous disturbances.

It is proper to point out that, on the other hand, it is not rare to find postmortem tumors and other changes in the brain, which must have affected decidedly the fourth ventricle, without glycosuria ever having been observed during life (Verron, Lépine).

In autopsies in other cases of diabetes there are found in the

central nervous system changes that there is good reason to consider as either the cause or the effect of diabetes. From what has already been said, it is generally easy to form an idea as to which of the two one has to deal with, and it seems worthy of remark that, in order to cause glycosuria, brain-disease need not necessarily directly affect Bernard's center in the floor of the fourth ventricle.

In chapter III it was mentioned that there have been observed in the brain after diabetes extravasation of blood, atheromatous processes, aneurysm, softening, sclerosis, colloid or fatty degeneration, new growths (fibroids, gliomata, sarcomata, osteomata), and the cysticercus racemosus, through which Michael's name has become familiar to all students of diabetes. It was also pointed out that general paralysis and akromegaly have often, and multiple sclerosis, tabes dorsalis, paralysis agitans, meningitis, and syphilitic disease of the brain have sometimes, been seen in association with either simple glycosuria or diabetes.

A common condition found after diabetes is dilatation of the smaller blood-vessels, with small hemorrhages into the brain (Frerichs), probably as a result of changes due to diabetes endarteritis (see below). The small cysts mentioned by Saundby and others are probably the residual products of such hemorrhages.

Dickinson, in 1870, described perivascular spaces filled with detritus occurring throughout the whole cerebrospinal system in cases of diabetes. It is a seductive theory to consider vasomotor paralysis, or paresis, strong dilatation of the vessels of more or less transitory character, and pressure with retrogressive metamorphosis of the surrounding central nervous elements in the floor of the fourth ventricle, as a cause of diabetes; but the perivascular spaces described by Dickinson often occur independently of diabetes, and neither German (Frerichs) nor English (Taylor and Goodhart) observers are inclined to ascribe any such significance to the condition named.

Glycogen, which seems, in severe causes of diabetes, to be increased in other organs as it is decreased in the liver, has been found in much greater quantity than normal in the brain after diabetes (Futterer).

It seems that diabetes not rarely causes certain changes in the spinal cord, the most common of which is sclerosis of the posterior

columns, especially Goll's and Burdach's tracts, more rarely of the lateral columns (Williamson, Leyden, Minor, Sandmeyer, Leichtentritt, Kalmus, Hensay).

Boccardi's studies of the spinal cords in dogs made diabetic by extirpation of the pancreas have yielded valuable information. The degeneration is not symmetric and has no systematic character. It was found essentially in Goll's and Burdach's tracts and in the zone external to them (Lissauer's tracts), close to the posterior nerve-roots. Sometimes it encroached almost upon the whole of the posterior columns, so that only the posterior parts of Goll's tracts and a thin zone of Burdach's tracts remained free. Changes in the lateral columns were much less common, and, when present, were found in Gowers' tracts and in the crossed pyramidal tracts. Alterations in the sheath and in the axis-cylinders of the nerves,—the former being thinner and the latter having a lacerated appearance—were found even a short time after the onset of severe diabetes. The proliferation of the areolar tissue and the process of sclerosis began subsequently. The gray substance also was changed; degenerated, enlarged, hyaline cells being found in the anterior and posterior cornua and in Clark's columns, and the nuclei of these cells staining with difficulty or not at all. Here and there were observed lacunæ, like those described by Charcot and Joffroy. Sometimes the endarteritis with endothelial desquamation, described by Ferraro, was noted; according to Boccardi, it was rather the exception than the rule.

Nonne observed (*in vivo* and postmortem) chronic anterior poliomyelitis as a complication in a case of severe pancreatic diabetes.

Toward the close of the eighties, Price, Eichhorst, and Auché described diabetic neuritis, all three finding parenchymatous degenerative neuritis with uneven, vacuolar sheath, with the axis-cylinder segmented or absent. It seems that these alterations are present most frequently in the anterior and posterior tibial nerves. Hensay noted similar changes in the facial and spinal accessory nerves. The crural nerve also has been found in this condition.*

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* The knee-jerk in this case had been absent during life. Changes in the peripheral nerves, however, unless sufficiently far advanced to destroy conductivity, could not alone cause loss of the knee-jerk. Even though our present means of investigation are incapable of detecting changes in the cellular nervous centers, such changes may exist, and

The *pneumogastric nerve* has several times been found abnormal, sometimes sclerotic and thickened (Percy, Fleury), sometimes compressed by tumors (Anger, Frerichs, Henrat, Neumann), sometimes atrophic from other influences than tumors (Lubinoff). Eichhorst found it the seat of a *parenchymatous neuritis.*

The sympathetic nervous system, which has been studied carefully, since it has been known that lesions of different parts thereof may give rise to glycosuria, has often been found in a pathologic condition. The changes have generally been found in the celiac ganglion, and have usually been of a sclerotic, more rarely of a simply atrophic, nature.

Circulatory System.

In inveterate cases of diabetes the heart is never very strong. The sounds are often weak and distant, the systolic elevation in the sphygmogram being often low and the pulse uneven, while the patient complains of the usual symptoms of weak heart if great demands are made on the circulatory apparatus. This deficiency is usually present in only a moderate degree, and the pronounced *fatty heart* is comparatively rare. Still, the fatal issue from this cause, by its similarity to sudden death in some cases of coma, has several times contributed to the number of false reports of death in coma apart from the severe stage and without "acidosis."

The pulse varies exceedingly in diabetes. Its frequency, however, is distinctly increased in about 75 per cent. of all cases of severe diabetes, and it is not rare in such cases, apart from complications and from diabetic coma, to find a pulse of 100 or more. I think this must be caused by the irritating influence of the toxins on the heart's own sympathetic centers more often than by any paralyzing action on the center for the pneumogastric nerve. If one should speak of a diabetic type of pulse, it would be the small, feeble pulse of great frequency.

Organic changes in the valves of the heart are generally brought

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may be expected after the operation of marantic and toxic influences of long standing. To such changes may be ascribed both the absence of the knee-jerk and an important rôle in the production of peripheral nervous disturbances.

about by chronic endarteritic processes and the aortic valves are most commonly attacked. Changes in the mitral valves do not seem to me to be much more common in association with diabetes than independently thereof, and Lecorché's statistics showing such changes in 12.3 per cent. of all cases of diabetes are to me inexplicable.

The most frequent macroscopic alteration in the circulatory system in diabetes consists in *atheromatous processes* tending to *arteriosclerosis* which, excluding the juvenile cases, may be detected by palpation during life in about 20 per cent. of all cases. It is a feature essentially of inveterate cases, and is thus much more common in those of long standing, though in what I persist in calling the mild stage, than in cases that belong to the severe stage and rarely persist for any considerable number of years. I should think that the glycemia and other blood-toxins are responsible for the condition ; but an influence arising from enfeebled vasomotor activity may possibly also contribute to the result. In the presence of *pronounced* arteriosclerosis one often finds alcoholic or syphilitic complications. In rare cases the atheromatous and consequent conditions of the arteries of the brain are not the effect but the cause of diabetes.

Atrophic and degenerative conditions of the myocardium sometimes attend diabetes, though they are much more rarely detected during life than after death.

Much has been said and written about *angina pectoris* complicating diabetes. The attacks of pain and the asthmatic disturbances that sometimes occur in cases of diabetes—more often during the night than by day, like all sensations called angina pectoris—are *either* the expression of organic disease of the heart, usually resulting from changes in the coronary arteries and in the myocardium, or they are manifestations of less important neuralgic or rheumatic conditions in the chest-wall, which, especially in "nervous" persons, may cause great momentary suffering. Both the first kind, the true, dangerous, "organic" form of angina pectoris, and the latter kind, the comparatively insignificant, "nervous" form of pseudo angina pectoris, are more common among diabetics than among other individuals. In most cases of diabetes presenting such disturbances that I have seen, the attacks recurring at

long intervals for years, the failure to detect symptoms of organic disease on careful physical examination, the presence of rheumatic infiltrations or of neuralgic symptoms in the chest-walls, the difference in the radiation of the pains from what usually takes place in true angina, and the manifest influence of purely rheumatic and nervous causes, have led me to attribute the symptoms to the "nervous" form, pseudo angina, which seems to me decidedly more common than the true angina.

Among the rarer complications of diabetes there occur sometimes, though only in advanced cases, numbers of petechiæ, due to *small subcutaneous hemorrhages*, most frequently on the lower extremities, and probably dependent on brittleness of the small vessels caused by the diabetic endarteritis described by Ferraro.

The heart, in autopsies of cases in which there has been pronounced marasmus, often appears in a state of brown atrophy. In other cases the organ shows no distinct alteration. In at least 15 per cent. of all cases some enlargement, which usually affects the whole organ, is manifest. Pronounced fatty degeneration is rare. Atheromatous changes in varying degree are common, but other endocarditis or valvular alterations are not.

Dr. Jaques Mayer found, clinically, enlargement of the heart in 21.6 per cent. of cases of diabetes in a first series; and in a later series 27 per cent. The latter figure is nearly twice as high as the 15 per cent. at which I arrived in the same manner—a difference that, as I have found after consultations with my esteemed colleague, depends upon differences in opinion concerning the physical basis for the diagnosis. Dr. Mayer himself, in an investigation of the postmortem records of the city of Berlin, did not obtain a higher figure than 13 per cent. He mentions the chemic irritation of the increased amount of sugar and urea in the blood as a cause 'of the hypertrophy without further explanation. O. Israel has shown experimentally that in extreme cases the kidneys become unable to fulfil their function of eliminating urea and that the heart attempts to make good this deficiency by hypertrophy of its left ventricle (injections of sodium nitrate and of urea in horses and dogs). For my part, I am inclined to ascribe the rather large percentage of cases in which hypertrophy of the heart attends diabetes to (1) the adiposity which is common in diabetes, and which often *per se* causes enlargement of the heart; (2) the atheromatous changes in the vessels and the obliterating and desquamative endarteritis of the small vessels (Lecorché, Ferraro); (3) the polydipsia and the increased quantity of water passing through the system. The last two influences must increase the burden of the heart and tend to produce a work-

ing hypertrophy. In some cases there coexist the causes of hypertrophy resulting from cirrhosis of the kidney, which, according to the prevailing views of trustworthy investigators, consist in more than the narrowing of the blood-current. An irritating action of the blood-toxins on the vasoconstrictors might especially be thought of. The mesenteric vessels, however, which exert so important an influence on the arterial pressure, are in diabetic patients probably much oftener dilated than constricted.

Diabetic endarteritis of the small vessels (Ferraro, Strauss, Boccardi) seems to be very common and may exert an important influence in the causation of hemorrhages and of degenerative processes in the tissues. It generally causes desquamation of the endothelium (Ferarro), and sometimes obliteration of the vascular lumen (Lecorché). The brittleness of the small vessels in cases of inveterate diabetes is manifest, and finds expression in the extravasations into the brain, the retina, and the cutaneous and other tissues.*

Diabetic blood presents distinct changes of a physical anatomic and chemic nature. To the last I shall return later. The percentage of water has been found both increased and diminished. Von Jaksch found it diminished in every one of 10 cases, in which it ranked from 66.46 per cent. upward, but never reached the normal, 72.28 per cent. The specific gravity was found by Hammerschlag to be increased to 1.064; by Davy, to be 1.061; by Nasse, to be diminished to 1.048. The number of red blood-corpuscles is usually high (A. James and others), except in bronze-colored diabetes (see below), in which the number is much diminished, and marked hemosiderosis, due to the products of disintegrated red blood-corpuscles, is found in almost all of the organs. Bremer, Williamson, and others have found that the red corpuscles in diabetic blood are stained in a different way by methylene-blue and other dyes than those in normal blood (see below). Habershon found marked leukocytosis in diabetic blood, the number of white

* Rosenblath, as early as 1888, saw the walls of the small vessels thickened in an advanced case of diabetes. The case is surrounded with some interest on account of the presence of numerous small hemorrhages or ecchymoses strewn over the skin of the legs. Above the ecchymoses the skin in many places presented necrotic areas, which invaded the papillary body and about half the depth of the entire cutis. The lungs contained circumscribed gangrenous areas, and the tongue and the esophagus were the seat of numerous ulcers.

blood-corpuscles diminishing with restriction of carbohydrates and increasing during coma. Bettman, in a case of diabetes complicated by exophthalmic goiter, observed the number of white blood-corpuscles undergo diminution with a free supply of carbohydrates. Neusser found around the nuclei of the leukocytes in diabetic blood small particles that stained black with a modification of Ehrlich's solution ("perinuclear basophilia").

It has been known since the end of the eighteenth century that the blood of diabetics sometimes exhibits a peculiar whitish color, owing to the numerous particles of fat present,—*diabetic lipemia*,—which may reach 11 or 12 per cent. (Lecanu, D. Gerhardt, after Naunyn). After a rich meal the percentage of fat in the blood may reach high figures in healthy persons; but the lipemia in diabetics, like that which attends some other pathologic conditions, may occur on an empty stomach (Naunyn). The intimate causes of the condition are unknown.*

Respiratory Organs.

The most common pulmonary complication of severe diabetes mellitus is *tuberculosis*. While this pulmonary disease ordinarily causes the sacrifice of from one-seventh to one-fifth of mankind, it attacks, according to Griesinger, 72 per cent. of diabetics in the severe stage and destroys 39 per cent. These figures apply *only* to severe cases, and are never reached outside of hospitals.

In private practice, especially in watering-places such as Carlsbad, the proportion of patients with tuberculosis of the lungs is a low one and the patients are usually in a light stage and in fairly good nutritive state. This observation would seem to show that hyperglycemia predisposes less to pulmonary tuberculosis than does marasmus. It is often said that tuberculosis of the lungs is much more quickly fatal when associated with, than when independent of, diabetes; but any practitioner with a large number of diabetic patients knows that the difference in this respect between diabetic and nondiabetic patients *with the same degree of marasmus* is but

* Our knowledge of changes of the blood in different diseases is only developing, and some of these observed in diabetic blood apparently do not belong exclusively to diabetes.

slight. The results in cases of pulmonary tuberculosis complicating diabetes is not rarely that usual with the condition first named; but in many of these cases, however, the termination is that common with severe diabetes, namely, diabetic coma.

Diabetes mellitus seems to some extent to predispose to acute croupous and lobular pneumonia, which, by reason of the tendency to severe complications, the weak heart, and the generally low condition, makes the prognosis worse than it would otherwise be. Still, one ought not to despair of a favorable issue, and I have had several diabetic patients that have passed through acute pneumonia —in one both lungs being attacked. When acute pneumonia occurs, the glycosuria is generally diminished in a marked degree; in rare cases the reverse effect has been observed (Naunyn).

Inflammatory processes in the lungs in diabetic patients, especially in inveterate or advanced cases, are much more likely to induce gangrene than in nondiabetics. In Naunyn's work, published after the Swedish edition of this book had appeared, the great German clinician distinguishes between two forms of pulmonary gangrene: the acute and the chronic. I have seen only instances of the first, but Naunyn considers one about as frequent as the other.

The acute form generally begins as a croupous pneumonia, and is often attended with hemoptysis and abundant bloody and purulent sputa, which generally lack the customary odor of gangrene. This disorder lasts at the longest for a few weeks. After death one finds in the lungs gangrenous and purulent cavities, which usually contain bacilli or other fungi (Zenker, Fürbringer), but which often are not very offensive to the sense of smell. One of my diabetic patients, who is still alive, recovered some years ago from this complication. Marklen has observed a similar case. A fatal issue is naturally the more common termination.

The other chronic form of pulmonary gangrene complicating diabetes begins as a catarrhal condition, with fever and bloody or purulent, often offensive, sputa, and may last for years, until hemoptysis or marasmus brings about a fatal issue. Naunyn observed this complication only in elderly patients.

Digestive Organs.

I have already mentioned the diabetic changes that take place in the cavity of the mouth. I would here refer only to the important circumstance that in the diabetic the *power of mastication* is likely to be much *impaired*, on account of caries or loss of the teeth.

The *saliva* is often distinctly diminished, and dryness of the mouth is a common complaint. Besides, the saliva, particularly in certain cases, is often acid; but, apart from the predisposing influence this may have with regard to caries, it is rather of theoretic than practical interest.

The *gastro-intestinal tract* in diabetic patients generally fulfils its functions quite well so far as digestion and absorption are concerned, and advanced changes are exceptional.

A most remarkable circumstance is the rarity of distinct dilatation of the stomach. One certainly finds often, clinically and post-mortem, that the limits of the stomach are rather extended, but not beyond what may be considered normal; and clinically pronounced dilatation certainly does not occur in one per cent. of all cases of diabetes.

The diminution in all of the secretions (except the urine), which there is reason to believe occurs in diabetes, is not sufficient to impair digestion, and may, in many cases, be made good in the stomach and the remainder of the digestive tract by a hypertrophy of the secretory glands (see below). When I began to make analyses of the gastric juice, I made examinations in a considerable number of cases of diabetes, but only rarely found anomalies of composition or of digestive power. This experience is in accord with the results obtained by Honigmann, Rosenstein, Gans, and others. Numerous and exact investigations into the absorption of various foods, as well as careful fecal analyses, also have demonstrated that absorption from the gastro-intestinal tract is, as a rule, normal or nearly normal.*

Slight dyspeptic and catarrhal troubles are, of course, quite common among diabetics as among other persons. During periods in which the use of bread and vegetables is interdicted or rigidly restricted, manifest gastro-intestinal catarrh, with diarrhea and

* See Weintraud's masterly treatise in "Bibliotheca medica," I, Cassel, 1893.

sometimes with fetid stools, is especially prone to occur, and not rarely necessitates a greater allowance of carbohydrates.

Then there is a small class of diabetic patients who exhibit a *digestive deficiency* of a grave nature. These cases generally belong to the severe, or at least to a very advanced, stage of diabetes, and depend upon primary or secondary degenerative processes in the pancreas or in other glandular elements of the digestive apparatus.

Hirschfeld * has published seven such cases from his own and from Frerichs' and Külz's experience. In these, from 29.4 to 47.2 per cent. of the ingested fat and from 30 to 45 per cent. of the ingested proteids were found in the feces. Even in these cases the carbohydrates were fairly well digested and absorbed. This certainly does not occur when the pancreas is in an advanced abnormal condition, and Abelmann found in the feces of Minkowski's dogs, after extirpation of the pancreas, almost the whole quantity of ingested carbohydrates, upward of 43 per cent. of the emulsified and nearly the whole of nonemulsified fat, and as much as 56 per cent. of the proteids. As a rule, the fat is the kind of food that most frequently and to the greatest extent remains undigested and unabsorbed, even independently of the great variations that occur in each individual case (Sandmeyer).

The deficient absorption of fat, which is apparent without closer investigation from the light color of the feces, has long been observed in diabetes, and has been ascribed to disease of the pancreas. Bright, Eliotson, Frerichs, Fles, and Silver observed fatty stools in diabetes, but their patients also suffered from retention of bile and icterus. Le Nobel noticed similar stools in diabetes without biliary retention. Claude Bernard, by experiment, came to the conclusion that the pancreatic juice is necessary for the absorption of fat. Senn observed fatty stools after extirpation of the pancreas. William T. Bull and Hartsen mark a like observation in patients with pancreatic cysts, and the latter found the extract with ether from pigeons' stools three times the normal after extirpation of the pancreas. Von Mering, Minkowski, and Abelmann,

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* See Hirschfeld's interesting paper in "Zeitschrift f. klin. Med.," Berlin, 1891. It is difficult to understand why these cases should be described as "eine neue klinische Form von Diabetes." The absence of polyuria is not rare in diabetes, and in most of the seven cases the polyuria, according to Hirschfeld's own figures, was manifest. The cases present no peculiarity beyond the deficient digestion, and the establishment of artificial clinical forms is undesirable. In one of the cases, which ended fatally from marasmus, the glycosuria ceased with a strict diet. The pancreas was either carcinomatous or atrophic or not distinctly changed.

finally, have observed analogous conditions after extirpation of the pancreas in dogs. Thus, it is finally established that pancreatic juice plays an important rôle in the absorption of fat. It is also known that the pancreas is in some way necessary to prevent hyperglycemia, and that the destruction of this organ is followed by glycosuria. It has, however, not been shown that every diabetic patient who, apart from retention of bile, does not digest fat suffers also from disease of the pancreas; while, on the other hand, it is positively known that this organ may be greatly changed without noteworthy impairment in the absorption of fat (Hartsen, Fr. Müller) and without diabetes resulting (Minkowski). It is known, further, that there are sometimes in cases of diabetes reasons unconnected with the pancreas for digestive deficiency.

Habitual constipation is, in consequence of marasmus, and an atonic state of the bowels, deficient innervation, etc., still more common among diabetics than among other individuals, and any tendency in that direction is likely to become manifest with rigid restriction of carbohydrates.

In connection with a consideration of the digestive apparatus in diabetics illustrations are not wanting of the great frequency of purely nervous symptoms in association with the diabetic syndrome. *Gastro-intestinal neuroses* are exceedingly common among diabetic patients. It would carry me far beyond my purpose—as it would be beyond my power—to describe here all of the different neuroses of this kind that may occur in diabetes. The most frequent of these belong to that group of which a part generally is called nervous dyspepsia or gastric neurasthenia, but which, on account of its manifold sensory and motor disturbances, referred to different parts of the digestive tract, I prefer to designate *gastro-intestinal neurasthenia.* The patient often suffers from inexplicable variations in appetite,—which may one day be excellent and the next fail entirely,—from eructations, a sense of pressure, of tension, or of pain in the epigastrium, or of nausea, etc. Sometimes flatulence is the chief complaint. Easily aroused and excessive peristaltic activity may cause attacks of diarrhea on slight provocation; spastic disturbances of stomach and intestines may cause severe pains, and, especially in the latter, may give rise to what Kussmaul calls "tormina ventosa." One sometimes may find a part of the alimentary canal distended by gas and giving for the moment the impression of a tumor. I believe that the much-talked-of diabetic *crises gastriques* usually are of spastic nature. They may be quite

painful and be followed by diarrhea, and in rare cases by vomiting. I can not find that they differ from similar manifestations in purely neurasthenic cases, and they certainly resemble these more nearly than the tabetic "crises gastriques," to which they have been compared.

Secretory neuroses certainly exist much oftener than they are noted, being sometimes difficult of detection, even on elaborate investigation. I have twice seen in diabetic patients what I believed to be an excessive secretion of gastric juice, a condition that is seldom mentioned. The glycosuric dystrophy is rather likely to diminish the secretions, but an exception in the other direction may occur with the gastric juice, just as sometimes hyperhidrosis is observed instead of the customary anhidrosis. Hyperacidity (from hydrochloric acid) has sometimes been noted (Riegel, Naunyn). I believe that it is not uncommon.

The most serious of all gastric neuroses that can attack the diabetic patient is nervous *anorexia* (Gull, Lasegue), which is sometimes found in neuropathic persons, but which, happily, is rare both in association with and independently of diabetes. In the few cases other than of diabetes in which I have encountered this curious affection—which has little in common with the refusal to eat in developed mental diseases—the course has been favorable, and the patients, after a few weeks of marked inanition, have been restored to normal appetite and health. This seems also to have been the almost universal rule in recorded cases. In diabetic patients, however, the prognosis appears to be much less favorable. The anorexia is sometimes particularly obstinate, and is especially pronounced with regard to meat and fat, and even if the patient is allowed a completely unrestricted diet,—which, I think, is to be recommended,—all remedies may fail to secure the ingestion of more than a small part of the food required for the generation of the necessary number of calories. Most of these patients are women. The last one under my care exhibited after the beginning of the anorexia no glycosuria, but pronounced diaceturia from the inanition, and died after several months of marasmus.

Gastro-intestinal changes have often been found after death, though they are rarely of a marked nature. The increased diges-

tive demand causes at first functional hypertrophy in different structures. Dittrich, Frerichs, Lancereaux, Rosenstein, and others found hypertrophy of the muscular layers in the stomach. Boccardi saw (in diabetic dogs) enlargement of the gastric glands and their ducts, and dilatation of the lymphatic vessels. [Hyperacidity of the gastric juice—0.4 per cent.—is not rare (Riegel).] Boccardi also found Brunner's glands and Lieberkühn's crypts hypertrophied. I have generally found, both clinically and after death, a rather large, but never decidedly dilated, stomach. I have several times on postmortem examination seen enlargement of the mesenteric glands, as first pointed out by Frerichs.

In advanced cases there is atrophy both of the muscular (Frerichs) and of the glandular elements (Ferraro, Boccardi). Armanni found in one of Cantani's patients pronounced atrophy of the peptic glands. Rosenstein mentions a decreased amount of hydrochloric acid. These changes and those that sometimes occur in the pancreas suffice to explain the severe digestive troubles in Hirschfeld's cases, previously mentioned. Catarrhal changes are exceedingly common.

Hemorrhage and ulceration are mentioned as occurring in different parts of the gastro-intestinal tract (Frerichs, Ferraro, and others).

The *pancreas* plays a most important part in the pathogenesis of diabetes mellitus, and I propose further on to describe pancreatic diabetes and to give a summary of v. Mering's and Minkowski's discovery of the results of extirpation or resection of the pancreas.

Clinically, anything noteworthy with regard to the pancreas is found with comparative rarity among diabetic patients. As I write, it happens that I have under observation such a case, in which the rapid development from day to day is striking. The patient, a Jewess, sixty-seven years old, has had upward of six per cent. of glucose in her urine, the sugar disappearing entirely with restriction of diet. In the beginning of the diabetes, which set in quite suddenly, there was no diacetic acid in the urine. Now, Gerhardt's reaction is pronounced as a result of inanition. The patient is often ravenously hungry, but can scarcely take any food when it

is brought to her. She sometimes vomits, and complains often of severe pains in the epigastrium and in the back. Palpation raises a suspicion of increased resistance over the head of the pancreas. No icterus is present, but a decided cachectic hue. The feces sometimes contain large quantities of fat. Unfortunately, I shall not be able to be present at the postmortem examination, which is certain to take place within a few weeks, and which probably will reveal a carcinoma of the pancreas.*

Since the connection between diabetes and disease of the pancreas was pointed out that organ is as much studied in diabetic patients after death as it was neglected in the past. Such changes in the pancreas as can be reasonably considered to have caused the diabetes are, however, found comparatively rarely—certainly not in more than ten per cent. of all autopsies after diabetes. In fully ninety per cent. or more of such cases the pancreas is either normal or diminished in size and flabby in consistence, with small but otherwise normal acini; it presents a condition of simple atrophy, which may with much better reason be considered an effect than a cause of the glycosuric dystrophy.†

Among the comparatively few cases in which disease of the pancreas may be considered as a cause of the diabetes the most common are atrophy and cirrhosis from the presence of calculi in the ducts, which may, in consequence, be much enlarged.

Cirrhosis of the pancreas, interstitial pancreatitis, may also exist without the presence of calculi (Heinemann), and in exceptional cases may cause diabetes.

Sometimes the pancreas is the seat of more or less fatty necrosis, as I have seen in cases in which the whole clinical picture has been that of fat, constitutional, gouty, nonpancreatic diabetes. Seyler recently recorded a case of ischemic fatty necrosis, which he considered due to atheromatous processes that were exceedingly pronounced in the celiac axis and its branches, with diabetes as a remote sequel.

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* Since this was written the diagnosis has been found to be correct. It is a curious fact that the woman's father also died of carcinoma of the pancreas.

† My opinion in this respect is based upon not a few personal autopsies and on information gained in Carlsbad, where a considerable number of postmortem examinations after diabetes are made.

Some observers mention interstitial lipoma of the pancreas (Hansemann, Naunyn).

Hyaline necrosis, with homogeneous, transparent contents in the enlarged, glandular cells, such as has been described by Armanni in the kidneys (see below), seems also sometimes to occur in the pancreas (Saundby).

Carcinoma of the pancreas has several times been found after diabetes, and is now and then diagnosticated during life. It may exist without diabetes, partly because a sufficient amount of the glandular tissue is left intact, partly, as Hansemann points out, because of the retention by the degenerated cells of some of their functional capability.

Other changes in the pancreas are rare. Abscess has been found, but seems only exceptionally to have time before death to cause diabetes. Cysts generally leave enough of normal tissue to prevent the development of diabetes. Frerichs has reported a case in which the postmortem findings seem to indicate the development of diabetes as a result of (Fitz's) hemorrhagic acute pancreatitis; Benda and Stadelmann have reported a similar case. The majority of instances of acute hemorrhagic pancreatitis are unattended with glycosuria (Seitz).

Hansemann * has recently published an excellent paper on the relations of the pancreas to diabetes. He believes—on insufficient grounds, it seems to me—in the occurrence of a specific variety of diabetic atrophy of the pancreas, and maintains that there exist anatomic differences between this and a similar state after nondiabetic cachexia or marasmus.

The liver is the organ in which one must look for the immediate cause of diabetes if, with Bernard and his many adherents, one considers the condition to depend upon an excessive production of sugar. We have already seen that a number of affections of the liver are sometimes, though inconstantly, accompanied by glycosuria, which may or may not be found after ligation of the gall-ducts, or, together with biliary fistulæ, after attacks of gall-stones, after trauma over the liver in association with pylethrombosis, organic heart-disease and a consequent stasis in the liver, acute yellow atrophy, phosphorus-poisoning, amyloid degeneration,

* "Zeitschr. f. klin. Med.," 1894.

and, above all, cirrhosis. I consider the frequency of the association of cirrhosis of the liver and glycosuria fully demonstrated since Naunyn, in his excellent work recently published, mentions 22 cases of incipient and 2 cases of advanced cirrhosis of the liver among 152 diabetics.

Still, it must not be expected that some distinct abnormity of the liver will be found clinically in a large percentage of diabetic patients. The character of Naunyn's figures depends on the enormous frequency of cirrhosis of the liver in and around Strasburg, where his observations were made; his earlier figures are much lower. The usual state of the liver is, so far as clinical investigation goes, a normal one. On percussion the size of the organ is found to be within the normal limits, and palpation yields no information of any change in form, consistency, or sensibility. In other cases, fewer though not very rare, there is some enlargement and perhaps some tenderness on pressure.*

Now and then any one who sees many diabetic patients will find one with a cirrhotic liver—generally of the usual atrophic variety. I will cite two cases under observation within the last few years:

Dr. ——, a Scandinavian, is an unmarried physician, fifty-four years old, who has a great aversion to pure water. He does me the honor to consult me in Carlsbad, where he appears in my office with watery eyes, a rough voice, trembling hands, and a flabby panniculus, and complains bitterly of loss of appetite and nausea, especially in the mornings, etc. When he discovers that I have, without asking any unpleasant questions or making further investigation, booked him as a case of chronic alcoholism, he indignantly protests, exclaiming that he has drunk "only" a bottle of claret and half a bottle of whisky a

* Glénard, of Vichy, has arrived at other conclusions in his "Resultats Objectifs d'Exploration du foie chez les Diabetiques," Paris, 1890. Among 324 diabetics he found, on palpation, by a method that he designates "procedé du pouce," a distinct change in 60 per cent., and these cases he classifies under 8 varieties and 42 subvarieties, which he illustrates by diagrams. So far as both classification and palpation go, this is entirely beyond me, as well as some others. The last medical friend to whom I showed Glénard's plate did as Voltaire's governor—"il releva sa moustache et sourit amèrement," but said nothing. Neither will I concede, without all reservation, the truth of Glénard's statement: tout foie percu par la palpation chez le vivant est un foie anormal. Glénard considers hypertrophy of the liver to be present in 34.5 per cent. of all cases of diabetes, and usually limited to the right lobe; the consistency to be increased in one-third and sensitiveness in one-fourth of all cases; and nontender induration to be present in 23 per cent. of all cases and in 40 per cent. of those in which the liver can be felt by palpation.

day. Even this concession probably represents only a part of the truth. Syphilis was denied.

The radial and the temporal arteries were sclerotic. The heart was somewhat enlarged in all directions; the second aortic sound somewhat accentuated. On percussion the right lobe of the liver appeared to be distinctly diminished in size, but there was no tenderness. The spleen was a little enlarged. There was no icterus, no bile in the urine, and no manifestations of stasis. The tongue and the breath were fairly normal; only a few teeth remained, and those were carious.

The patient was irritable, slept badly, and could not approach steep declivities. Sexual power was "highly satisfactory." The knee-jerks were normal.

When the patient received about 120 grams of starch with his food, he passed 1700 cu. cm. of urine of a specific gravity of 1.019 and containing a trace of albumin and about 0.05 per cent. of glucose. On microscopic examination quite a remarkable number of calcium-oxalate crystals were found, and only a few hyaline casts. Single samples of the urine contained as much as 0.5 per cent. of glucose. Glycosuria was first observed fourteen years ago.

The patient died about a year after my examination, and I received word that the liver was fairly well advanced in cirrhosis.

Mr. ——, a Jewish Bavarian brewer, thirty-nine years old, whose father had been a diabetic and who himself had always been "nervous," forgot the law and the prophets and the usually temperate Jewish customs, drank for many years much "Kornbranntwein" and beer, smoked ten cigars a day, and was far from moderate "in puncto sexus." He insists that he never had syphilis. Two years ago he began, from mere thirst, to attack the beer-casks even more energetically than before, and his physician found four per cent. of glucose in the urine. Since then the patient has lived under a moderate restriction of carbohydrates.

The man was exceedingly neurasthenic, and had a "smoker's heart." The reflexes were normal. The breath was natural; one tooth was missing, and the remainder presented very little caries. The liver was somewhat reduced in size. The left lobe was distinctly palpable. The spleen extended a little beyond the anterior axillary line. Slight icterus existed. About 120 grams of carbohydrates caused scarcely 0.5 per cent. of glucose to appear in the daily 2500 cu. cm. of urine, with a specific gravity of 1.016 and containing a trace of albumin.

I have already mentioned the frequency with which gall-stones complicate diabetes mellitus.

On postmortem examination the liver often appears normal to the naked eye and on microscopic examination. In other numerous cases the liver is slightly enlarged, probably as a result exclusively of dilatation of the vessels. The hyperemia is of the active kind. The veins usually are not distended, but the arteries and

capillaries are distinctly so, and the organ presents a more or less rosy color, often limited to certain parts. In some cases the vessels may be dilated "ex vacuo" as a result of atrophy of the liver-cells (Armanni). Now and then one finds what Hanot has described as a liver "couleur chamois," with a reddish-yellow color, and the intralobular veins distended. Simple atrophy, with diminution in size and a brownish-yellow color, is not rare. The same can be said of the typical fatty liver. Under these conditions the glycogen, which is always likely to be diminished, especially in cases of severe glycosuric dystrophy, reaches its lowest figures (Boccardi). Cirrhosis, moderately developed, is not rare, but rarer than any of the other states mentioned. Abscess, probably somewhat more frequent in association with than independently of diabetes, is, nevertheless, quite exceptional. When the fatal issue has been immediately preceded by high fever, the parenchymatous change designated by the Germans as cloudy swelling is found in cases of diabetes, as under other conditions.

Boccardi observed in dogs, after extirpation of the pancreas, hyperemia of the liver, but no true hypertrophy. Atrophy or fatty degeneration quickly came on. While the nucleus remains perfectly visible, vacuoles are discernible in the protoplasm, as after arsenical poisoning (Steinhaus, Gianturco, Sampacchia). The vessels become markedly dilated, partly, at least, in consequence of an influence "ex vacuo"; and small hemorrhages occur, especially near the surface. Boccardi found also in the liver diabetic desquamative endarteritis, but not the hyaline necrosis observed in the spinal cord (Boccardi), in the kidneys (Armanni), in the pancreas (Saundby), and in the liver (Ferraro).

Roque, Devie, and Hugonenq found here and there among the liver-cells crystals which they believed to be leucin or tyrosin.

Bonome,* after extirpation of the celiac ganglion, noted neuroparalytic dilatation of the vessels and hemorrhage and atrophy of the lobules; *i. e.*, a state similar to which Boccardi found in the liver of dogs after extirpation of the pancreas.

The spleen may be mentioned here on account of its relation to

* "Riforma Med.," 1842.

the liver. It is, like all the abdominal organs, often hyperemic and somewhat enlarged. Clinically, distinct enlargement is of importance, as it may strengthen a doubtful diagnosis of incipient cirrhosis of the liver. In advanced diabetic marasmus the spleen is often small and flabby, and it participates in the general atrophy.

Urinary Organs.

The kidneys are often slightly changed in diabetes, but comparatively rarely show excessive alterations.

Fully a third, perhaps more, of all diabetic patients show *albuminuria*. The albumin in most cases is present only in traces, or at least in small quantities, and it usually does not reach so much as one part in a thousand. Almost all patients, who have lived for some time within the severe stage, present some albuminuria, which in the mild stage occurs only in a small minority of cases.

Slight albuminuria in a diabetic patient is usually considered of less clinical and prognostic significance than under other conditions; and in the presence of conflicting therapeutic indications, as between the kidneys and the glycosuric dystrophy, physicians generally regard chiefly the latter. In some cases the albuminuria is an effect of stasis in the kidneys from the weakness of the heart that is common among diabetics. In cases that have reached the severe stage it is often undoubtedly of toxic origin, resulting from the irritation of the kidneys in consequence of the "acidosis." Arteriosclerosis *per se* also not rarely causes some degree of albuminuria without the presence in the urine of epithelial elements from the kidneys; such vascular changes are likely to be found earlier in life in diabetics than is usual in others. Further, true nephritis is not rare in diabetes. As Grube correctly remarks, it is usually a form of mixed parenchymatous and interstitial character; casts can then usually be found without difficulty in the urine. (From the presence in the urine of *hyaline* casts no conclusions as to more profound alterations are to be reached, as such formations are extremely common, especially in senile individuals, in connection with or independently of true nephritis.) The typical gouty kidney is occasionally found. It sometimes causes no albuminuria,

but only polyuria, the urine being of low specific gravity, and containing only small quantities of glucose.

Like almost all writers on diabetes, I have a number of times observed the curious change in the glycosuria that takes place in cases with cirrhotic processes in the kidneys. As the arterial pressure and the quantity of the urine increase and the specific gravity falls with the advancing cirrhosis, the glycosuria *ceteris paribus* slowly but quite considerably grows less marked. The same patient that in the incipient stage of interstitial nephritis with a fixed supply of carbohydrates excreted twenty grams of glucose in the twenty-four hours, may five years afterward, under the same conditions, excrete only one gram of glucose. Such cases may finally resemble the rare combination of diabetes insipidus with insignificant but pathologic traces of glucose in the light, abundant urine. The state of the glycemia in these cases can not at present be considered settled, and the result of injections of phloridzin in patients with interstitial nephritis is still uncertain (Klemperer *versus* Magnus-Levy, Naunyn, and others). Naunyn, in his recent work, expresses the opinion that the curious increased tolerance for carbohydrates in cases of diabetes complicated with chronic interstitial nephritis is only an analog to the same tolerance observed in all cases in which diabetes is associated with some other severe organic disease attended with cachexia and marasmus. Still, I have seen cases in which the cirrhotic process in the kidneys, though developed, has left a fairly good general state of health, and in which this increased tolerance has been perfectly evident. Concerning the influence of the kidneys on glycosuria, reference is made for further particulars to what is said in chapter III on renal glycosuria.

Diabetics are often gouty, and gouty patients often suffer from renal calculi, which are not rare in diabetes of the mild "lithemic" type. Budde found 28 cases of nephrolithiasis among 256 diabetics.

Otherwise, diseases of the urinary organs do not occur much more frequently among diabetic patients than among others. Schmitz, who sometimes gathered amazing statistics, quite incorrectly mentions cystitis as a common complication. Senator, Fr. Müller, Guiard, and others have seen pneumaturia; Ernst,

Naunyn, and Hartge have found microorganisms (leptothrix, sarcina) in different parts of the urinary tract. Such vegetations easily occur in places in which the sweet urine comes in contact with the air, but the germs do not, as a rule, spontaneously ascend the urethra, and complications of this kind are comparatively rare.

The kidneys show after death distinct and frequent, but not constant and not marked, changes. With the naked eye generally some enlargement and hyperemia of the whole organ is appreciable. On section the cortex often presents some slight fatty and opaque change of color; and the glomeruli are enlarged, while the medulla is distinctly hyperemic. Next in frequency to these conditions the kidney is found without distinct changes. Advanced parenchymatous or interstitial alterations are exceptional. The nephritis of diabetics usually represents a slight development of morbid processes both in the interstitial and in the parenchymatous (epithelial) tissue. Sometimes changes like those of the large white kidney are seen, but I know of no typical case of this kind.

Under the microscope some degree of fatty degeneration may be found, especially marked in the convoluted tubules, but only rarely developed to such a degree as to obliterate the nuclei or otherwise to compromise the integrity of the cells.

Fichtner, in 1888, described the curious appearance of a transverse section of the convoluted tubules showing large particles of fat, arranged like a string of pearls, in the degenerated epithelial cells along the basement membrane. Besides, fatty particles are found strewn all over the section of the cells, which, however, almost always retain their structure.

The most characteristic (frequent, but not constant) microscopic change is represented by what Armanni * designates hyaline metamorphosis, Ebstein hyaline necrosis, and Straus vitreous degeneration. I believe that all these designations denote the same thing,

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* Armanni was the first to describe this curious change, which he considered a metamorphosis of leukocytes that had entered the tubes: "Il est peu probable qu'il s'agisse d'une métamorphose spéciale des éléments epitheliaux," he says in the French edition of Cantani's work. The Germans were the first to interpret correctly the change as one of the epithelial cells. See the works of Frerichs, Straus, Marthen, Albertoni and Pisenti, Trambusti and Nesbi, Ferraro, Obici, Boccardi.

which also is identical with what Frerichs and Ehrlich described as enlarged, polygonal, hyaline, epithelial cells, as found in Henle's tubes. Frerichs and Ehrlich did not, however, consider the change a necrosis, the nuclei in their cases always retaining the property of taking the stains distinctly. They laid especial stress on the brown reaction with Lugol's solution, distinct even to the naked eye, especially in the limiting zone, in the section of the kidney, and denoting marked infiltration with glycogen. Later investigations leave scarcely any doubt that the hyaline metamorphosis that is probably found in several organs besides the kidneys, and perhaps even apart from diabetes, is an independent occurrence, and may exist without any infiltration with glycogen, which substance, however, seems to have a predilection for the altered cells in the loops of Henle.

Marthen * noted that van Gieson's stain (hematoxylin and picric acid) colored the hyaline contents of the enlarged polygonal cells a vivid red. Albertoni and Pisenti observed hyaline metamorphosis in dogs, both in the straight tubes and in the convoluted tubules, after large doses of acetone (?); and Trambusti and Nesbi noted the same conditions after continued large doses of phloridzin. Pisenti and Acri, according to my opinion without sufficient reason, distinguish between Armanni's hyaline metamorphosis, which they consider identical with Frerichs' and Ehrlich's cells with intact nuclei in the isthmus of Henle's loops, and Ebstein's hyaline necrosis in the convoluted tubules, which disintegrates the nuclei of the cells.

Boccardi often found the kidneys normal in dogs that became diabetic after extirpation of the pancreas, but sometimes found the vessels and the tubules dilated; the interstitial tissue somewhat increased, least in the cortex, most in the limiting zone; Bowman's capsules with thickened epithelium, desquamation of the endothelium, and immigrated white blood-corpuscles; glomeruli either enlarged or atrophic; epithelial cells in a state of fatty degeneration, which sometimes went so far as to disintegrate; hyaline degeneration without any glycogenic infiltration in 3 of 40 cases; in the arteries the adventitia thickened and the intima exfoliated.

The sexual organs in cases of diabetes often undergo functional and other changes.

Impotence has already been mentioned among the nervous symp-

* "Arch. f. path. Anat.," 1895.

toms. It is rarely absolute, apart from advanced senility; but "facultas cœundi" is often distinctly weakened from the moment the glycosuric dystrophy, however mild, makes its appearance. In rare cases sexual vigor remains normal.

Sterility is common and does not depend on "impotentia cœundi," as it exists also in women. The cause must rather be looked for in some influence exerted by the excess of sugar or by toxins in the blood, on the sperm and on the ova, or in atrophy of the testicles, or the ovaries, or in the diabetic metritis of which Lecorché speaks. Still, both diabetic men and women may produce children, and sometimes conception takes place even in the severe stage. Pregnancy in a diabetic woman is often interrupted by miscarriage in the fourth or fifth, or as late as the seventh, month (Seegen, Gaudard). Further, pregnancy, which sometimes *per se* causes glycosuria or true diabetes, often accelerates the progress of an existing diabetes. The mortality among both mothers and newborn children is very great. Of the latter, 41 in every 100 die soon after birth (Gaudard).

I have seen two cases of diabetes in which *orchitis* appeared as a complication without obvious cause.

Those parts of the diabetic patient's skin that often are moistened by the sacchariferous urine readily become the seat of vegetation for a small flora of low fungi, which cause eczema, excoriations, pruritus, and, especially in the labia majora, sometimes a series of furuncles. *Vulvitis* in women, *balanitis*, *balanoposthitis*, and sometimes *phimosis* in men, are induced, and recur readily if not restrained by the use of antiseptic lotions. Both in men and in women the irritation thus caused gives rise to the development of papillomatous excrescences, which are known to have changed into epitheliomata (Naunyn).

Straynowski mentions atrophy of the uterus and of the ovaries as occurring in diabetic women. Analogous changes in the testicles may be quite distinct in marantic cases in men.

Organs of Special Sense.

Diseases of the eyes are extremely common in diabetics, and there is no part of these organs that has not been named as the seat of

pathologic processes caused by the glycosuric dystrophy. Though most of these diseases develop only after the diabetes has existed for a long time, they not rarely constitute the primary reason for the patient's seeking medical aid, and they thus lead to the discovery of the dystrophy. It has been said that two-thirds of all diabetic patients suffer from some affection of the eye. This estimate must certainly be based upon hospital statistics and upon observations among severe cases, as in private practice, with its large number of mild cases, the proportion is much smaller. All the deleterious influences already named as belonging to the glycosuric dystrophy are efficient with regard to the eye, but the toxins in the blood in many cases play the most important rôle; and some of the diabetic affections of the eye are very similar to those that occur during long-continued poisoning with alcohol or tobacco, or to those that may be produced in quite a short time by injections into the blood of common salt, sugar, naphthalin, and other substances.

The most frequent diabetic affections of the eye are *cataract*, *anomalies of accommodation* (especially *premature presbyopia*), *retinitis*, and *inflammation of the optic nerve*.

Diabetic *amblyopia* or *amaurosis*, *iritis* and *iridocyclitis*, *opacities* in the vitreous body, *processes in the cornea and sclera*, *paralysis of the muscles*, and some other dystrophic troubles are less common.*

Diabetic cataract generally develops after the dystrophy has been present for many years, but in exceptional cases and in the specific soft form it may appear after a few weeks; this happens especially in children. The affection is almost always bilateral, and is found in both stages of diabetes, although it is more frequent in severe cases, without bearing any fixed relation to the intensity of the diabetes.

Weir Mitchell caused cataract in frogs by subcutaneous injections

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* For more extensive information on diabetic affections of the eye, reference may be made to the works of Leber, Græfe, Foerster, Jacobson, Wiesinger, Bouchard, Schirmer, Knies, Hirschberg, Schmidt-Rimpler, O. Becker, Deutschmann, Berger, Papanikolau, and others. The essential facts can be found in the "Archiv für Ophthalmologie." The notes of my own cases are incomplete with regard to the ocular state, as I always refer the patient for this information to the best specialist at hand.

of sugar; Richardson noted the same result in frogs and fishes by keeping them in a dilute solution of sugar; and cataracts have since been induced in rabbits and frogs by introducing sugar into the fold of the conjunctiva. Thus, there can be no doubt as to the efficiency of the hyperglycemia to bring about cataract, whether it be due to direct irritation of the tissues of the lens or to their desiccation. The cataracts induced artificially begin by the formation of vacuoles in the cells; and this may also be the case with diabetic cataract before proliferation and disintegration of the cells take place. The diabetic changes in the vessels, with local nutritive disturbances, the marasmus, and other common influences, may contribute to the result, and may in many cases, especially in those not representing the typical diabetic soft cataract, be the chief etiologic factors. The hypothesis of the formation of lactic acid in the aqueous humor of the eye has been abandoned, since investigations have proved this liquid always to be alkaline. In the liquids of the eye, in the lens, and in the vitreous body, where glucose also has been found apart from diabetes, this substance seems to be increased when diabetes develops (Deutschmann, Görlitz, Hedon and Truc).

Typical diabetic cataract, which is the customary variety in young persons with severe diabetes, is of the soft kind. The process begins, according to Knies, in the small polygonal cells on the posterior aspect of the anterior part of the capsule of the lens; the adjacent cellular elements of the lens next begin to undergo changes. Becker states that opacities appear at first in the equatorial zone, then in the posterior, and afterward in the anterior, cortical substance. Whether the first change begins behind or in front, it is certain that, contrary to what takes place in the common senile cataract, the most superficial parts of the cortical substance are the first to undergo change in the development of the typical diabetic cataract. The first macroscopic manifestation of this is the appearance of a milky layer in the field of the pupil; then the whole mass of the lens whitens, and mother-of-pearl-like patches become visible therein. The entire development and appearance of this typical, soft, diabetic cataract strongly resemble what Bouchard has described in speaking of the experimental cataract caused by naphthalin.

The soft cataract is, however, by no means the only variety found in diabetic patients, and so far as my experience goes, it is not even the most frequent. In elderly diabetics one often finds the usual variety of senile cataract, with central, yellowish sclerosis, and bluish-gray, radial streaks between this and the still normal peripheral parts of the lens and (before the maturity of the cataract) the shadow of the iris, etc. There is good reason to believe that these changes are favored by the glycosuric dystrophy, and that they, like diabetic gangrene, are an expression at the same time of diabetes and of senility.

König found among 500 diabetic patients only 10 cases of cataract. Most other writers made the proportion higher. I have certainly seen more than 10 cases of cataract in association with diabetes, though I have not yet reached 500 cases of the latter. This may be due partly to the fact that several cases from Dr. Nordenson's extensive clinical material have been referred to me in Stockholm. I suppose that among diabetic patients in Carlsbad from three to four per cent. exhibit cataractous changes.

Sometimes, and especially in severe cases of diabetes, one finds that the visual near-point, even in young persons, grows more and more remote, and that *premature presbyopia* develops. This condition has been attributed to marasmus, with its weakening influence on the muscles of accommodation, to alterations in the vessels, to neuritic processes, and to hemorrhages. Diminished elasticity of the lens may also be a contributing cause.

Mydriasis may arise from toxic influences. In the presence of coma the sphincter of the pupil may be seen to resist and to react in quick succession to the paralyzing influence of the poisons in the system. Still, the pupils in diabetic persons may be large altogether independently of diabetes—" Cette dilatation des pupilles, associée le plus souvent aux symptomes de depression est un bon signe des états neurastheniques," says Bouveret (" La Neurasthenie ").

Myopia from the tumefaction of the lens is the most frequent anomaly of accommodation in cases of diabetes, if it develops in middle age or later. This fact should be borne in mind, and the urine in such cases of myopia should always be examined for glucose.

Hypermetropia is mentioned by Horner as occurring in association with diabetes.

Diabetic retinitis (elaborately described by Hirschberg) belongs in general to one of two groups, and may be either *exudative* or *hemorrhagic.*

Exudative diabetic retinitis—retinitis diabetica centralis punctata—presents small, glossy, nonpigmented exudations around the central portion of the retina. The exudates have uneven borders without being so distinctly stellate as the exudates of albuminuric retinitis; here and there a small point of blood may be visible. There is no discoloration of the papilla; if there is, a renal complication and albuminuric retinitis should be suspected.

Hemorrhagic diabetic retinitis is characterized by the presence of a number of ecchymoses of varying size distributed over the retina. They sometimes cause amblyopia and occasion quite a dubious prognosis, as they often represent only a part of hemorrhages extended over different regions of the central nervous system. I have seen them attended with serious symptoms, sometimes even with perfect loss of consciousness. They often occur successively over some length of time, and they may be found in all stages in the same eye, as recent hemorrhages and as whitish residual patches. I consider these small retinal hemorrhages as analogous in type to the small hemorrhages in the brain, which I suspect to be frequent in inveterate cases of diabetes, and which often may be unattended with manifest symptoms.

Diabetic optic neuritis is so much like the neuritis due to alcohol or tobacco that its diabetic nature has been called in question even in recent times (*e. g.*, by Mauthner). Still, Schmidt-Rimpler found this complication in 34 among 140 cases, and Leber in 14 among 50 cases of diabetic disorders of the eye, and it can not be doubted that inflammation of the optic nerve is not uncommon in inveterate cases of diabetes independently of both alcohol and tobacco, though it often escapes detection. When developed, it presents a central scotoma, with deficient color-perception, corresponding to the macular part of the optic nerve, and a whitish discoloration of the temporal part of the papilla. The differentiation from neuritis due to alcohol or tobacco can be made only from the history; in some cases all three causes may contribute to the result. Peripheral contraction of the field of vision and atrophy and dis-

coloration of the entire papilla may ensue. Diabetic optic neuritis, though it often exhibits temporary improvement, has a worse prognosis than the analogous affections caused by alcohol or tobacco, which, as is well known, are themselves quite obstinate, even after the removal of their causes.

Amblyopia and amaurosis may arise in the course of diabetes from such alterations within or without the eye as ordinarily give rise to them, but they may also result from the action of diabetic toxins (Leber). In the latter event the danger of coma is never to be lost sight of. In the last case of this kind that I have treated exceedingly elaborate investigation by Dr. Nordenson failed to disclose any other than a toxic cause; the deflection of the ray of polarized light to the left, due to β-oxybutyric acid in the urine, equaled a little more than 0.5 degree with Hoppe-Seyler's instrument. The patient died about two months afterward in coma.

Diabetic iritis * is a torpid, suppurative process without ulceration of the cornea; it usually appears in both eyes, and is observed in advanced cases. Leber noted hypopyon in two among nine cases. A fibrinous deposit over the whole pupil was present in several cases, but disappeared quickly and completely under the influence of sodium salicylate. In some cases only an adhesive iritis is found, with synechiæ. Finally, there seems to exist exceedingly torpid forms of the disease, which develop almost imperceptibly until they cause a change in the color of the iris. The whole process may lead to atrophy of the iris, sometimes to glaucoma.

The choroid may participate in the process and cause opacities in the vitreous body. Leber observed detachment of the choroid.

Hemorrhages and opacities in the vitreous body have their origin in the retina or in the choroid.

Diabetic keratitis presents itself as a parenchymatous inflammation of neuroparalytic character, and may lead to ulceration and suppuration.

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* Leber, "Arch. f. Ophthal.," 1885.

Scleritis and *episcleritis* are also mentioned, but their relation to diabetes seems undecided.

The eyelids may become the seat of *hordeolum*, *chalazion*, *eczema*, or *herpes*. *Hemorrhages in the conjunctiva* are considered to be an effect of diabetes and a special reason for analysis of the urine.

The intracranial hemorrhages that are likely to complicate diabetes of long standing sometimes cause *paralysis of the muscles of the eye*, and any one that has seen a large number of diabetic patients must also have seen such disturbances of function on the part of the abducens, the oculomotor, the trochlear, or the facial nerve, with strabismus, lagophthalmos, ptosis, etc. In some cases rapid absorption and complete restitution take place. I have also seen paretic symptoms remain for several years and for the remainder of the patient's life.

Being constantly on the alert for the many severe diseases of the eye that threaten the diabetic patient, one is likely to overlook symptoms of a purely neurotic and less dangerous nature. If, however, the physician makes it his custom to ask concerning such symptoms, and sometimes even if he does not, he will gain information indicating the frequency, also in this field, of neurasthenic symptoms in cases of diabetes. The practitioner who is not well versed in the use of the ophthalmoscope will often find difficulty in excluding organic disease. Sometimes *neurasthenic asthenopia*, with local subjective sensations and deficiency of endurance in the use of the eyes, is observed. Many diabetics display marked *hyperesthesia* for light.

*Diseases of the ears** are much rarer complications of diabetes than diseases of the eyes. Central disturbances of the acoustic nerve, whose center is quite near to the situation of Bernard's puncture, are exceedingly rare.

Otitis follicularis externa, or furuncle of the external auditory

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* See Kuhn, "Archiv f. Ohrenkr.," Bd. XIX; Kirchner, "Deutsche med. Wochenschr.," 1887; Körner and v. Wildt, "Zeitschr. f. Ohrenheilk.," Bd. XXIII.

canal, is undoubtedly more common in diabetics than in other individuals.

Otitis media diabetica sometimes leads to suppuration of the internal ear and its osseous parts, and one now and then sees patients with scars after operations in the mastoid region. Inflammation of the middle and internal parts of the ear may cause meningitis, but few such cases are recorded; and these processes in the ear, which owe their origin to bacteria (streptococcus, staphylococcus, etc.), scarcely occur in more than one per cent. of all cases of diabetes.

I have had under observation a rare and interesting case of trauma of the inner ear in a case of diabetes. Mr. ——, a Scandinavian merchant, sixty-six years old, had suffered from diabetes for about eighteen years. He was in the mild stage of the dystrophy, and the glycosuria disappeared when the carbohydrates were restricted to about thirty-five grams. I was called early one morning to the patient, who had fallen out of bed during the night, and somehow had been struck on the left side of the head by a basin filled with water that had fallen over him. The left tympanic membrane had ruptured and the pillow was stained with serous liquid slightly mixed with blood. The pulse was at least normal in frequency, and thus indicated no irritation of the pneumogastric nerve. There were no symptoms referable to the eyes, *but the patient presented a complete inability to maintain equilibrium.* I supposed a fissure through the labyrinth and the semicircular ducts had taken place. During proper local and general treatment the patient otherwise recovered in the course of some weeks, but the inability to maintain equilibrium, subsiding very slowly, remained for several months.

Ordinary functional nervous troubles of auditory character are not absent. The diabetic patient often exhibits a marked acoustic hyperesthesia, which sometimes causes him to make elaborate arrangements to avoid noise. Subjective acoustic perceptions, especially during the night (tinnitus aurium, etc.), are not rare. *Otalgia* is sometimes complained of. The cause may then be looked for in the teeth, which are so commonly carious in diabetes. In other cases the otalgia is only a secondary manifestation of an extensive neuralgia in the distribution of the fifth pair of nerves (auriculotemporal branch), or of neuralgia in the distribution of the occipital or the auricularis magnus nerve. The differentiation must then be made between a merely nervous and a rheumatic affection. Rheumatic infiltrations in the soft parts of the head, which constitute one

of the most attractive hobbies of the professional masseur, may be the cause. Sometimes pruritus or hyperesthesia or paresthesia of the outer ear is spoken of.

The skin often presents local or general changes.

General changes are observed in the severe stage or in advanced cases in the mild stage. I have already mentioned the diminished secretion of the sebaceous and the sudoriferous glands—the *asteatosis* and the *anhidrosis*—and the resulting marked *dryness* of the skin. The cause of this condition resides not only in the more tenacious retention of the water of the blood within the vessels by reason of the hyperglycemia, but also in the *atrophy of the skin*, not rarely found in the severe stage, especially on the hands, and still more often in the face, where one observes the change that, in its fully developed state, is called "glossy skin." The skin is manifestly thin, and there is a marked, circumscribed, cyanotic redness of the cheeks.

It is in such cases that *diabetic pruritus* is best marked. It is usually much less intense than in cases of icterus, for instance, and it rarely constitutes a serious annoyance.

I have already mentioned the furuncle, the carbuncle, the "mal perforant" and Raynaud's disease, the different forms of diabetic gangrene and the different forms of eczema, and other changes that result when the skin is often moistened by the urine. It is chiefly these latter eruptions that the French call "diabetides," which appellation should not suggest an idea of anything pathognomonic.

So far as I know, there is not a single change in the skin in diabetes that may not occur apart from this dystrophy. This is true even of the rare "xanthoma tuberosum diabeticum," observed hitherto, in all, in about thirty cases. The one case that I have seen presented the customary solid, yellowish-red excrescences, as large as peas, distributed in considerable numbers chiefly on the extremities. They were most numerous over the triceps muscle on the upper part of the arms and over the extensors on the lower part. A few were to be seen on the flexor aspect. On the legs they were exceedingly numerous over the quadriceps femoris, especially in the vicinity of the knee-joint. A few were to be seen on the outer sides of the calves and on the dorsal aspect of the

tibiotarsal joint. There were a few on the shoulders and on the neck, and one in the left external auditory canal. Neither in their distribution * nor in any other feature could I discover any difference from what I have seen of "xanthoma tuberosum" attending icterus. The patient was a man twenty-eight years old, suffering from severe diabetes, without icterus.

The formations that Kaposi calls "*dermatitis papillosa diabetica*," with excrescences in patches on an inflamed base, may probably also be seen independently of diabetes, in association with which they are extremely rare.

Besides the skin-diseases already mentioned, diabetic patients frequently yield the dermatologist varied clinical material. I have seen *erythema*, *urticaria*, *lichen*, *acne*, *impetigo*, *rupia*, *herpes* (including *herpes zoster*), *pemphigus*, *pityriasis*, *ichthyosis*, *psoriasis*, all sorts of *eczema*, *petechiæ*. *Purpura hemorrhagica* (Dujardin-Beaumetz) and *pityriasis rubra* (Harden) have been mentioned. For some of these affections we may look to the marasmus as the chief cause. In other cases the hyperglycemia may be efficient. In a great many instances the connection with diabetes may consist only in the angioneurotic constitution common in diabetic patients, who, in fact, often mention that they suffered from their cutaneous troubles long before glycosuria arose.

The hair of diabetic patients offers two peculiarities: in consequence of the asteatosis and anhidrosis it is often dry, and therefore presents a ragged appearance; and it is often prematurely gray.† Diabetes may have some influence in causing baldness, and "defluvium capillorum" is mentioned by more than one writer on this subject. Marked effects of this kind are not conspicuous, and I

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* The distinction between diabetic and icteric xanthoma is said to be that the former is equally spread over the whole body, while the latter is distributed as in my diabetic patient. Kaposi does not acknowledge the existence of a specific diabetic xanthoma.

† Susruta, about 1200 years ago, mentioned a peculiar, wild appearance of the diabetic patient's hair. I suppose that the gray hair has no direct connection with diabetes, but depends on the great emotional sensitiveness common among diabetic patients. The curious and sometimes remarkably sudden influence depressing emotions have in this respect is well known. Thus, it is related that a Hindu suddenly turned gray just before his execution during the great mutiny ("Ind. Med. Times and Gazette," 1859); as did also Ludovico Sforza when he was taken prisoner, and Guarini da Verona when he lost his Greek manuscripts. (See H. C. Wood, "Nervous Diseases," Philadelphia, 1887.)

know many patients who, after long years of abundant glycosuria, still keep a luxuriant growth of hair on their heads.

The nails sometimes show distinct alterations. *Paronychia* is not rare and sometimes causes the nails to fall out. In other cases the nails change without any cause whatever discoverable to the naked eye. They become thick, brittle, discolored and brownish, markedly curved in both directions, and may then fall out. It seems to me that this occurs chiefly in inveterate cases complicated with gout, and in cases with distinct neuritis. It is certain that such changes are not related to the intensity of the diabetes, and one often finds the nails on the hands and feet perfect in patients toward the close of life after years of the dystrophy in its severe stage.

Organs of Locomotion.

The patient in the mild stage of diabetes is generally an indolent person, of sedentary habits, to whom the physician must preach long sermons as to the utility and the necessity of bodily exercise, and whose muscular strength and endurance usually are much smaller than seems indicated by his often robust appearance. The diabetic patient in the severe stage often drags himself along with an unsteady gait, and is made excessively tired by exercise that constitutes a daily salutary habit in healthy persons, but which in some cases of diabetes may be sufficient to cause coma. A patient of this kind will rise late and go early to bed, and his *lassitude*, his feeling of *excessive muscular weakness*, will sometimes even keep him in bed throughout the twenty-four hours.

The muscular neurasthenia is partly the cause of the diabetic's constant feeling of tiredness. The dryness of the muscular tissues —much dwelt upon by Dieulafoi—probably is an important causative factor in cases of marked hyperglycemia. The excessive amount of sugar in the blood in a similar manner also directly affects the motor nerves. In marantic cases the *muscles* often are extremely *atrophic* and reduced to ribbon-like proportions, of which no great mechanical effects can be expected.

The *bones* in cases of severe diabetes have been found remarkably light and porous, and fractures often heal slowly and imperfectly. The enormous amount of those salts that enter into the constitution

of the bones sometimes found in severe cases (v. Ackeren, Fodor) in the urine seems also to denote disintegration in those structures. So far as I know, there have been no systematic investigations of these processes and of the consequent *osteoporosis* in diabetes. Charrin and Guignard, with many others, accept the existence of this diabetic osteoporosis and believe it due to the acidosis. Considering that the acids only diminish, but never entirely neutralize, the alkalinity of the blood, I am more inclined to believe in a general marantic or in a purely trophic influence, analogous to that observed by Kassowitz in the bones of rabbits' legs after section of the sciatic nerve.

As there are to be found all stages between a normal power of assimilating carbohydrates and the greatest possible reduction of that power, so also, with regard to the general clinical picture, there are all possible intermediate gradations between the healthy individual and the patient approaching diabetic coma. There are, especially, many persons who live on the border-land between what may still appropriately be called the mild and the severe stage, and there may be only a slight clinical difference between a patient who is free from glycosuria during abstinence from carbohydrates and one who even under such dietetic conditions excretes a few grams of glucose in the course of the twenty-four hours. If, however, a patient is selected from the middle of each of the two stages, quite marked clinical differences will generally be found between these two representatives of the glycosuric dystrophy.

The history often presents remarkable points of difference. Mild diabetes is often discovered by mere accident ; *e. g.*, on examination for life-insurance. In other cases neurasthenic symptoms, or some local trouble, or some slight signs of dystrophy guide the suspicions of the physician in the right direction. The diabetic symptoms, if there are any at all apart from the glycosuria, have developed gradually, and the dystrophy has only slightly affected the patient, who often is unable to give any definite information as to the time of the beginning of the diabetes. Severe diabetes—often in a short while—changes a state of health into one of marked ill-health, and the patient is often able to name at least the month, and sometimes the day, of appearance of the first symptoms. Even in such

cases, in which at first restriction of carbohydrates suppresses the glycosuria, sudden appearance of diabetic symptoms is an unfavorable sign, and makes probable the future development of the severe stage of the disease.

The actual state of the representatives of the two classes mentioned usually presents a number of salient points of difference. The patient with mild diabetes may, even after years, appear as a man of quite fair, sometimes even of florid, health, with a normal complexion, a robust form, and active habits. He is sometimes troubled with adiposity or with gout, almost always with "nervousness." He may, however, perform quite important duties in a private or a public capacity, and can easily conceal his diabetes, with its insignificant and vague symptoms, from the world. The severely affected patient, with acid toxins in the blood,—the "acidosis,"—often manifestly presents evidence of that marasmus which constitutes the most essential distinction between severe and mild cases. He is generally thin, often extremely so; his movements are weak; his gait uncertain; the expression of his face either languid and drowsy or uneasy, sometimes desperate; the complexion either of a cachectic pallor or marked by an unhealthy cyanotic redness of the cheeks. His mere aspect reveals his serious state, and his family and friends, even without recognizing the nature of his disease, often realize that his days are numbered.

Then, the issue in the two stages of glycosuric dystrophy is different. Mild diabetes is in no specific way fatal; if it does not develop into a severe diabetes, the patient will live until stricken by some accidental intercurrent or complicating affection, which, though perhaps less frequently, may occur apart from diabetes, such as acute pneumonia, carbuncle, cerebral hemorrhage, heart-failure, etc. Severe diabetes, however, leads to death in most cases through a specific complication caused by the presence of toxins in the blood. Acetone may exert some slight contributory influence; the diacetic acid and the low fatty acids, by reason of their small amounts, can not *per se* bring about the result. The β-oxybutyric acid, which may be formed in large quantities, is the chief factor in the production of the acid diathesis, the "acidosis," and of the final acute poisoning, which, when once begun, gener-

ally in a short time leads to paralysis of the nervous centers, and is known as—

Diabetic Coma.*

The development of diabetic coma may be excited by some inconsiderable depressing incident, such as emotion, fatigue, or a slight indisposition. A common cause, or, perhaps better, a common forerunner, of coma is obstinate constipation, which, after coma has set in, may give way to profuse fetid diarrhea. Coma is, however, promoted not only by all depressing influences, but by any cause that increases the acid diathesis, the acidosis. Every agency that has both these effects is especially dangerous, and I believe that the most frequent immediate cause of coma arises from a too rigid restriction of carbohydrates, with consequent inanition and increase of diacetic acid and of β-oxybutyric acid in the blood.

A feeling of extreme weakness, of drowsiness, and of headache generally precedes the attack. Sometimes there is complete loss of appetite. Severe epigastric pains, sometimes accompanied by vomiting, are not rare, and may continue for some time before the paralytic stage develops.

The first manifest, and the most characteristic, symptom of coma is a sudden dyspneic frequency and depth of respiration; at the same time the frequency of the pulse increases. Respiration follows no distinct type,—especially not the Cheyne-Stokes,—inspiration taking place forcibly and deeply twenty or thirty times a minute in a blowing manner, even in cases in which postmortem examination subsequently shows a normal state of the lungs. The pulse runs up to from 130 to 150 or more, becomes extremely small, and can soon be no longer counted. The pupils may be strongly contracted. Mental excitation, often of great terror, may precede the depressing symptoms. Sometimes the dyspneic respiration and the

* Diabetic coma was first described, in 1854, by v. Dusch, but it was little known in the profession until described twenty-one years later by Kussmaul. The majority of my diabetic patients in the severe stage have died in coma. Frerichs, among 250 patients, diabetic at the time of their death, found 150 cases of coma. A. James, of Edinburgh, however, encountered only 24 instances of coma among 50 fatal diabetic cases. In the other 26 cases death was due to pulmonary tuberculosis in 16 and to acute pneumonia or gangrene of the lungs in 8 cases.

quick, small pulse may continue for many hours, or even for days, before paralytic symptoms set in. Sometimes the first stage of excitation may pass so quickly and be so little marked, and the paralytic stage set in so suddenly, that the condition can hardly be distinguished from apoplexy or primary paralysis of the heart. Sooner or later the sensorium becomes clouded; but even before this is manifest, the speech may denote incipient motor disturbance. The depression is generally supreme, signs of excitation being only slight and of short duration, and spasm being sometimes scarcely perceptible. The extremities become icy cold; the temperature, which often before the attack was below the normal, now sinks still further. During this period the glucose, the urea, the toxic acids, and the other products of metabolism in the urine may be diminished.* I may refer also to the small casts from the kidneys that Külz, among others, found to be numerous and constant (?) during coma. The comatose state may last for days, rarely for weeks, and sometimes only for hours. The average duration of life after the first manifest symptoms have appeared may be estimated at two or three days. Even if the patient, as sometimes happens, almost completely regains consciousness, and all symptoms of comatose depression recede, restitution to the preexisting state—though it is mentioned in literature by trustworthy observers—is extremely rare. When the nervous centers have once been attacked, all treatment, however energetic and quickly applied, almost always fails to bring about permanent recovery, and the physician does well not to let transitory improvement deceive him as to the approaching fatal issue. The last hours are generally quiet, with scarcely any other signs of life than the respiration and the pulse, and dilatation and contraction of the pupils, the latter often asynchronous.

Diabetic coma is a state of poisoning—there is no doubt about that in the mind of any physician who has once seen it; but opinions as to the kind of poison differ greatly. At one time the hyperglycemia was suspected as a cause, but I consider this view to have only historic interest. The increased amount of sugar in the blood may reach higher figures in mild cases of diabetes with a free diet than in severe cases with restriction of the carbohydrates; but mild cases of diabetes—*i. e.*, cases in which glycosuria disappears when carbo-

* Münzer and Strasser, however, have found the nitrogen in the urine increased during coma; the excess may, however, have been produced before.

hydrates are excluded—do not develop coma. I consider that all reports of such an occurrence are the result of mistake, and represent cases of uremia or of primary heart-failure, etc. Complete exclusion of carbohydrates causes diminution in the hyperglycemia, but notoriously increases (the acidosis and) the danger of coma. Diabetic coma is sometimes not unlike uremia, from which it differs in several respects, and especially in the marked dyspneic respiration, though this may to some extent be present in the final stages of a number of different diseases. Besides, patients die in diabetic coma in the absence of serious changes in the kidneys. The Scotch theory as to fat-embolism in the brain has scarcely any basis at all, and has not survived. From 1857, when Petters, in a case of coma, found acetone in the blood and in the urine, the theory of acetonemia as the cause of diabetic coma was widely accepted; but Kussmaul refutes this theory, and Frerichs, in the seventies, Albertoni, in 1884, and others proved that the toxicity of acetone, especially in view of the small quantity produced in diabetes, is insufficient to be considered a cause of death. Feré, in fact, does not consider acetone much more poisonous than ethylic alcohol, which is drunk in such quantities by millions of human beings.

Gerhardt, in 1865, discovered his most important reaction; and when Deichmüller, Tollens, and v. Jaksch had found it to be due to diacetic acid, suspicion fell on this substance; but here, again, the toxicity and the quantity were too small. When acetone and diacetic acid both pass over during distillation as acetone, scarcely ten grams of the latter can be obtained from the daily urine; and Brieger showed that injection into the blood of twenty grams of diacetic acid left the nervous system perfectly intact.

Hallervorden had found the quantity of ammonia excreted in severe cases of diabetes enormously increased, and he and Coranda found that this increased ammonia corresponded to an increased excretion of acid. Walther, in 1877, showed that injection of acids into dogs produced a state quite similar to diabetic coma. On this basis Stadelmann, in 1883, made further investigations in cases of severe diabetes, and found what he first considered as α-crotonic acid, but what Minkowski and Külz later proved to be β-oxybutyric acid. Since Külz afterward found that the excretion of β-oxybutyric acid may amount to more than 200 (226.5) grams in twenty-four hours, this acid, not without good reason, has been considered to be the principal cause of diabetic coma, though the other acids (diacetic acid and fatty acids of low order), the acetone, and perhaps other still unknown toxins * may exercise a contributory influence.

In this book I have adhered to the old division of diabetes into a mild and a severe stage, and this I believe to be the best and most practical, founded, as it is, on the absence or presence of glycosuria with abstinence from carbohydrates. Of late, however,

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* Ammonia may be present in increased quantity through the influences of other acids than β-oxybutyric acid (Rumpf, Strasser, and Münzer).

another classification has been made, namely, *pancreatic*, *neurogenic*, and *constitutional* diabetes.

The pancreatic and the neurogenic varieties are considered, as a rule, to form together what I have called severe diabetes, characterized by its sudden, comparatively acute appearance, its rapid development, the autophagy, the acidosis, and the frequency of death in diabetic coma. Pancreatic diabetes is distinguished from neurogenic diabetes by (1) the absence of a nervous, etiologic factor; (2) the presence of local symptoms referable to the pancreas; (3) peculiar qualities of the feces.

The absence of a nervous etiologic factor only rarely helps in the differentiation, because almost all human beings have been subjected to such nervous influences as may cause diabetes, and because nothing is more common than an hereditary neurotic predisposition. In rare cases a tumor may be felt in the pancreas during life. Icterus also, when there are no other distinct causes for it, speaks for disease of the pancreas, which *per se* often causes icterus. Then there are sometimes colicky pains referable to the pancreas (not rarely accompanied by vomiting or by diarrhea) (Fleiner, Lichtheim, Naunyn). These pains may increase in severity for hours, are felt in the epigastrium, and radiate to the back. Sometimes they are observed in cases of calculi in the pancreatic ducts, and the stones, consisting chiefly of phosphates and calcium carbonate, may be passed with the stools (Minnich). Often, when the functions of the pancreas are impaired, the feces contain abnormal quantities of fat. Such stools, conspicuous by their light color, strongly suggest a pancreatic origin. Le Nobel also considers the absence of salts of the fatty acids simultaneously with the presence of large quantities of fat as characteristic of the feces in cases of pancreatic diabetes. As the pancreas is important in the assimilation both of proteids and of carbohydrates, the presence in the feces of abnormal quantities of undigested remains of both of these kinds of food also speaks for pancreatic diabetes. Finally, Le Nobel lays stress on the decrease in or absence from the feces and the urine of indol and skatol, and of the corresponding series of products of decomposition, with their combined sulphuric acid, in pancreatic diabetes. Naunyn, in his recent work, also mentions the late appearance in the urine, in cases of pancreatic diabetes, of the

reaction for salicylic acid after administration of salol, which substance, under the influence of the pancreatic juice, is quickly decomposed into salicylic acid and phenol. Otherwise the urine affords no information concerning the pancreas. The glycosuria, the phosphaturia, the azoturia, and the amounts in the urine of all products of metabolism are exactly the same in pancreatic as in other forms of diabetes. Von Ackeren's and Le Nobel's maltosuria seems to represent a mistake, as the sugar in the urine in dogs after extirpation of the pancreas is found to be glucose (v. Mering, Minkowski), and as many other pancreatic cases afterward observed constantly presented glucose in the urine. The liver, which Lancereaux first described as unduly large in neurogenic, but as of normal size in pancreatic, diabetes, may, as he now acknowledges, be equally large in both conditions. It must further be remembered that symptoms referable to the pancreas need not be present in all cases of pancreatic diabetes. Neither need pancreatic or neurogenic diabetes always be the severe type; it has been *proved* that severe lesions of the pancreas, as of the nervous system, may cause mild diabetes. In practice, many cases are encountered in which it is quite impossible to decide between pancreatic and neurogenic diabetes.

Fully two hundred years elapsed between Brunner's original attempt at extirpation of the pancreas (1686) and Minkowski's and v. Mering's discovery of the glycosuria resulting from that operation. Yet Cowley, in 1788, noted atrophy of the pancreas due to concretions in a case of diabetes, and Haller observed intense hunger after extirpation of the pancreas. Within more recent times Bouchard, in 1851, expressed his opinion of a causal connection between diseases of the pancreas and diabetes, and Lancereaux's three cases (1877) established the matter in the mind of the profession. Later, N. Senn observed several symptoms of diabetes in dogs after extirpation of the pancreas, and William T. Bull, after such an operation on a patient, observed diabetes. Both of these distinguished American surgeons, however, were concerned chiefly with the surgical features of their work, and they just missed adding a great discovery in experimental pathology to their other successes. The same fate befell Finkler and Orth, who had undertaken extirpation of the pancreas in dogs in order to observe

any possible diabetic effect. They evidently failed in their purpose by not effecting *complete* extirpation.* Finally, v. Mering and Minkowski, in 1889, announced their great discovery at Strasburg. If we have been rather slow in acquiring facts, some of us, however, are really much too quick in drawing conclusions, and there are some, especially in France, who consider that all cases of diabetes are of pancreatic origin, and who, as soon as glycosuria is mentioned, at once think of the pancreas, as quickly as they do of alcohol when delirium tremens is referred to. The clinician, however, who learns that a broker was attacked by diabetes after great losses, a statesman after a political failure, a woman after the loss of her husband, and any one after a severe blow on the neck, will scarcely believe that this effect has been brought about by the pancreas; and when one finds postmortem that the pancreas, in fully nine out of ten cases, after diabetes is either normal, macroscopically and microscopically, or presents no greater change than a slight degree of atrophy, such as is found in many other organs, he does not gain the impression that the cause of diabetes is constantly to be found in the pancreas. Whatever information the future may bring, it is to-day absurd to insist upon a primary pancreatic cause for every case of diabetes, and facts rather point to the conclusion that pancreatic diabetes represents only a small minority of all cases of diabetes.

Then there is the "constitutional," "fat," "gouty," or "herpetic" diabetes, which often seems to be a distinct type. These designations are used to indicate the mild cases with a course covering many years, which develop slowly in middle age or in senility, and which often constitute rather a weakness than a disease. This condition is found almost exclusively among the upper classes, and usually among brain-workers. A diabetic of this kind generally has some hereditary neurotic, gouty, or adipose predisposition, which may have developed in several directions. He has usually been "nervous" throughout his whole life, and he has often suffered in youth from cutaneous eruptions (eczema, lichen, psoriasis). In middle-age he becomes sedentary, delights in the pleasures of the table (which often have to make up for a somewhat lowered virility), suffers from neuralgic, rheumatic, and gouty troubles,

* Medical Congress at Wiesbaden, 1886.

and begins to show glycosuria, which may amount to a mild diabetes, with slight dystrophic troubles, cutaneous eruptions, furuncles, neuritis, brittle nails, defective teeth, etc. With many of these patients, especially those that suffer from gout, the chances of reaching advanced age are almost as good as with the average man, and their diabetes continues to be slight. An affection that begins as a "constitutional" diabetes *may*, however, in rare cases, later appear as a neurogenic one; neither is it perfectly certain that such an affection does not depend upon changes in the pancreas.

It is impossible at present to decide what is *hepatogenic* diabetes; it is not even quite certain that this designation may not be applicable to all varieties of diabetes. In equal degree *muscular* diabetes is a mystery. *Gastro-intestinal* diabetes—with all respect to the honored name that first advocated this designation—according to all evidence does not exist at all. *Renal* diabetes is not deserving of the name diabetes, and has been mentioned among the glycosurias.

Bronze-colored Diabetes.*

Since 1882, when a treatise by Hanot and Chauffard appeared,† about a dozen cases of a most peculiar form of diabetes have been described, almost all of which have occurred in France. This form of diabetes offers, clinically, a good deal of resemblance to pancreatic diabetes, but it is apparently a disease *sui generis*, and is called "le diabète bronzée," from the color of the patient's skin. Bronze-colored diabetes generally appears in men between forty and sixty years old; in most cases there has been a previous history of alcoholism or malaria. It presents the clinical picture of a severe diabetic syndrome, and is usually complicated with tuberculosis. In addition, there may be marked dyspeptic symptoms, considerable swelling of the abdomen, with a small amount of ascites, a hypertrophic, hard, and sensitive liver, some dilatation of the abdominal veins (rarely a distinct "caput

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* "La Cachexie Bronzée dans le Diabète," Gonsalez Hernandez, Thèse, Montpellier, 1892. Pierre-Marie, "Sem. Méd.," 1895. Brault and Gallard, Letulle, and others.

† "Revue de Med."

Medusæ" around the umbilicus), high-colored urine, and pronounced cachexia. The most conspicuous symptom of all, however, is a dark brownish-gray color of the whole skin, most pronounced in the face, on the extremities, and on the genitals.

The disease invariably leads to death—usually in marasmus or coma—in about a year's time.

Besides the usual diabetic changes, almost all of the organs, but chiefly the liver, the pancreas, the walls of the alimentary canal, and the mesenteric glands, are found the seat of an abundant ocher-colored deposit, derived from the hemoglobin of the blood. This substance increases up to several thousand per cent. the amount of iron of the tissues (Hanot, Lapique, Parmentier and Carrion). (The same pigment is present in the malarial cachexia, in hypertrophic cirrhosis of the liver, and in Addison's disease.) The liver is found in a state of diffuse hypertrophic cirrhosis with pigmented cells. Its arteries are almost occluded as a result of endarteritis (Triboulet), and the portal system is remarkably dilated. Other organs also are often more or less cirrhotic. The red blood-corpuscles are diminished in number; Parmentier and Carrion found about 3,500,000 to the cubic millimeter. Several observers—*e. g.*, Anselme—consider the disintegration of the red blood-corpuscles from some unknown cause responsible for the diabetes by invading the pancreas and inducing cirrhosis.

I have already mentioned that habitual excretion of glucose, however inconsiderable, generally becomes permanent, in so far that it occurs daily for some time after meals; and that simple glycosuria usually remains unchanged, though there are exceptions to this rule.

In cases of true diabetes definitive cessation of glycosuria with a free diet is still rarer, and such complete and permanent restoration to health certainly does not occur in more than about one per cent. of all cases. I think it likely that this occurs chiefly in cases in which the diabetes has been caused by trauma or by infection, and that, when it takes place, the restoration is effected within a comparatively short time.

One often hears patients, and sometimes physicians, speak of recovery from diabetes and restoration to complete health. Almost

all such reports will be found incorrect on careful investigation. Sometimes the glucose has disappeared with a restriction of carbohydrates and reappears with a free ordinary diet. In other cases transitory or periodic increase in the power of assimilation is responsible for the mistake (see Periodic Diabetes). Other reports of like character refer to simple transitory glycosuria from some accidental cause, or even to the casual occurrence in the urine of reducing-substances other than glucose.

I have, in practice, seen disappearance of glucose from the urine with a free diet only in three cases in which sugar had appeared * in diabetic quantities. In one of these cases there remained a distinct polyuria,—*i. e.*, diabetes insipidus,—as has happened in several reported cases.

My first case of recovery from diabetes was the one following influenza mentioned under glycosuria due to infection. Both the fully developed diabetes and the restoration of normal conditions for at least several months appear to me to be certain.

The second case was that of a Scandinavian lady, fifty-one years old, who, after a violent blow on the forehead, felt exceedingly weak, and lost in weight for a considerable time. She did not remember any symptoms of diabetes other than pruritus vulvæ. After a year and a half she at last consulted a physician, who found the urine to have a specific gravity of 1.037, and to contain a large amount of glucose; the presence of the latter was ascertained by a fully reliable investigation. When I saw the patient, half a year later, there was nothing noteworthy beyond some neurasthenic symptoms and a cataract in drop-form, which probably had nothing to do with diabetes. After five days of free diet with a considerable amount of carbohydrate the urine did not contain glucose; nor was there any pathologic trace of it in the urine collected for six hours after ingestion of 120 grams of glucose. Some time before this was written, three and a half years after her accident, the patient appeared to tell me of her complete recovery. She has observed no dietetic rules, but the urine has always been found free from sugar, and is so at present.

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* I have seen rather large quantities of glucose (for simple glycosuria) in typhoid fever disappear after the end of the fever, and I have seen diabetic quantities of glucose after influenza dwindle to simple glycosuria.

The third case was Mr. F. D., a teacher from Boston, forty-five years old, who had, five months previously, without manifest cause, been seized with symptoms of diabetes; a chemist of Harvard University had found 7.5 per cent. of glucose in a specimen of his urine. The patient had for three months before arriving at Carlsbad observed a most rigorous diet. Under my care he gradually received an increased supply of carbohydrates, until more than two hundred grams a day were given. The urine, which contained no albumin, remained free from glucose during his four weeks' stay in Carlsbad; but the quantity reached three liters a day, and the specific gravity was about 1.012.

Thus, it sometimes, though rarely, happens that a true diabetic may be restored to health. Whether this ever happened in a case of severe diabetes is another matter; so far as I know, not one certain instance of this kind has been recorded. In my own experience, I have never seen any case with diacetic acid (apart from inanition and in association with a full supply of food) in which this acid has disappeared.*

Mild diabetes is compatible with long life, and I know of cases that in all probability have lasted forty years, and with certainty more than thirty years. A duration of twenty years is by no means rare. The outlook is the better, the later in life the disease sets in, the greater the power of assimilating carbohydrates, and the better the general somatic and mental state. A strong digestion is of very favorable moment. Trauma and infection as causes afford a better prognosis with regard to both complete recovery and a mild course. Gout and adiposity as complications are favorable signs, especially gout. Heredity does not seem to me so pernicious an influence as some authorities would make it. I have at least several times seen sons of diabetic fathers or mothers present through many years mild diabetes or simple glycosuria. Independent pecuniary resources and the ability to live without care in a suitable climate, and to afford a generous diet, are highly advantageous to the diabetic patient.

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* Dr. Toepfer, of Carlsbad, has told me of such a case in a young diabetic girl, who one summer presented a distinct Gerhardt's reaction, even while increasing in weight, and who the following summer exhibited no diaceturia. Such an occurrence is certainly exceedingly rare.

Mild diabetes more commonly remains mild diabetes than it develops into severe diabetes. On the other hand, a transition from the mild into the severe stage is no very rare occurrence, and it is difficult to understand how even specialists of wide experience can have failed to observe it.

Severe diabetes rarely lasts more than four or five years; the average duration can not be much above three years. In very severe cases, and especially in young persons (see below), the dystrophy may lead to death in a few weeks.

I make the following twenty-four extracts from my records of diabetic patients. The cases are related as briefly as possible, and they are intended only to convey an impression of the general clinical picture of the diabetic syndrome and its common complications. The cases are arranged so as to represent different stages and to illustrate the gradual failure of the power of assimilation and the development of the glycosuric dystrophy. If one is anxious for appellations, he may call the first 8 cases simple glycosuria, the next 8 cases mild diabetes, and the last 8 severe diabetes, at the time when *last* investigated. Matters of local significance, of nationality, of treatment, etc., are here omitted. The patients include Scandinavians, Americans, Germans, and Englishmen; the first alone belonged to the Semitic race.

1. Mr. ——, thirty-two years old, came to Carlsbad with dyspeptic troubles, which showed themselves, however, to be only the gastric manifestations of a pronounced neurasthenia, partly inherited and partly acquired, chiefly through sexual excesses. The patient had of late years grown exceedingly "nervous." His restless sleep was of the usual neurasthenic type, with an interruption of complete wakefulness from 1 to 4 or 5 A. M. The man was irritable, often giddy, had a "casque neurasthenique," a beautifully pronounced "plaque sacrée" and other rhachialgic manifestations, shooting-pains in the legs after standing for some minutes, etc. The usual fear of suspected tabes was (as always) entirely unfounded; thorough investigation demonstrated, even to the patient's satisfaction, the absence of all symptoms of that disease, and, rather strangely, he had escaped syphilis. The man declared somewhat mournfully that coitus was no longer "what it had been, what it could be, and what it ought to be"; besides, the act had been of late succeeded by a feeling of extreme weakness.

The urine obtained one hour after the end of dinner constantly underwent reduction, which disappeared after fermentation. When reduction was most marked, the urine caused a slight deflection of the ray of polarized light to the right instead of the customary deflection to the left (from combined glycuronic acid).

2. Miss ——, twenty years old, had been informed by her physician, eight years previously, that her urine contained sugar. There was no direct hereditary

cause and no etiologic point other than some intellectual overwork and a disappointment in love just before the discovery of the glycosuria.

At sixteen the patient had hysteric attacks and several stigmata. She was of a marked nervous temperament, and suffered still from periods of sleeplessness, "terreur nocturne," and other manifestations of similar character. Sometimes during nervous exacerbations the patient herself was cognizant of polyuria and pollakiuria, with the almost colorless ("spastic") urine secreted periodically by "nervous" persons.

When the young woman consulted me she was at her best, and made the impression of a lively, fairly healthy individual, with no distinct hysteric* and only moderate neurasthenic symptoms, and presenting nothing remarkable apart from the urine, which repeatedly, in samples obtained an hour after meals, contained from 0.05 to 0.2 per cent. of glucose. On a perfectly free mixed diet the tall young woman passed 1850 cu. cm. of urine, with a specific gravity of 1.021 and a faint trace of glucose. Eight years after the discovery of the glycosuria I learn that the state has not changed, and that the general health is fairly good.

3. Mr. J., fifty-nine years old, had a diabetic father, had himself worked hard intellectually for a large part of his life, felt a strong attraction to the fair sex, and thought American whisky a most delightful and wholesome beverage. He had been a hard smoker. The still deeply affected father was scarcely able to mention the terrible loss of a daughter two and a half years before.

The patient came to Carlsbad for adiposity and gout (in the big toe !). Sleep was fairly good; sexual power, considering age, likewise; and the knee-jerk present. The heart was somewhat weak, with distant sounds; the organ was somewhat enlarged, the pulse small and weak, but fairly regular. The functions in general were tolerably well performed, and after a mild dietetic course and systematic exercises the patient took quite long walks in the hills around Carlsbad. The teeth were partly absent and partly affected with caries.

On the back a gouty eczema existed.

The ophthalmoscope disclosed a distinct picture of optic neuritis, chiefly marked on the right side (from tobacco and whisky).

The patient assured me that his urine, recently analyzed, was normal. Finding him a sensible and not at all a hypochondriac person, I told him that, from his "tout ensemble," I was quite certain that during some parts of the day it would contain small, clinically insignificant, but abnormal quantities of glucose—and a specimen obtained after dinner contained about 0.25 per cent.

4. Dr. X, a physician, was descended from families both of which were free from developed psychoses, but which, together with some instances of great intellectual capacity, included others of "eccentricity" and extremely choleric temperament.

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* The field of vision was not examined.

The patient himself was strong, but sensitive and lively as a child. He had suffered now and then from eczema, and had worked hard and participated a good deal in the customary dissipations at the university. At the age of twenty-three he was subjected to a powerful depressing emotion, and some weeks afterward a series of furuncles appeared. The patient at this time worked hard for academic honors, and a year later began to suffer from sleeplessness; diminution in sexual desire and other neurasthenic symptoms developed. At twenty-five the patient for the first time accidentally found a distinct trace of sugar in his urine; this again happened when he had reached his thirty-second year. He then also found distinct oxaluria. Shortly afterward the patient, at a postmortem examination, contracted a severe pyemia, which wrecked him somatically and depressed him mentally for some time. At the age of thirty-eight the patient again accidentally found sugar in his urine, and in view of the two previous observations of the same kind, subjected himself to a thorough investigation. It was then found that a liberal supply of carbohydrates (several hundred grams) did not cause sufficient glycosuria to permit a distinct reaction with Nylander's solution of the urine for the twenty-four hours, which amounted to between 1500 and 1800 cu. cm.; that the first specimen obtained an hour after dinner usually contained between 0.1 and 0.2 per cent. of glucose; that the patient generally could take a large amount of rice or 300 grams of cane-sugar without the development of glycosuria; and that the slight amount of glucose that appeared in the urine after mixed meals with some wine could temporarily be increased quite considerably under the influence of emotional disturbances. On one occasion the patient, immediately after a rather sumptuous dinner, was seized with an intense fit of anger; a specimen of urine passed shortly afterward contained 1.4 per cent. of glucose, the largest quantity observed among more than 100 analyses, of which only one other had yielded so much as 0.4 per cent. The patient now for three days lived chiefly on carbohydrates; then collected the urine for twenty-four hours, and to his delight saw the phosphates form a beautifully white precipitate on boiling with Nylander's solution. But few analyses have since been made, and these showed specimens of the urine collected for twenty-four hours to be practically free from glucose. The patient has presented gouty symptoms from his thirty-third year. The joints of the fingers from time to time suddenly swell and become tender. The great toe of the right foot also has been involved. Dr. X is now (1899) in his fifty-second year, and is rather healthier than twenty years ago. He is unwilling to permit further analysis, which formerly kept him in a hypochondriac state. His weight keeps at the level of 95 kilograms. The patient was married eighteen years ago, and has six mostly strong and healthy children. One otherwise healthy child suffered for a long time from nocturnal enuresis and from psoriasis.

Another physician, an apparently healthy, hard-working man, on hearing of Dr. X's glycosuria, mentioned the fact that he had himself accidentally found sugar in his own urine sixteen years ago. An hour had just passed since his frugal dinner when this was mentioned. I expressed my opinion that the urine probably still contained glucose, and we found fully 0.2 per cent. of it in the specimen.

5. An apothecary, forty-eight years old, whose father had suffered for many years in old age from diabetes, was terrified by finding sugar in his own urine.

The patient presented the outward appearance of an unusually healthy, powerful man. During the preceding ten years his weight has kept at about 107 kilograms, and his height was about six feet. Investigation failed to disclose anything abnormal. Even most of the usual neurasthenic symptoms were absent, except a fear of approaching great depths and slight weakening of sexual power.

The urine was collected several times for twenty-four hours, with an allowance of 120 grams of white bread and some green vegetables in the diet. The secretion varied from 870 to 1200 cu. cm. in amount, and from 1.033 to 1.023 in specific gravity. A specimen of the twenty-four hours' urine contained scarcely so much as 0.05 per cent. of glucose.

The patient took 300 grams of cane-sugar in one liter of Giesshübler water, and after four and a half hours the urine was found free from glucose. The amount collected equaled 500 cu. cm., with a specific gravity of 1.016, and it contained about 0.05 per cent. of glucose. After being boiled with sulphuric acid the urine reduced as a solution of 0.24 per cent. of glucose.

6. Mr. G. W., a bank clerk, fifty-six years old, was free from known hereditary predisposition or other etiologic influence worthy of mention other than a severe malaria thirty years before. He came to Carlsbad on account of constipation, which, together with flatulence, constitutes his chief complaint. He was a fat, exceedingly "nervous" man, with a melancholy, "fussy" temper; had a pronounced "casque neurasthenique"; slept badly; did not like to go out on a balcony; had weak sexual power; and was easily made tired by physical or intellectual exertions.

I found glucose in the urine, which contained, besides, many crystals of calcium oxalate. The patient ate nearly 300 grams of bread a day, and whatever he liked besides. A specimen of urine an hour after dinner contained 1.1 per cent. of glucose; but the mixed total quantity for twenty-four hours,—1500 cu. cm., with a specific gravity of 1.024,—not quite 0.1 per cent.

The patient told me five years afterward (in Stockholm) that he went to Lindewiese, in Silesia, and lived exclusively on white bread, and that the sugar then disappeared from his urine. Investigation, however, proved the state to be exactly what it had been in Carlsbad.

7. Mr. ——, forty-six years old, a noted barrister, came to Carlsbad on account of dyspeptic troubles and not excessive adiposity—he weighed 94 kilograms. The condition was much like that described in case 3. The patient had hereditary adipose and gouty tendencies; had worked hard and smoked hard; had led a sedentary life and greatly enjoyed a good table. He was quite irritable, slept badly, and had incipient symptoms of smoker's heart. I found 0.4 per cent. of glucose in a specimen of urine after dinner. Free diet is attended with the elimination of a normal quantity of a somewhat "lithemic" urine, containing a distinct trace of sugar.

Seven years afterward I saw the patient in his home. He was very active in his profession, had made a large fortune by speculation, and did not know anything about his glycosuria, suffering only from slight neurasthenic symptoms.

Nine years after our first acquaintance I again saw the patient. He had worked and speculated a great deal, had twice made and lost a large fortune, and had, still more than before, led a life of constant emotional activity. The former simple glycosuria now sometimes reached diabetic figures (two per cent.) in large specimens, and occasionally slight symptoms of diabetes manifested themselves.

8. Professor ——, fifty-eight years old, a distinguished surgeon, had had a rheumatic and gouty father, and had himself, eleven years before, discovered two per cent. of glucose in a specimen of his urine, having for some time previously felt tired and worn out.

A specimen of urine after a dinner with a moderate supply of carbohydrates had a specific gravity of 1.037, but was found (by titration and polarization) to contain only 0.25 per cent. of glucose. With a customary diet and some restriction of carbohydrates the urine amounted only to somewhat more than a liter, with a specific gravity of 1.024 and somewhat more than 0.1 per cent. of glucose.

The patient was slightly neurasthenic and distinctly "lithemic." Some trouble with the toes, especially the great toes, probably was of a gouty nature.

9. Mr. E., judge, forty-seven years old, belonged to a family with strong neurotic tendencies, including several instances of diabetes. The patient had in his youth been addicted to masturbation, and several years afterward suffered from neurasthenia. Six years before coming under observation he had applied for life-insurance, but was refused on account of the presence of glucose in the urine. Shortly afterward he was seized with a violent attack of influenza, and during convalescence a specimen of urine obtained after dinner contained 3.2 per cent. of glucose.

The patient was a heavily built man, who had recently, with rigorous dietetic restrictions, lost in weight. Finding that this régime affected his general health badly, he returned to a somewhat more liberal diet, with a moderate allowance of carbohydrates, felt considerably better, and regained his previous weight. There were no distinct diabetic symptoms except the glycosuria. Even the teeth were normal. There was a moderate degree of neurasthenia, with some disturbance of sleep, and other cerebrasthenic symptoms. The sexual power was somewhat impaired. There were five healthy children in the family.

A perfectly free diet without any restriction whatever, and with quite a large quantity of carbohydrates, was attended with the secretion of 1300 cu. cm., with a specific gravity of 1.025 and 0.28 per cent. of glucose. A specimen obtained after dinner contained 1.34 per cent. of glucose. The patient was again put on a systematically but moderately restricted diet, and the urine con-

tained only traces of glucose. Ten years after the discovery of the mild diabetes I again met the patient and found the general state unchanged.

10. Dr. H., a widely known physician, at the age of twenty-seven years accidentally discovered over two per cent. of glucose in a specimen of his urine. There was no hereditary influence, but a history of much intellectual effort. Nor were there other symptoms of diabetes. The quantity of urine had always been rather large, though it had never amounted to distinct polyuria. The patient kept himself under some dietetic restriction, and the glycosuria disappeared for several years *and did not reappear even upon a free diet.* Six years after its first discovery the glycosuria again appeared, following an attack of typhoid fever, and sometimes reaching considerable proportions.

Fourteen years have now elapsed since the sugar first appeared in the urine. The patient, a man of iron will, adheres constantly to a diet with an allowance of about seventy grams of carbohydrate a day, and is free from determinable glycosuria. When for experimental purposes a greater allowance is made, the sugar again appears in moderate but quite determinable quantities. This most valued friend of mine, who is a hard worker, suffers from no other symptom than periodic insomnia.

11. Lieutenant-Colonel R., a retired officer, eighty-one years old, has no knowledge of hereditary or other morbid predisposition. Thirty-nine years before coming under observation the man suddenly had a succession of furuncles, and he dates his diabetes from this time; the glycosuria, however, was not discovered until sixteen years later.

The patient, who has been under my care for many years, is at the present time (1899) a lively old gentleman, with a healthy appearance. Only during the last two years has he observed any failure of memory; he has also prudently left off playing whist, in which pastime he was, up to his eightieth year, considered to have few equals. The patient suffers from insomnia. Sometimes there is giddiness. The reflexes, especially the knee-jerks, are weakened. Most of the teeth are absent, but the cavity of the mouth is otherwise normal. There is no odor of acetone from the breath. The patient is presbyopic, but the visual acuity is fairly good. Gerontoxon is not very strongly developed. There is some slight rigidity of the radial and temporal arteries.

When the patient partakes of a moderate but undetermined quantity of bread and green vegetables, he passes about two liters of urine containing about two per cent. of glucose or a little more. There is no albuminuria. One hundred grams of Graham bread (about forty grams of carbohydrate) and some green vegetables yield 1750 cu. cm. of urine, with a specific gravity of 1.025 and containing 0.8 per cent. of glucose.

The patient's wife also suffers from mild diabetes.

12. Baron X, fifty-eight years old, a statesman, had a gouty inheritance; his mother also probably suffered for many years from diabetes. The patient has for forty years been a heavy smoker, and had been much interested in his good table. His restless spirit, quarrelsome temper, and heavy responsibilities

had caused him a life full of emotions. In early manhood he suddenly increased considerably in weight. Twenty-six years before coming under observation he had several furuncles. Already at this period his teeth began to show caries, and they successively fell out; the patient had often suffered from gingivitis. The last molar tooth was sneezed out two years before my first investigation. The glycosuria, which in small specimens of urine has reached over six per cent., was discovered only a year before the patient came to me. There was no albuminuria and no diaceturia.

The patient had a weak nervous system, and periodically suffered from violent supraorbital neuralgia. Some years previously he was troubled with agoraphobia; he always carefully shunned steep declivities. Creeping sensations in the legs and nocturnal cramps in the calves caused annoyance. There was no distinct neuritis. The left knee-jerk was weakened.

The spleen was somewhat enlarged (the patient had had malaria eleven years before). The liver appeared of normal size on percussion and palpation. The heart was somewhat large and not powerful.

During two seasons in Carlsbad I found that the patient, who was a little less unreliable during his "cure" than at home, when taking 120 grams of white bread and some green vegetables with his food, presented a gradual diminution in his glycosuria, until in the third week he was passing about 1800 cu. cm. of urine containing only a trace of sugar.

13. Herr S., forty years old, an engineer, had some months previously suffered from a remarkably obstinate ulcer on his leg, and his physician found six per cent. of glucose in the urine.

The patient was free from neurotic or diabetic inheritance. He had rarely neglected free libations of strong grog in the evening and had smoked immoderately. During the preceding few years he had suffered from gouty troubles. Four years before he had passed through a violent attack of influenza. The patient denied syphilis, but his wife had twice miscarried in the sixth month.

The patient is a robust man, without obvious manifestations of the glycosuric dystrophy. Even the cavity of the mouth exhibited nothing abnormal beyond caries of two teeth. Sexual power was rather weak. The knee-jerks were just perceptible. The patient now and then felt pain "deep in the head."

His heart was somewhat enlarged, the sounds weak and distant, the impulse not perceptible; the pulse 76, not quite regular, and weak. The temporal arteries were unduly distinct on palpation.

One hundred grams of white bread and some green vegetables with the food yielded regularly about 2100 cu. cm. of urine, with a specific gravity of 1.027 and containing 0.9 per cent. of glucose, a trace of albumin, and some granulated tube-casts. After two days of abstinence from carbohydrates the patient was able to take regularly sixty grams of white bread a day with green vegetables, without any determinable glycosuria.

Nearly three years after this the patient again consulted me. He had, two weeks before, while driving about in a cab, suddenly lost first his sight and shortly afterward consciousness, having previously suffered from acute, deep-

seated pains in his head. Consciousness returned after some hours. There were no distinct paretic symptoms, but amblyopia persisted for several weeks. The patient could at first only count fingers, but not read. Vision gradually returned to the previous state. The patient's physician believes the symptoms to have been due to uremia, while I attribute them to cerebral hemorrhage. The ophthalmoscope disclosed a hemorrhagic retinitis, with ecchymoses in different stages. The glycosuria was now, probably in consequence of the cirrhosis of the kidneys, slighter than it had been three years before; 120 grams of white bread and some green vegetables causing only faint traces of glucose to appear in the urine, of which about two liters were excreted in the twenty-four hours, and which had a specific gravity of 1.021 and contained a trace of albumin.

14. A., a restaurateur, forty-seven years old, developed three "maux perforants" on the right foot, and consulted Dr. H. Toll, who found a large quantity of glucose in the urine and called me in consultation. The patient admitted having "wet his tongue now and then," which means in Sweden that he has drunk enormously.

The man was somewhat maudlin, slept badly, presented no knee-jerks, had weakened sexual power, and complained of right genitocrural neuralgia. The pupils differed distinctly in size. The patient denied all history of syphilis. His heart was somewhat large, his pulse small and weak, but regular. Pronounced arteriosclerosis was obvious in the radial, temporal, and femoral arteries. There were no appreciable signs of cirrhosis of the liver.

Restriction of the diet caused disappearance of the glycosuria and of the distinct polyuria, and the patient excreted in twenty-four hours 1500 cu. cm. of urine of a specific gravity of 1.035 and, rather remarkably, free from albumin.

The three "maux perforants" had made terrible ravages in the foot, which was already resected through Chopart's joint; the process now continued chiefly along the tendons of the peroneal muscles. Sensibility was distinctly diminished on this leg, and there was a distinct retardation of the perception of needle-puncture. There being no indication of a clot in the popliteal artery, I proposed amputation below the knee, which was effected, with an excellent result after a few weeks of dietetic and restorative treatment. Nearly three years later I learned that the patient was still alive and in possession of a good stump.

15. E., fifty-four years old, manager of a factory, ten years ago sought life-insurance, but was not accepted on account of the existence of glycosuria. The history gave no clue to the origin of the diabetes.

The patient one night awoke with an attack of serious indisposition, felt a sensation of pressure or weight in the occiput, and vomited profusely. The next day the lower branch of the facial and the abducens nerve on the right side were paralyzed. The patient now consulted Dr. Nordenson, who made the following note: "In both eyes numerous small hemorrhages in the retina; around the macula lutea round whitish patches, with small points of blood.

Field of vision, normal extent; normal color-perception. Left eye: hypermetropia, 1 D.; visual power, 0.3. Right eye: hypermetropia, 1.50 D.; visual power, 0.3.

Seven weeks later the patient came to Carlsbad. I then found the lower branch of the right facial nerve and both abducens nerves paralyzed—the right eye alone seemed to be used. Other symptoms referable to the nervous system, besides the usual neurasthenic symptoms, included a feeling of heaviness in the occiput and some giddiness. The knee-jerk was absent on the left and barely appreciable on the right. A large specimen of the urine contained about three per cent. of glucose, but no albumin and no diacetic acid. Eighty grams of Graham bread and some green vegetables a day yielded a urinary secretion of from 2700 to 3000 cu. cm. a day, and, quite constantly, about 26 grams of glucose. A strict diet would, beyond a doubt, have caused entire disappearance of the glucose. With the use of syzygium jambolanum on three different occasions the glycosuria, *ceteris paribus*, sank to 15 grams, without any other appreciable change. In the autumn the neuroparalytic symptoms had disappeared, but otherwise the state of the eyes had undergone no change.

A few months after his visit to Carlsbad I was called early one morning to the patient in Stockholm. He had again had at night a cerebral attack like the previous one. After a rectal injection, application of an ice-bag to the occiput and of hot bags to the feet, and elevation of the head, the attack was soon over without leaving any noteworthy sequel.

Half a year later gangrene made its appearance in the left leg, and while the patient was under treatment for this a renewed cerebral attack suddenly ended his life. I was not at hand and there was, unfortunately, no postmortem examination.

16. E. T. B., a farmer, seventy-two years old, was considered by his family and friends to be a healthy and active old man. Apart from his eyes he had suffered from no disease whatever, and he knew of no reason for believing that any existed. He himself and others, however, were struck by a "peculiarity" that had made its appearance about thirty years previously—namely, that he drank more water and passed a greater quantity of urine than other persons.

The patient complained that his eyes had for many years been a source of trouble, and stated that he had used only the left one. Some days before coming under observation this eye began to ache; the patient obtained from a neighboring physician some atropin, which made the eye ache "horribly." He then consulted Dr. Nordenson, who found the cause of the "peculiarity," and sent the patient to me on account of his diabetes.

The right eye presented an absolute glaucoma. The upper lid was somewhat swollen, the conjunctiva of the bulb was hyperemic, and there was marked pericorneal injection. The cornea was smoky, the pupil dilated, and the anterior chamber was wanting. The vitreous body yielded a yellowish-brown reflection (hemorrhage).

In the left eye there was found hypermetropia of 1.50 D, with a visual acuity

of 0.8; except for a pronounced gerontoxon, the cornea was normal. The iris also was normal and reacted well. At the bottom of the eye small yellowish patches could be seen between the inferior temporal and the inferior nasal vein. A considerable hemorrhage and some small ecchymoses were visible.

The patient did not complain of any nervous disorder; the sensibility in the left leg, however, was much impaired. The knee-jerk in the same side was almost destroyed; the toe-nails were discolored, strongly curved, thick and brittle; on the plantar aspect of the great toe, beneath the interphalangeal joint, there was a circular scar attached to the bone and evidently from a "mal perforant," which had healed a couple of months before, under treatment by a surgeon, who, by the way, seemed to have omitted to look for diabetes.

On the right leg there was no "mal perforant," and the nervous and dystrophic changes were much less marked than on the left leg.*

The temporal and radial arteries were somewhat rigid, pulse 104, at noon, before lunch. The amount of urine secreted with free diet was 2.5 liters, with a specific gravity of 1.046, and it contained eight per cent. of glucose.

A diet including an abundance of green vegetables, about 100 grams of potatoes, and 100 grams of rye-bread yielded 1600 cu. cm. of urine containing five per cent. of glucose, but no diacetic acid. It is probable that with a strict diet the urine would have been free from glucose.

Three years later the patient was said to have been in about the same state.

17. A judge, sixty-one years old, nine years before coming under observation, after some loss of weight and a sense of weakness, was discovered to be diabetic. The patient himself believed the dystrophy to be due to exposure to cold, and no other cause, hereditary or acquired, could be elicited. During his first season at Carlsbad the patient felt fairly well, and the neurasthenic symptoms, which constituted his chief complaint, subsided with the complete rest of his sojourn at the spa.

The power of assimilation was quite good, and with a daily allowance of some green vegetables and 150 grams of Graham bread, the patient passed 1600 cu. cm. of urine, with a specific gravity of 1.025, and containing only faint traces of glucose.

Two years later the patient looked much less well and complained of increasing weakness and incapability of fulfilling his public duties. Investigation shows, apart from the results of urine analysis, only one important change from the state of two years before—namely, there was now a distinct odor of acetone on the breath. The glycosuric dystrophy had made considerable progress, and 75 grams of Graham bread and some green vegetables yielded 1800 cu. cm. of urine containing 1.3 per cent. of glucose. There was then no distinct Gerhardt's reaction. The patient, who seemed entirely reliable, was for a

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* About the same time Dr. Kinnicutt, of New York, to whom I mentioned my case, had a similar one under observation, with marked neuritis, knee-jerk almost destroyed, "mal perforant," and other dystrophic changes in the one leg, with a comparatively normal state in the other.

whole week put on strict diet, with exclusion of carbohydrates. He then lost weight from 95.3 kilograms to 93.4 kilograms, and the urine yielded a faint Gerhardt's reaction indicative of the presence of diacetic acid. There was even now about 0.1 per cent. of glucose in the urine; this could scarcely have been derived from carbohydrates, but it seemed to be derived partly from albumin. The patient undoubtedly has arrived at the boundary line between the positively mild and the positively severe stage, but his exact place can not be determined under the conditions that prevail at Carlsbad.

Four years later I learned that the man was still alive.

18. A merchant first became my patient in his thirty-sixth year. His father had been diabetic, and a paternal uncle diabetic and insane. Seven years previously the patient contracted syphilis, and he had always been a hard drinker. Half a year before coming under observation the patient observed that white spots were left by his urine, which was found to contain six per cent. of glucose after dinner. Beyond this and moderate neurasthenia the man was, during his first season in Carlsbad, fairly healthy and quite robust-looking. Thirty grams of bread and some green vegetables were permitted with the food, without the development of glycosuria. As the patient with this restriction maintained his weight (92 kilograms) the diet was continued for five weeks.

In the following summer the condition of affairs appeared pretty much the same. Sixty grams of bread and some green vegetables caused a trace of glucose to appear in the urine; the bread being increased to 90 grams, the normal quantity of urine for twenty-four hours contained fully 0.1 per cent. of glucose. The patient had entered into matrimonial plans, and combated energetically my somewhat feeble opposition, asserting that Providence itself was strongly interested, but promised moderation in all respects.

Two years later the man again appeared in Carlsbad, having carried out his plan of marrying, but having entirely forgotten his promise of moderation. Sixty grams of bread and some green vegetables now yielded 1450 cu. cm. of urine in twenty-four hours, with a specific gravity of 1.032 and containing 0.2 per cent. of glucose and no diacetic acid. When carbohydrates were entirely excluded for some days the patient lost somewhat in weight, while the glucose entirely disappeared, and a faint Gerhardt's reaction developed with ferrichlorid. As the drops of the solution fell in the urine they were, for a moment, surrounded by a purple zone, the urine above the phosphates having the color of sherry. In the following year the power of assimilation had again decreased, and the patient was in the severe stage of the dystrophy. Abstinence from carbohydrates was no longer followed by disappearance of the glycosuria, though only a few grams of sugar were excreted during the twenty-four hours. Gerhardt's reaction was now well pronounced. About 70 grams of bread and some vegetables yielded 1500 cu. cm. of urine, with a specific gravity of 1.034 and containing rather more than one per cent. of glucose. Upon this diet the patient kept his weight, but a distinct though faint Gerhardt's reaction could still be elicited.

Two years again passed and the patient returned to Carlsbad. The bodily

weight was almost the same; the glycosuric dystrophy had again made some slight progress. Mentally the patient was an altered man. He suffered from melancholia, without stupor or hallucinations, but with unfounded ideas of financial ruin, many expressions of "tedium vitæ"; terrible anxiety for the future mental and somatic fate of a new-born son, great restlessness, with an occasional "raptus" during the nights, and general profound depression, etc.

The "cure" at Carlsbad somewhat improved the man's condition; but during the autumn the melancholia again regained its sway over the patient, who, some months after my losing sight of him, was found lying across a railway track dead and mutilated.

19. H., a clerk, forty-six years old when I saw him for the first time at Carlsbad, had known for two years that he was diabetic, but distinct polydipsia and polyuria had been present for five years.

A history was obtained only with the greatest difficulty, owing to the stupidity of the patient, who did not seem to know anything of his whole past life, except that he had acquired syphilis twenty-nine years before and had successively passed through five antisyphilitic cures.

The man was extremely peevish and irritable; he slept badly. Sexual power was enfeebled. Supraorbital neuralgia was present on both sides. The teeth were partly carious and partly gone.

The urine, which had lately contained so much as seven per cent. of glucose, was now found to contain three per cent. There was no odor of acetone on the breath, no diaceturia, no albuminuria. A restricted diet put an end to the glycosuria, which afterward did not return in determinable quantities so long as the patient took no more than 60 grams of white bread and some green vegetables.

Ten years afterward the man returned to Carlsbad. His breath now distinctly smelled of acetone; the teeth were almost all gone; the tongue showed longitudinal and transverse furrows "*à la crocodile.*" Sexual potency was entirely gone. There was a suspicion of neuritis in both legs. The apex of the right lung exhibited signs of tuberculosis, and in one place there was a small cavity. The pulse was 84, the temperature slightly elevated. The patient complained of night-sweats.

Exclusion of carbohydrates for several days reduced the glycosuria to 0.6 per cent., 1500 cu. cm. of urine with a specific gravity of 1.026 being secreted in twenty-four hours; and a distinct Gerhardt's reaction was present. Eighty grams of bread and 100 grams of levulose and some green vegetables with the food considerably increased the glycosuria, but distinctly diminished the diaceturia (which, however, still continued), caused some restoration of weight previously lost, and maintained the bodily weight at 77 kilograms. Syzygium jambulanum, even in large doses, had no appreciable effect.

20. Mrs. L., thirty-eight years old, knew of no hereditary or other etiologic causes for her condition than an excessive fondness for sweets. Her diabetes, to judge from the polyuria and the polydipsia, had probably set in two years before. The patient was extremely stout, and did not lose in weight until her diet was restricted.

During her first season in Carlsbad the lady appeared in fairly good general health. There was no smell of acetone on the breath. Some teeth were carious, and now and then gingivitic troubles arose. Some of the usual neurasthenic symptoms were present, and on the left side supraorbital neuralgia and sciatica. Cramp occurred at night in the calves of the legs. There was a tendency to profuse perspiration. Finally, the patient complained of pruritus vulvæ, which speedily ceased on application of a solution of mercuric chlorid (1 : 1000) twice a day. The urine, which had contained four per cent. of glucose, became normal in quantity and quality upon a restricted diet, and remained so, except for small traces of sugar excreted, when 60 grams of white bread and some vegetables were added to the dietary.

Eleven years after the beginning of the diabetes the patient again appeared in Carlsbad in a very different state. She had diminished in weight from 86 to 67.15 kilograms and she felt very weak. The skin was dry and of cyanotic hue upon the cheeks. The patient was no longer troubled with profuse perspiration. The breath smelled of acetone; the teeth were defective; the tongue was dry, partly coated, and of an angry red at the apex. Restriction of diet no longer stopped the glycosuria. The weight could not be maintained with less than 100 grams of Graham bread and some vegetables with the food, upon which the patient passed 2500 cu. cm. of urine containing 2 per cent. of sugar and with a distinct (but not marked) Gerhardt's reaction, but no albumin.

A year later small ecchymoses or petechiæ, sometimes observed in advanced cases, began to appear. The petechiæ disappeared when the patient remained in bed, and reappeared as soon as she moved about. They were present almost exclusively on the legs, only a few being visible on the trunk and none on the arms.

Another year added iritis on both sides and cyclitis on the left side to the other symptoms. The patient was then in an advanced cachectic state, and died in coma a few weeks after the appearance of the ocular symptoms.

21. Captain ——, forty-four years old, an officer of the Guards, had in the spring received from his physician the information that he was diabetic, and in August he came to Carlsbad.

The patient had during the preceding months at home felt some increased thirst and some need of passing his urine more frequently than before; still, the quantity did not distinctly exceed the normal limits. Apart from the urine—which at the time of the patient's arrival contained a considerable quantity of glucose—there were scarcely any symptoms at all. All carbohydrates were excluded from the food, and during a week of strict diet the patient's weight went down from 86.7 kilograms to 85.3 kilograms. The man now gradually received increased amounts of carbohydrate. The urine remained normal in quantity and quality until more than 90 grams of Graham bread and some vegetables were given. The patient had a splendid appetite, and one day passed 18 grams of nitrogen with his urine. When 120 grams of Graham bread were given, the mixed urine for twenty-four hours contained fully 0.1 per cent. of glucose. The patient maintained his weight and felt as well as ever.

The next year the man again appeared at Carlsbad, on May 7th. His general appearance had undergone a change for the worse, and there was an ominous smell of acetone on his breath. The bodily weight had fallen to 83 kilograms. The urine contained much glucose, and yielded a distinct though not very marked Gerhardt's reaction. After an exclusion for five days of carbohydrates the patient passed 2200 cu. cm. of urine, of a specific gravity of 1.018, with 0.5 per cent. of glucose, and yielding a somewhat more pronounced reaction with the solution of ferric chlorid than at the patient's arrival. The patient now received, daily, a large piece of Seegen's almond-bread, which, as it is sold in Carlsbad, contains a not inconsiderable quantity of starch, and a generous supply of fish, meat, butter, and eggs. He then excreted 19.5 grams of glucose daily and Gerhardt's reaction was less pronounced, though distinct. He still lost in weight, and added to his bill of fare 100 grams of levulose daily. The glucose in the urine increased from 19.5 to 34 grams in the twenty-four hours, but the diaceturia evidently decreased and the patient maintained his weight, which now was only 82.4 kilograms. Some ordinary bread was now given, and the bodily weight rose to 83.3, which it still was when patient left for home, after a stay of five weeks. There had constantly been some diaceturia.

The patient, whom I asked concerning the presence of fat in the feces, was able to detect no difference from the ordinary appearance.

On October 17th, while upon a fair amount of carbohydrates allowed by his physician at home, the man expired in diabetic coma. No autopsy was performed.

This case represents the most rapid transition from a distinctly mild to a distinctly severe diabetes that I have ever witnessed.

22. V. X., thirty-five years old, a diplomatist, belonged to a family that has given me diabetic, fatty, and gouty patients. The man had been a hard smoker. In the course of a diplomatic mission to Asia he had to stand a good deal of fatigue and of emotion. In the south of Europe he contracted malaria. A few months afterward diabetes suddenly set in, and took the patient to Carlsbad during three successive seasons.

The man was exceedingly sensitive in every respect, slept badly, and a steep declivity made him giddy. The knee-jerks were present and moderately strong. The sexual power was somewhat weak, although the patient begot a child about two years after the beginning of his disease. The bodily weight had lately kept at about 73 kilograms. A few days after our first acquaintance he invited me to breakfast, where he consumed a piece of Graham bread, a large piece of butter and another of cheese, one partridge, two sausages, a considerable quantity of ham, and four eggs. We often afterward took meals together, and I always found him with an enormous appetite.

The teeth grew more and more carious, and the tongue showed more and more of the customary appearance in severe diabetes. The pulse was rarely below 100. The skin was dry and the patient was often troubled by itching.

The urine after a few days' absolute diet contained between 1.4 and 1.6 per

cent. of glucose in about three liters. With the moderate quantity of carbohydrate necessary for the maintenance of the bodily weight and of a fairly good general condition it increased to about four liters, containing between 2.6 and 3 per cent. of glucose. During the whole time Gerhardt's reaction was quite distinct, and the urine was repeatedly found to contain some β-oxybutyric acid. A trace of albumin was always present.

When the patient arrived at Carlsbad for the third time there was no opportunity to analyze the urine. He was then in a state of utter exhaustion; the frequent pulse and the dyspneic respiration already foreboded coma, although they were to some extent affected by a left-sided pneumonia. The patient was seized with a chill on the cars. A flat sound on percussion was elicited over the lower part of the upper lobe of the left lung, and in the same area distinct, though distant, bronchial respiration was audible. Constipation had been present for four days.

A large, tepid, rectal injection, with the addition of potassium permanganate, whisky and enormous doses of sodium bicarbonate by the mouth, were immediately given. Coma gradually overwhelmed the patient, the specific gravity of the urine, which from the beginning of his disease had always been above 1.035, falling to 1.019, and the glucose to 1.3. Gerhardt's reaction, which had been very pronounced, became much less so; still, there seemed to remain some β-oxybutyric acid to the end. There was some expectoration of pneumonic sputa. Death took place six days after the patient's arrival.

On postmortem examination a central, small pneumonia was found in the left lung. The pancreas was perhaps somewhat too soft in consistency and undersized; otherwise it was normal. The liver was in a state of pronounced fatty degeneration. The spleen was hyperemic and about twice the normal size. The kidneys were large, hyperemic, with the cortex slightly discolored by fatty degeneration.

23. Miss B., a teacher of music, after a severe attack of influenza was seized with severe diabetes.

Her general health failed rapidly, and she lost quickly in weight, in spite of an enormous appetite. She passed daily about four liters of urine.

One year and a half after the beginning of the glycosuric dystrophy she came to Carlsbad in a most miserable cachectic and marantic condition. Eighty grams of Graham bread and some vegetables in the food yielded 2000 cu. cm. of urine, with a specific gravity of 1.037, containing 4.4 per cent. of glucose and yielding a strongly marked Gerhardt's reaction. The day before coma set in I took a specimen of the urine and found, after thorough fermentation and precipitation with ammonia and lead acetate, the ray of polarized light deflected to the left between 0.4 and 0.5° in Hoppe-Seyler's instrument.

During her three weeks' stay at Carlsbad a most wonderful contrast was evident between her miserable somatic and her splendid mental state; her courage not only keeping her in a happy frame of mind, but enabling her constantly and patiently to cheer another (most intractable) diabetic lady. I had not omitted to warn her of the danger of any continued constipation; nevertheless she remained in such a state for four days without taking the prescribed

measures. She then, during a walk in the woods, was seized with the prodromes of coma, and was brought back to her hotel, where I immediately arrived. The brave little patient presented a pulse of 120 and the ominous "blowing" respiration. An immediate purging injection was given; she besides received whisky, enormous doses of sodium bicarbonate in Geisshübler water, and general massage. Being able to take no solid food, the patient drank a good deal of levulose in Geisshübler water. After a distinct but transitory improvement the coma gradually overpowered the patient, and after more vigorous clonic convulsions than I ever saw before with this kind of death, the girl succumbed on the third day.

24. Augusta J., forty years old, a widow who had married again, grieved greatly at the drunkenness and general moral degeneracy of her second husband, a laborer, and was suddenly seized with symptoms of diabetes. On October 29, 1891, about a year after the beginning of her diabetes, the woman entered Queen Sophia's Hospital, in Stockholm, to be operated on for cataract by Dr. Nordenson, who, previously to the operation, confided her to my care for her diabetes.

The patient was very thin, with a dry, scaly skin. Her tongue was thickly coated at its base, and presented the customary diabetic type, "*à la peau crocodile*," with some fleshy-looking patches and an atrophic mucous membrane. The teeth were carious and the breath smelled of acetone.

The patient suffered from continuous headache and slept badly. There was no knee-jerk. Hearing was poor; vision, which was excellent a year before, was destroyed by the soft, diabetic cataract. At the apex of the right lung there was in a small area a somewhat sharp respiratory sound and a higher-pitched percussion-note. The pulse was 100.

The headache might have been a precursory sign of coma; but it had lasted for a whole year, and could be more easily explained in almost any other way. The urine,—which with an almost free diet amounted to about three liters, of high specific gravity, and contained six per cent. of glucose and a trace of albumin,—after fermentation of the glucose and precipitation of the combined glycuronic acids with lead acetate and ammonia, deflected the ray of polarized light to the left only slightly (0.2° with Hoppe-Seyler's instrument), and yielded a moderately pronounced Gerhardt's reaction. On account of the presence of but a small amount of β-oxybutyric acid, I considered it not dangerous for three days to exclude carbohydrates from the food. The patient received an abundant food in eggs, fish, different meats, and butter—a seemingly much better diet than her poor fare at home, chiefly consisting of herring and potatoes. After three days, when I had found out how much glucose was being excreted with the strict diet, the patient was to receive 60 grams of white bread and a considerable amount of vegetables every day.

Polyuria and glycosuria quickly diminished, but Gerhardt's reaction became much more marked, even comparatively, and during the night of November 2d–3d violent diarrhea began. When I visited the patient on the morning of November 3d, coma evidently was threatening. Respiration was blowing and dyspneic, the pulse 120, the temperature in the rectum 35° C. (95° F.) in

the morning and 34.4° C. (93.9° F.) in the afternoon. The patient was given brandy in strong tea, together with eggs, biscuits, and enormous quantities of sodium bicarbonate water. When she could eat no biscuits, and no levulose could be had, I gave her cane-sugar in my anxiety to increase the carbohydrates. Marked improvement followed, and when the danger of coma seemed much diminished, some opium was given for the diarrhea. The patient improved greatly. On November 7th the pulse was 84, the temperature 36.8° C. (98° F.), respiration almost normal, the sensorium and intelligence seemed quite free, and I began to hope that I should escape too severe consequences of this ill-timed dietetic system, still defended by powerful authorities. Diarrhea, however, again began on November 8th, and the patient became more and more comatose, and died on November 16th. During the period of coma the glucose sank to 0.7 per cent., the urea to 0.35 per cent., the chlorids likewise to a minimum, and the specific gravity to 1.013. The phosphoric acid decreased less, and was 0.1 per cent. The temperature, which before had constantly been somewhat below the normal, during the last days went up to 38° C. (100° F.) in consequence of the pulmonary lesion.

On postmortem examination the muscles were found dry and atrophic, the dura somewhat thickened, the pia distended with edema, the heart small, pale, and flabby, while the right lung contained a caseous focus. The liver was partly in a state of fatty degeneration and partly exhibited rose-red spots and an appearance suggestive of the nutmeg-liver. The pancreas was in every respect normal. The kidneys were large, flabby, pale, with the cortex somewhat discolored. The spleen was normal. A strong smell of acetone filled the room.

CHAPTER V.—DIABETES INFANTILIS.*

The pathologic excretion of glucose is much rarer in children than in adults, and almost always represents either a simple, transitory glycosuria from some accidental cause, or a severe diabetes, which may lead to death in the course of a few weeks, and hardly ever fails to do so in the course of a few years. Still, in exceptional cases it happens that a child suffers from protracted diabetes in the mild stage.

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* Niedergesäss (1873), Redon (1877), Külz (1878), Leroux (1880), Stern (1889), and others have written on Diabetes infantilis.

Simple glycosuria in children generally occurs in conjunction with neuroses and with the infectious fevers, but it may arise from any cause that has the same effect in adults. It has been observed by a number of clinicians in cases of diphtheria, scarlet fever, and measles, and also in cases of epilepsy, chorea, supraorbital neuralgia (Franque, Goolden, and others). In cases of pertussis and croup it may be the result of asphyxia (Laborde). Lecoq mentions the appearance of from 0.1 to 0.2 per cent. of glucose in the urine of healthy children who had eaten sweets (? ?). Parrot found glucose in more than one-third of all athreptic children, especially in those that were cyanotic. I have several times found distinct traces of glucose in boys that had been addicted to masturbation. I believe that in many such cases true diabetes may develop in middle age, though one may see glycosuria disappear in other cases. Protracted glycosuria is much rarer, and is of much greater significance in children than in adults.*

True diabetes is so rare in early childhood that many an experienced children's physician and many a specialist in diabetes have never seen a diabetic patient under ten years of age. Romberg observed among 5900 infant patients but a single case of diabetes. Schmitz encountered among 2115 cases of diabetes 10 patients in the first and 75 patients in the second decad of life.

Prout saw among 700 cases of diabetes one child under five years old.† It is only by mere accident that in the course of little more than a year (1895–1896) I have been consulted in four cases of diabetes in children under ten years of age, while previously I had seen but a single such case. On the other hand, I have seen a not inconsiderable number of cases in children between ten and

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* Cantani urges the necessity of looking for glucose in cases of nocturnal enuresis. If one does so, and in the presence of a reducing-substance verifies it as glucose by the fermentation-test, he will find that in the great majority of the common cases of nocturnal enuresis the urine is free from glucose.

† I have, unfortunately, taken notes of my diabetic cases only during recent years, and do not know their number; but my 5 cases of diabetes in children under ten years occurred—one in a girl six years old, in the central part of Sweden; another in a girl four years old, in Stockholm; 2 boys of four and of nine years, respectively, in Stockholm; and one boy of four years, in New York. For two of my cases in Stockholm and for the case in New York I am indebted to my esteemed friends, Dr. Nettelbladt and Dr. Kinnicutt, respectively.

fifteen, and some in girls and boys between fifteen and twenty years old. Statistics show that the third quinquennium of life,—viz., from ten to fifteen years,—of the first four quinquenniums is that in which diabetes occurs most frequently. In the period from fifteen to twenty years diabetes again becomes rarer, while from the latter age it continues to grow more frequent.

It is of great interest to see how the total frequency increases, and how the greater frequency among boys than among girls shows itself from the second decad, in which both sexes begin to be somewhat strained intellectually, and in which, unfortunately, sexual excesses (masturbation) among boys already begin to become frequent. Among 136 cases of diabetes up to the age of fifteen years, there were 27 cases during the first, 32 during the second, and 77 during the third quinquennium of life (Leroux). Pavy has observed 5 girls and 3 boys in the first, and 35 boys and 22 girls in the second decad of life.

In children under ten the relative frequency in the two sexes differs from the analogous figures later in life. In adults the ratio between diabetic men and diabetic women is best represented by the figures 3 : 1. But among diabetic children under ten years of age we find at least as many girls as boys. Among 102 cases at this period there were 57 girls and 45 boys. Leroux alone has observed what he calls a "*statistique favorable aux garçons*" : namely, 22 boys and 16 girls. Külz's and Leroux's figures from different sources and my own 5 cases make up the usual small majority for the girls in early childhood : 75 girls and 70 boys.

The causes are, of course, the same for children as for adults, but there is some difference in their relative efficiency. Hereditary influence is exceedingly important in childhood. Isenflamm, as early as 1784, mentions an instance of diabetes in 7 brothers, who all died at the age of seven or eight years. Roberts observed 8 diabetic children in the same family ; Watson, Bence-Jones, and West each saw 3 ; and in India such cases are common. I am inclined to believe that infectious diseases are the most frequent accidental cause of diabetes in children ; in adults emotions and mental sufferings play a much more important rôle. Trauma is the cause of a greater percentage of infantile than of other cases. Finally, both from reports in literature and from two of my own cases, I am inclined to believe that starvation is a relatively more frequent cause in childhood than later in life (Andral, Heine, Senator, Ingerslev, and others have seen such cases).

Infantile diabetes usually is like the worst cases in adults, and presents itself as a terrible dystrophy with a rapid course. It

is especially in these cases that one sometimes hears the date of the attack named. "The 20th of April my boy was in perfect health; the 21st he was very ill, and drank as much as he could the whole day," the father of a four-year-old diabetic boy told me some time ago. The little victims suddenly stop playing and become quiet and drowsy, irritable and peevish. The diabetic symptoms rapidly reach a maximum of intensity. There are on record reports of cases in which sixteen liters of urine and one kilogram of glucose were secreted in the twenty-four hours. The urine usually is pale, greenish-yellow in color, and of high specific gravity. In a case seen by Redon the latter was 1.070. Gerhardt's reaction is often distinct from the beginning. In a few months the cavity of the mouth may present a furrowed tongue, partly with a thick, brownish covering, partly with fleshy, flayed-looking patches, and carious teeth; it often becomes the seat of a luxuriant vegetation of Oidium albicans. The soft, diabetic cataract may develop in an amazingly short time, and at quite an early age. In one of my cases, to be related later, the patient was fourteen years old. The face is either pale or it may present a circumscribed, cyanotic, red discoloration on the cheeks; the skin is dry and squamous. Girls suffer from vulvitis, boys from phimosis and balano-posthitis. The loss of flesh can not be checked, and the children become exceedingly weak and have to keep their beds. The temperature, apart from febrile complications, keeps below the normal, but even in these cases rarely below 36° C. (96.8° F.).

The prognosis is extremely bad, and I do not know that in any of the typical infantile cases the patient has returned to health.*

In cases of diabetes in the first decad of life death often takes place within a year; a longer duration than two years after the first appearance of symptoms at this age is rare, and the rarer, the younger the patient. In some cases the dystrophy leads to death

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* There are many reports of complete recovery even from infantile diabetes. Of 96 cases from 11 different writers I find 83 with a fatal issue and 13 in which recovery ensued. These reports are as unreliable as the analogous ones concerning adult cases. But as in cases of diabetes from infections and from trauma the prognosis is better than in other cases, and as these causes are relatively frequent in infantile cases, I presume that true diabetes in a child—which *may* be a mild diabetes—now and then has disappeared.

in a few weeks. The fatal issue in most cases is brought about by coma or marasmus.*

As infantile cases are comparatively rare, I record here one of my own from each of the four first quinquenniums.

Ellen W., four years old, had an insane aunt. The father is very "religious." On December 16th I was called to see the child, and on asking about the duration of the disease the mother answered: "She fell ill the 5th of November."

The girl was pale and almost only "skin and bones." The tongue already presented the diabetic type, the teeth were carious, and the breath smelled of acetone. Thrush reappeared in several places constantly as quickly as it was got rid of. The child was irritable, but otherwise drowsy; a certain degree of poisoning was already manifest. The reflexes were extinguished. Severe epigastric pain caused the patient to cry out with anguish. The pulse was 80, the temperature in the rectum 36.2° C. (97.2° F.).

The child received about 75 grams of bread with her food. The urine excreted amounted to 2500 cu. cm., had a specific gravity of 1.040, and yielded a pronounced Gerhardt's reaction, some β-oxybutyric acid, and a large quantity of glucose. The introduction of this allowance of carbohydrate after the previous strong restriction was followed by decided improvement; coma, however, was only put off for four weeks. No postmortem examination was held.

B., a boy nine years old, had a "nervous" mother, two insane aunts, and an uncle who died by suicide. (There are, however, reasons for suspecting the boy's diabetes to be of pancreatic origin. See below.)

About a year before the child came under my observation he began to wet his bed, and the family physician found an abundant quantity of glucose in the urine.

When I saw the boy on April 1, 1896, he was in an exceedingly miserable state. His appetite was voracious. He had, however, lost a great deal of weight, and the outlines of the wasted muscles were distinctly to be seen through the dry, atrophic skin. The mental state had lately gone from bad to worse, and the boy, who had previously been of a gentle disposition and of quite excellent parts, was now usually apathetic, but on the slightest provocation was subject to attacks of violent rage, followed by deep depression. Sleep rarely came before three in the morning. After exertions attacks of general clonic spasms occurred, with full consciousness. A continuous headache exacer-

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* In 21 cases collected by Redon from different writers there were 9 deaths from marasmus without coma, 3 from marasmus with coma, 4 from pulmonary tuberculosis, 3 from acute inflammation of the lungs, and 2 from cerebral affections. Concerning these statistics, it may be remarked that the number of deaths attributed to coma is doubtless much too small; coma seems to be the most frequent mode of death in cases of infantile as well as those of other severe forms of diabetes.

bated in the morning and in the evening. Sciatica was present on both sides. The knee-jerk was slight on the left, but almost normal on the right side. On the left leg sensibility was distinctly diminished. Psoriasis was present on both knees. Vision was normal. The pulse was 66, the temperature in the rectum 37.3° C. (99° F.). Later, the patient's mental state did not permit thorough examination.

The feces consisted partly of white-colored fatty masses. (Were it not for this symptom, one might be inclined, on account of the strong neurotic inheritance, to consider the case one of neurogenic diabetes.)

After considerable though not absolute restriction of carbohydrates a large sample of urine was found to have a specific gravity of 1.038 and to contain 6.6 per cent. of glucose, some diacetic acid, but not an appreciable amount of β-oxybutyric acid. The disease, which probably for some time had kept within the light stage, had lately, according to a chemist's calculation, caused a loss of nearly one kilogram of glucose a day. The maximum measured quantity of urine in my observation, however, did not exceed eight liters.

The boy had previously lived on a more or less rigid diet, but on account of his despair with regard to his food some concessions had lately been made. The state was such that none of the three physicians who saw him believed that his life would be spared for more than a few weeks. The treatment now was directed chiefly against the nervous symptoms. The diet was changed, and the patient was allowed to eat as much bread as he wished, and green vegetables and levulose were added to his bill of fare. The polyuria and the polydipsia, of course, increased at once, but the mental and general state improved manifestly, and the hitherto continuous loss of flesh stopped. To our amazement the patient lived not only through the whole of 1896, but also through the greater part of 1897, and died in October of that year, not from coma or marasmus, but from a carbuncle on the head. I did not dare to ask for a post-mortem examination.

It is my firm opinion that any considerable restriction of carbohydrates would have led to a much earlier death, though I fully acknowledge the small value of the patient's last year for himself and others.

Anna Charlotta J., fourteen years old, did not know much about her family, but described the evident epilepsy of her sister.

At the age of twelve the girl lived for two months as a servant with some poor people, and literally starved. When she again returned to the comparatively good table of her home, she became diabetic.

Somewhat more than two years afterward the child was admitted to Queen Sophia's Hospital in Stockholm to be operated upon for typical, diabetic, soft cataract on both eyes (Nordenson). I found her very thin, pale, and anemic, with a dry, scaly skin. She was moderately depressed, somewhat irritable, slept fairly well, had normal knee-jerks, and felt "creepings" in the arms and legs. The teeth, though still fairly good, now began to be carious, and the tongue was dry and of a vivid red, while fissures formed in both angles of the mouth. The appetite was voracious. The liver was normal in size, consistency, and sensibility. The bowels were somewhat sluggish.

Over the apex of the right lung in one place there was some flatness of the percussion-note.

The pulse was 120 in the morning. The temperature was somewhat below the normal during the whole time. The weight was 28¦kilograms.

A sample of urine obtained when the patient, who had eaten whatever she wanted, arrived had a specific gravity of 1.046, contained 9.2 per cent. of glucose, was free from albumin, and yielded a dark bluish-purple reaction with ferric chlorid.

During the first days the patient received 90 grams, and afterward 60 grams, of rye-bread, some green vegetables, and four glasses of unskimmed milk a day, with much butter, meat, fish, and eggs.

The bodily weight increased from 28 kilograms on December 1st to 30 kilograms on December 23d. Then dyspeptic troubles arose, with diarrhea and a loss of weight in one week of nearly two kilograms. Opium was given and the patient was allowed 80 grams of white bread daily.

By January 5th the girl had regained her bodily weight and reached her maximum of 30.3 kilograms. The general state also was at its best. The daily portion of bread was again reduced to 60 grams. With this diet the urine amounted to from 2 to 2.5 liters and contained upward of 5 per cent. of glucose. Gerhardt's reaction constantly was pronounced, as manifested by a rich Burgundy color; after fermentation and precipitation with ammonia and lead acetate the urine still deflected the ray of polarized light in Hoppe-Seyler's instrument about 0.2 degrees to the left (β-oxybutyric acid). The urine from 8 P. M. to 8 A. M. generally was a little more abundant than the urine collected during the day, but not rarely the contrary happened.

On January 7th the urine for twenty-four hours amounted to 2125 cu. cm., and had a specific gravity of 1.034, with 4.4 per cent. of glucose. It yielded, as usual, a marked Gerhardt's reaction, and, for the first time, contained a small quantity of albumin.

On January 10th the patient presented the well-known prodromes of coma. She had been very uneasy during the night, and was then in terrible anguish, but intelligence and sensorium were still clear. The patient complained, at times with loud cries, of violent epigastric pains. The pulse was nearly 150, the respiration 28. The girl was given tea with brandy, liquor ammoniac, anisatus, a rectal injection of tepid water, a warm bath (39° C.) (102.2° F.), and general massage. The diet was unrestricted, and enormous quantities of sodium bicarbonate were given in soda-water. After a marked but transitory improvement the patient struggled on, with slight changes, until the 12th, when drowsiness became manifest. The epigastric pains had now stopped, the respiration was 25, the pulse 132; the 2125 cu. cm. of urine had a specific gravity of only 1.021, with 2.7 per cent. of sugar and some diacetic acid. On January 13th the specific gravity was 1.019 and the glucose 1.2 per cent. The patient remained conscious until noon, with only slightly impaired intelligence, but then became comatose and died quietly at 7 A. M.

Upon postmortem examination the dura mater was found somewhat thickened, the pia distended by an abundant edema. The fourth ventricle and the aqueduct of Sylvius and adjacent parts seemed to the naked eye normal,

beyond some perivascular spaces, such as Dickinson has described. A large part of the sympathetic nerves was carefully dissected, and seemed perfectly normal. The heart was pale and small. At the apex of the right lung was a caseous nucleus of the size of a pea. The pancreas was normal. The liver was somewhat hyperemic. The mesenteric glands were enlarged; one of them was caseous. The kidneys were large and hyperemic.

Miss G. V., nineteen years old, with a maternal neurotic inheritance, began to feel exceedingly thirsty in November, and consulted me January 28th.

There was polydipsia, polyuria, and pollakiuria. The formerly gentle disposition of the patient was changed into one of great irritability. Sleep was bad, and there was constant headache. The knee-jerks were very weak. The teeth were partly carious, partly absent. The gingiva around a molar tooth was swollen, and an incision was followed by the escape of a drop of pus; a probe passed rather deep along the root of the tooth. The tongue was coated, and with a dry, bright-red apex. A strong smell of acetone was present on the breath.

The patient was exceedingly anemic, and over the jugular vein a pronounced "*bruit du diable*" was audible. The apex of the right lung was slightly infiltrated.

A specimen of urine had a specific gravity of 1.040, with 8.2 per cent. of glucose, a marked Gerhardt's reaction, and a small quantity of β-oxybutyric acid.

Sixty grams of white bread and some green vegetables in the food yielded about 170 grams of glucose a day in 3000 cu. cm. of urine.

At the end of May the patient died in diabetic coma.

CHAPTER VI.—DIABETES MELLITUS FOLLOWING EXTIRPATION OF THE PANCREAS.

As I have mentioned, a connection between lesions of the pancreas and the glycosuric dystrophy had long been suspected by many and accepted by some. Finally, in 1889, v. Mering and Minkowski communicated to the Association for Natural Sciences of Strasburg their great discovery that total extirpation of the pancreas gives rise to severe diabetes, characterized by glycosuria under all dietetic conditions, polydipsia and polyuria, rapid loss of weight, the presence of acetone, diacetic acid, β-oxybutyric acid,

and an increased amount of ammonia in the urine, and death in diabetic coma. These admirable and successful investigators had discovered the only certain method yet known of producing "artificially" true severe diabetes. They had, further, studied this form of diabetes conscientiously. Minkowski afterward continued the researches in a careful and extensive scientific investigation. About the same time De Dominicis, in Italy, independently of others, also observed (in dogs) diabetes after extirpation of the pancreas.

Later, Aldehoff, Sandmeyer, Lépine, Hédon, Gley, Thiroloix, Chauveau and Kaufmann, Gaglio, Caparelli, and others made researches on diabetes after extirpation of the pancreas. Unfortunately, these researches have on many points led to such different results that definite conclusions are at present impossible, though, on the other hand, many important facts have been added to our stock of knowledge.

Diabetes mellitus following extirpation of the pancreas has been observed in dogs, cats, and hogs (v. Mering and Minkowski), hawks (Langendorf), falcons (Weintraud), geese (Kausch), turtles and frogs (Aldehoff, Marcuse, Velisch). Kausch observed the extremely interesting fact that in birds hyperglycemia may reach much higher figures—up to 0.5 per cent.—than in mammals without causing glycosuria. This doubtless is the reason why the urine after operations on birds (pigeons and ducks) has sometimes been found free from glucose. The normal glycemia in birds seems to amount to only 0.14 or 0.15 per cent. (Kausch).

For the details of the operation reference may be made to the special works. The technical difficulties are quite considerable, and the object of the experiment is often frustrated by necrosis of the duodenum and other complications. The French experimenters have generally injected paraffin, asphalt, etc., into the pancreatic duct, resulting in atrophy and induration of the gland, and a couple of weeks afterward they have performed the operation of extirpation.

I here follow chiefly Minkowski; the facts, when no mention is made to the contrary, refer to the dog.

Glycosuria generally begins a couple of hours, sometimes much later, after the operation; in 50 per cent. of the cases it appears within five hours (Lépine). It generally reaches its maximum on

the third day, with from 10 to 12 per cent.* of glucose in about 1.5 liters of urine. The hyperglycemia may reach 0.9 per cent., but rarely exceeds 0.5 per cent. As already mentioned, the relation between the hyperglycemia and the glycosuria is not a fixed one, and some influence on the part of the kidneys must be admitted. If the animals escape other complications, the glycosuric dystrophy leads in a few weeks to diabetic coma.

If any considerable part of the pancreas—one-eighth or one-twelfth—is left, diabetes does not result. Hédon found the retention of even about one-thirtieth sufficient to prevent the development of the glycosuria. By leaving a small part of the gland one may restrict the effect to a slight glycosuria or to a mild diabetes, and it has been found that all the different stages of the glycosuric dystrophy may be effected by resection of the pancreas.

Chauveau and Kaufmann have found that if the spinal cord is divided in the lower cervical or upper thoracic region before extirpation of the pancreas, the operation is not followed by glycosuria. I shall recur later to their experiments and conclusions.

Hédon and Thiroloix both are of the opinion that a gradual and slow destruction of the pancreas (by injections of different substances into it) may take place without causing glycosuria (?).

Fever diminishes and phloridzin increases the glycosuria following extirpation of the pancreas.

The sugar in the urine has been proved to be glucose, not maltose.

When carbohydrates are excluded from the food after total extirpation of the pancreas, there gradually arises a fixed relation between the glucose and the nitrogen in the urine, a relation which is represented by the figures 2.8 : 1. When carbohydrates are given, it seems that during the highest intensity of the dystrophy *all* the glucose produced is excreted, and this fact and the fixed relation between the glucose and the nitrogen in the urine during exclusion of carbohydrates would—if one does not accept the presence in the blood of a "*materia peccans*"—seem to indicate that with the destruction of the pancreas something is lost to the organism that is necessary for the combustion of every molecule

* Hédon, by giving only bread as food, increased the glycosuria to 22 per cent.

of glucose. During other periods of the diabetes following total extirpation of the pancreas, however, according to all researches, a certain part of the ingested glucose is used up in the organism. Then,—though the conditions for the production of glucose from proteids are not fully known,—theoretically, out of 100 grams of proteid, minus the carbon necessary for the production of urea, there might be produced 213 grams of glucose and only 16 grams of nitrogen—*i. e.*, much more than only 2.8 times as much glucose as nitrogen.

It thus seems that though the pancreas is proved to have a specific function in the utilization and combustion of glucose, it may not be alone concerned in this phase of bodily activity.

Minkowski, after giving large amounts of levulose, observed increased glycosuria, but found that a smaller part of this monosaccharid had passed unchanged into the urine. After 200 grams of levulose by the mouth the urine contained 105.6 grams of glucose and 15.6 grams of levulose. There were 7.8 grams of nitrogen, so that 21.84 grams (7.8×2.8) of glucose were derived from proteids. The rest—83.76 grams of glucose—was thus derived from the levulose.

Minkowski failed, after giving considerable amounts of maltose, saccharose, and lactose, to find any of these disaccharids in the urine unchanged, probably because the quantities were not large enough; in fact, none of them seems to have been given in as large amount as the levulose. The glycosuria was increased by all three of the disaccharids.

After extirpation of the pancreas the animals quickly lose flesh, sometimes in the course of a fortnight losing more than one-third of their bodily weight. This is a necessary effect of the deficient digestion and of the enormous glycosuria. Abelmann found 43 per cent. of fat ingested in emulsion, almost all other fat and 56 per cent. of ingested proteid in the feces, which also contained large quantities of undigested bread. Kaufmann found that diabetic dogs of from 8 to 15 kilograms in weight, subjected to absolute starvation, lost from 250 to 500 grams in weight a day, while normal dogs of the same size under similar circumstances lost only between 160 and 175 grams.

Glycosuria and impaired digestion, according to the opinion of

most investigators, are not the only causes of autophagy in these and in other cases of severe diabetes. A third cause is the almost universally accepted *protoplasmic*, *toxic* disintegration of the proteid cellular substances of the organism.

Minkowski failed in some cases after total extirpation of the pancreas to find diacetic acid and β-oxybutyric acid in the urine, both of which, so far as my experience goes, are constantly found in equally severe cases in man. Further investigations in this respect seem necessary, but it is possible that the production of these acids, which certainly are in some way connected with the excretion of glucose produced by proteids, is governed by other conditions in the dog than in human beings. The diabetic animals completely oxidize ingested acetone (Schwarz), but the ingestion of diacetic acid (Schwarz) and of β-oxybutyric acid (Minkowski) is followed by acetonuria.

The lactic acid in the muscles was found to be greatly diminished. The glycogen was also greatly reduced in the liver and in the muscles—probably on account of the acidosis, which in most cases was quite pronounced. Syzygium jambulanum had no decreasing effect upon the glycosuria.

The diabetes following extirpation of the pancreas is a direct effect of the removal of the gland. It does not result from the absence of the pancreatic juice, for ligation of the pancreatic duct or the production of a fistula through which the juice is conducted outside the organism causes no diabetes. Neither does the dystrophy result from a lesion of the solar plexus, as has been supposed. Minkowski proved this theory to be false by leaving a part of the pancreas in connection with its vessels outside the peritoneal cavity under the skin, without the development of diabetes, while subsequent removal of this remaining piece of pancreas was followed by the customary diabetes.

Either the removal of the pancreas causes something to disappear from the blood that is necessary for the normal combustion and utilization of the sugar, or it causes something to remain in the blood that prevents the combustion and utilization of sugar.

It has been proved that injection of diabetic blood into the veins of a healthy animal does not produce even transitory diabetes. On

the other hand, it was shown by Claude Bernard that the normal blood contains something that causes the sugar in it to disappear after it has been for some time outside the organism. These facts have led many to the acceptance of a theory that extirpation of the pancreas causes diabetes by removing something that is produced in the pancreas as an "internal" secretion and is given up to the blood, where its presence is necessary for the combustion of the sugar. Lépine and his disciples, and even some of his antagonists, found that the blood of dogs, diabetic after extirpation of the pancreas, both within and without the organism, loses its sugar less quickly than does normal blood. Kausch saw an analogous phenomenon in birds. Schwarz found that, though dogs after extirpation of the pancreas seem to oxidize as large amounts of acetone as normal dogs, the former, diabetic dogs, unlike normal dogs, after ingestion of diacetic acid exhibited acetonuria. All this has strengthened the position of those who consider diabetes an effect of decreased consumption of sugar. In the next chapter we shall find that, even if these observations are correct, they alone do not settle the question of the immediate causes of diabetes—a question the solution of which is one of the most difficult and complicated tasks that are at present engaging the attention of students of experimental pathology.

CHAPTER VII.—METABOLISM AND NUTRITIVE NEEDS.

Notwithstanding the progressive strides that have been made in recent years, the metabolic changes that take place in diabetes are but imperfectly known.

By following as well as we can the carbohydrates, the fat, and the proteids on their way through the organism we may, however, obtain a conception of the respective processes, which is not without considerable theoretic and practical value. In doing this we must not omit to give some attention to corresponding processes in normal organisms; neither must we lose sight of the differences

between cases of mild and severe diabetes—*i. e.*, between the patient that excretes sugar only after ingestion of carbohydrates and the one that exhibits glycosuria at the expense of proteids, and with a diet consisting exclusively of these and of fat.

We have already seen that in the great majority of diabetic cases digestion is perfectly normal. In such cases Pautz recently found 7.59 per cent. loss of nitrogen and 3.54 per cent. loss of fat. The maximum and minimum figures for nitrogen were 12.97 and 1.74; for fat they were 9.12 and 1.06—*i. e.*, just about what we are accustomed to see designated as normal. As to carbohydrates, Heller, as early as 1852, showed that they are, as a rule, normally digested in cases of diabetes, and Hirschfeld's cases prove that this often takes place, even when digestion of proteids and fat is impaired. Of ingested starch, normally from 1 to 7.4 per cent. appears undigested in the feces.

The normal changes that carbohydrates undergo in the alimentary canal must be borne in mind. Starch (or glycogen) digested by the mixed saliva (or by the secretion of the parotid gland alone) yields achroodextrin and maltose* and only small quantities of glucose (Musculus and v. Mering, Külz). The diastatic ferment found in the stomach in the acid gastric juice is not very active; but in the duodenum the pancreatic juice is most efficient in the same way as the saliva. The final products, however, of the digested starch, found almost entirely in the portal system and only in comparatively minute quantities in the lymphatics, consist almost exclusively of glucose, together with some traces of dextrin and maltose (C. Voit, Bleile, v. Mering), whether this result has been brought about by the "invertin" from the mucous membrane of the bowels (Tebb), or by the epithelium itself (Bunge), or by the blood (Bial, Röhmann).

Cane-sugar partly is decomposed into glucose and levulose, partly remains unchanged in the stomach, and is so far absorbed in this state; in the duodenum this part of the disaccharid is also quickly decomposed into its monosaccharid, levulose, and glucose by the pancreatic juice (Köbner). When taken in large amounts like all saccharids it remains unchanged for some small part as cane-sugar, not only in the bowels, but in its passage through the whole organism, and it is found as such in the urine.

Maltose probably is already changed in the bowels into glucose (Voit).

Lactose, so far as it is not changed into lactic acid, etc., probably remains in large part unchanged in the alimentary canal (Lusk); the different results of numerous researches seem to me to indicate great individual and accidental

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* *Disaccharids* and *Monosaccharids*. Maltose = glucose + glucose. Cane-sugar = glucose + levulose. Lactose = glucose + galactose (Hammarsten).

variations. Lactose passes unchanged into the urine after smaller amounts are taken than do the other saccharids (G. Voit, Bischoff, Hofmeister, and others), and does often so during lactation.

In chickens and rabbits levulose seems to be absorbed in an unchanged state (Fr. Voit, Lusk, Otto). Like all other saccharids, it passes partly unchanged into the urine after large amounts have been taken.

Cane-sugar and maltose are in larger part (70 or 80 per cent.) absorbed during the first hour after ingestion. Glucose seems to remain a little longer, but lactose a less time in the stomach.

These results are gained chiefly in dogs whose food and digestion are similar to man's. Still, there seem to be differences, and normal dogs seem to excrete glucose after the ingestion of large amounts of cane-sugar, which is not the case with man. Rubner, by feeding dogs with cane-sugar exclusively, found almost only this disaccharid in the urine on the first day, but afterward gradually more and more glucose. Seegen found in dogs after the ingestion of cane-sugar this saccharid in part in its unchanged state, in part as invert-sugar (= glucose + levulose), while Praussnitz made the same observation in chickens.

Lusk obtained the following results six and one-half hours after the ingestion of 30 grams of cane-sugar by rabbits:

	Cane-sugar.	Glucose.	Levulose.
Stomach, ...	0.269	1.498	0.858
Duodenum and jejunum, . .	0.002	Traces.	Traces.
Cecum, ...	0.	0.846	1.321
Colon and rectum, ...	0.	Small amounts.	Small amounts.

With regard to the digestion of fat it must be remembered that during an abundant supply of easily digestible quality, often only 1.5 per cent., rarely more than from 4 to 6 per cent., is lost; that fat with a low-melting temperature is absorbed better and more quickly than fat with a high-melting temperature (Müller and Arnschink); that the presence of free fatty acids facilitates absorption, in which process both bile and the pancreatic juice are of great importance, if the fat is not ingested in a state of emulsion (Levin, Buchheim); that a mixed diet promotes absorption, though the most advantageous relation in the quantities of the different kinds of food has not yet been determined (Rosenheim, Munk). Finally, it is known that catarrhal conditions first impair the absorption of fat, while proteids and carbohydrates still continue to be absorbed normally (Fr. Müller). Individual and accidental circumstances have a great influence even under normal conditions.

We shall here entirely pass over the highly complicated chemic processes by which the ingested proteids are converted ultimately into albumoses and peptones, as well as the manner in which these substances are absorbed in consequence of the specific cellular activity of the mucous membrane. There are

in this respect no known or even suspected differences between the diabetic and the normal individual, nor in the processes by which the albumoses and the peptones are again changed into true albumin in its different modifications. According to differences in the quality of the food, from 3 to 5, or from 6 to 10 per cent., or even more, of the proteids may normally remain undigested in the intestines (Rubner). During the passage of proteids through the alimentary canal there are formed, as is known, many substances that are not proteids (leucin, tyrosin, tryptophan, amido-acids, asparagic acid); in the colon and rectum are found a whole series of "aromatic" substances and other products of putrefaction (indol, skatol, parakresol, phenol, phenyl-propionic acid, phenyl-acetic acid, paraoxyphenyl-acetic acid, hydroparacumaric acid, free fatty acids, carbonic acid, marsh-gas, hydrogen sulphid, etc.). Often secreting a smaller amount of bile than normal, and partaking of food rich in proteids and often suffering from habitual constipation, which allows of a longer period for putrefactive process, diabetics are likely to produce large quantities of the aromatic substances mentioned. In consequence their urine usually contains large quantities of "ethereal" combined sulphates resulting from the oxidation of the "aromatic" substances.*

When with an ordinary diet the ingested carbohydrate, changed into glucose (together with some small quantities of dextrin, maltose, and perhaps still other carbohydrates), is carried by the blood in the portal vein to the liver, it there forms the anhydrid of glucose or glycogen,† and to this most important substance we must devote a good deal of attention.

It seems certain that not *all* the glucose carried by the portal vein to the liver is, under all circumstances or at once, transformed into

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* The phenols, skatol, and indol are oxidized in the organism and pass into the urine as indoxyl-sulphuric and skatoxyl-sulphuric acids. The quantity of these and other ethereal sulphates normally equals about 0.25 gram a day, and bears a ratio to the sulphuric acid of the sulphates of 1 : 10 (from 1 : 15 up to 1 : 67).

† Glycogen, as is well known, is a polysaccharid closely related to starch; its formula probably is $6(C_6H_{10}O_5) + H_2O$ (Külz). Under the influence of dilute acids it is entirely changed into the monosaccharid glucose; saliva and pancreatic juice transform it into achroodextrin, maltose, and small quantities of glucose. In the cells of the liver glycogen is uniformly diffused in small granules embedded in larger granules of the so-called paraplasm (Kupfer), an imperfectly known substance, probably representing a form intermediate between glycogen and its mother-substances. The muscles constitute the other important repository of glycogen, containing about as much as the liver; it is present in the interfibrillary substance (Frerichs). From whatever substance glycogen is formed it is itself completely homogeneous (Salomon, Luchsinger, Otto). Still, there is some difference between the glycogen of the liver, which is colored brownish-red by tincture of iodin, and the glycogen of the muscles, which with the same tincture develops rather a violet color.

glycogen. After the ingestion of large amounts of glucose even normal individuals excrete some glucose in the urine. Under ordinary and normal circumstances a considerable part of the glucose may also pass through the liver and be either used immediately in the tissues or stored as glycogen in the muscles or elsewhere, or it may return to the liver and be stored there after having passed through the whole circulation. It is certain that the glycogen in the liver continues increasing for a much longer time after the ingestion of carbohydrate than the glucose needs to pass through the whole organism. After the ingestion of a large amount of glucose the glycosuria appears within thirty or forty minutes; after the ingestion of syrup the maximum amount of glycogen in the liver is reached (in rabbits) only after from sixteen to twenty hours (Külz). After the ingestion of small amounts six hours, and after the ingestion of large amounts from twelve to sixteen hours, elapse before this maximum is reached in chickens (Hergenhahn). The liver generally stores its maximum long before the muscles acquire theirs; after the ingestion of very large amounts, however, the glycogen is stored about as quickly by the latter as by the liver (Hergenhahn).

Glycogen is formed in the liver from both carbohydrates and proteids, and its amount can be maintained or increased there by many different substances. Glucose and levulose (or starch) yield the highest values, up to 20 per cent. or even more. Those saccharids that do not ferment with yeast do not yield more than a small percentage.

The researches on the formation of glycogen, since its discovery in 1857, already represent an enormous amount of work, and the subject certainly will be the object of further investigation. The experiments consist in subjecting the animals to starvation until the glycogen is supposed to be wholly consumed, in feeding them afterward with the substance in question, and, finally, in determining the quantity of glycogen in the liver.

Bernard proved that both carbohydrates and proteids—*i. e.*, meat and fibrin—produce glycogen, Woroschiloff that the latter is formed from glue. [That carbohydrates are formed from proteids can be demonstrated to any one who does not accept their formation from fat by the fact that diabetics in the severe stage continue for months to excrete more glucose than can possibly be made up by the carbohydrates in their food.] Külz's "Beiträge zur Kenntniss des Glycogens," Marburg, 1891, contains a good exposition of what has been done in this connection by Bernard, Stokvis, MacDonnell, Tcherinoff, Hoppe,

Doch, Weiss, Luchsinger, Naunyn, Nencki, Wolfberg, v. Mering, Finn, Pflüger, Hergenhahn, Nebelthau, and by Külz himself, who fed chickens with muscle, fibrin, casein, serum-albumin, and egg-albumin. The last-named thus, beyond a doubt, proved that these substances yielded from 1 to 2.5 per cent. of glycogen in the liver. Pavy (in rabbits) with starch and cane-sugar succeeded in depositing 27.6 per cent. of glycogen in the liver; with starch, cane-sugar, and albumin the amount was 17 per cent. Meat yielded at the utmost 7 per cent., gum-arabic 9 per cent., gelatin traces, and olive oil also only traces (probably remaining from before the experiment). MacDonnell's, Tcherinoff's, and Seegen's experiments led to similar results. Seegen besides found 1.67 per cent. of glycogen in the liver of dogs after eight days without food, and after feeding the animals during the following eight days exclusively on fat in large quantities he found 0.93 per cent. Külz, in chickens fed with cane-sugar, found 8.24 per cent.; with glucose 6.63 per cent.; with levulose 6.07 per cent.; with galactose 3.28 per cent., and with lactose 2.32 per cent. of glycogen in the liver. Kausch and Socin (1898) have found as much as 9 per cent. with lactose.

It will thus be seen that the power of the different saccharids to form glycogen in the liver in normal individuals does not bear any relation to their power of causing glycosuria in diabetics. Glucose and levulose normally yield about the same amount of glycogen, but glucose causes much greater glycosuria in diabetes than does levulose. The glycogen in the liver in diabetics again is increased in much greater degree by levulose than by glucose (Sandmeyer)—a quality of the levulose, which presumably is the cause for its producing less glycosuria in such individuals. The more easily a saccharid undergoes fermentation the more glycogen it forms normally, according to C. Voit; the less it normally passes into the urine, according to Cremer; and the better it forms fat, according to Liebig.

It is in many respects interesting to learn the effect of subcutaneous injections of different saccharids. Fritz Voit, in 1896, made such injections (of ten per cent. solutions) of monosaccharids: levulose, galactose, and glucose; and of the disaccharids: maltose, lactose, and cane-sugar. All of the monosaccharids were completely consumed in the tissues even after the injections of considerable amounts. After the injection of large amounts a small quantity appeared unchanged in the urine. Thus, the injection of 60 grams of glucose yielded a trace of glucose in the urine, while the injection of 100 grams yielded 2.6 grams of glucose in the urine. Maltose, too, was readily consumed. The disaccharids, cane-sugar and lactose, however, were not consumed, and passed almost com-

pletely through the organism, and appeared unchanged in the urine. Only the monosaccharids and the disaccharid, maltose, whose molecules are believed to consist of two molecules of glucose, seem to form glycogen without being first changed. Cane-sugar can be stored as glycogen in the liver only after being converted into glucose and levulose, lactose only after being converted into glucose and galactose.

Besides the substances already mentioned, Külz found that the following substances also have some power of maintaining glycogen in the liver: Raffinose, glycerin, gum-arabic, sorbin, ethylene, glycol, erythrite, dulcite, mannite, inosite, saccharin, isosaccharin, dextronic acid, saccharic acid, mucic acid, glycuronic acid, calcium dextronate, sodium tartrate, and citrate. Urea also yielded glycogen. Inulin yielded small quantities and olive-oil traces. Nebelthau found some power of maintaining glycogen in the liver in ammonium citrate carbonate, lactate, and formate in benzamid and formamid, in glycocolla and asparagin, in antipyrin, cairin, quinin, and chloral, chloramid, paraldehyd, and sulphonal. Ether, chloroform, and alcohol seemed somewhat efficient, while urethan yielded a dubious result. Cremer found that some glycogen formed after use of the pentoses * (xylose, arabinose, and rhamnose); Salkowski also found some after use of arabinose; Fræntzel obtained a completely negative result from xylose.

From the foregoing it will be understood that glycogen can be formed or maintained in the liver in many different ways. From glucose it is formed by dehydration, a comparatively large amount resulting. Lactose forms glycogen only indirectly, after having been divided into its monosaccharids; but though a large part of the ingested lactose may have been changed into lactic acid before this happens, the rest usually gives rise to the presence of quite considerable quantities of glycogen in the liver (Kausch and Socin). Olive-oil and other fatty substances, which are believed to maintain the glycogen in the liver only by undergoing oxidation themselves, seem to afford very little protection for it. As for the power of antipyrin to maintain glycogen in the liver, this must be derived

* The pentoses do not seem to promise the diabetic patient anything. Ebstein found arabinose and xylose unchanged in the urine after quite small doses. Lindemann and May found about eight per cent. of rhamnose unchanged in the urine of normal individuals. Sixty-five grams of rhamnose caused some glycosuria in a diabetic patient previously free from it; besides 7.27 grams of rhamnose appeared in the urine and 2.85 grams in the feces. Rhamnose is suspected of having no wholesome influence on the kidneys.

from some specific influence, and can result neither from direct formation nor from oxidation.

The glycogen in the muscles is formed in and by the muscles themselves from the sugar of the blood. It may, perhaps, be furnished to them also to some small extent as glycogen. Böhm and Hoffmann found 0.4 per cent. in the cat; Hasse between 0.4 and 0.9 per cent. in dogs, cats, and rabbits. Külz considered these figures somewhat too small.

The glycogen in the liver and the glycogen in the muscles are, under ordinary circumstances, about equal in amount, and together make up the organism's whole store of this substance, except a comparatively insignificant amount in other tissues. The storage in the liver and the storage in the muscles depend on the same influences, and are both increased or decreased by the same causes. The glycogen of the muscles manifests greater stability, and is slower both in increasing and in decreasing. Heat increases the glycogen, and rest has the same influence. By severing the central from the peripheral nervous system glycogen is stored in great quantity, partly on account of the paralysis of the muscles, partly, perhaps, on account of the withdrawal of other nervous influences (Claude Bernard, Nebelthau). Cold diminishes the amount of glycogen and is capable of causing its disappearance from both liver and muscles in thirty hours (Böhm and Hoffmann). Mechanical work is most effective in the same direction. Weiss found only about half as much glycogen in tetanized muscle as in the corresponding muscle at rest. Chauveau and Kaufmann had a similar experience. Rosenbaum, Demant, and Hergenhahn saw the glycogen almost totally disappear during the convulsions from poisoning with strychnin; and Külz found the glycogen in both its great storehouses reduced to a minimum after a short period of starvation and hard work combined. Starvation decreases the glycogen. Külz, however, still found traces of it in the liver and somewhat more in the muscles of the dog after twenty days of abstinence from food. After extirpation of the liver the glycogen suddenly decreases in the muscles (Laves). Acids in the blood decrease and alkaline salts increase the amount of glycogen (Külz). After ligature of the choledoch duct with biliary stasis the glycogen disappears from the liver and is not formed again (Frerichs, Wick-

ham Legg). After death glycogen disappears from the liver and (somewhat more slowly) from the muscles. Praussnitz, after only half an hour, found 75 per cent. of the original amount. Werther, after three hours, found scarcely anything left. This change takes place more quickly in a warm than in a cold room.

In the blood the glycogen is found in the leukocytes ; a liter contains only about 0.01 gram (Huppert). The lymphatics also contain a small quantity (Frerichs). Glycogen has besides been found in the skin (Paschutin), in the hair-bulbs (Neisser), in the kidneys (Wiersma, Paschutin, Abeles, Ehrlich), in the spleen (Hoppe-Seyler), in the lungs (Abeles), in the testicles (Kühne), and in new growths (Hoppe-Seyler, Brault). It seems to occur especially in inflamed tissues (Sotniskewski, Pavy, Kühne), and during this state it has also been found in the brain (Paschutin), where it does not seem to be found normally (Abeles, Seegen, Kratschmer, Paschutin). Finally, it is much more abundant in embryonic than in fully developed tissues (Bernard). In view of this fact, and of the further fact that it is found especially in inflamed tissues and in tumors of rapid growth, it would seem to be indicative of a condition of energetic cellular life.

It may now be considered as settled that in cases of diabetes the amount of glycogen is diminished both in the liver and in the muscles. Frerichs, with admirable presence of mind, plunged a trocar into the liver of three submissive individuals, of whom one was in good health and the other two were diabetic. Although the stage of diabetes is not stated, it was probably an advanced one. It was found that between four and one-half and five and one-half hours after an abundant mixed meal the liver-cells of the healthy person contained a large amount of glycogen, while those of the two diabetics contained a moderate amount and a very small amount, respectively. Both the liver and the muscles of diabetic dogs contain little glycogen (v. Mering, Minkowski, Sandmeyer). Pieces of liver excised shortly after death in diabetic coma were found to contain very little glycogen (Frerichs) ; and it could not be found at all in the muscles of such patients (Abeles). The diabetic liver in a state of fatty degeneration seems to contain the smallest amount of glycogen (Boccardi).

I presume that if a diabetic in the mild stage and a healthy

person receive the same food with so much carbohydrates that the diabetic excretes sugar in his urine, the latter will store less glycogen than the healthy person, and the glycogen will thus never reach such high figures as are reached normally after the ingestion of large amounts of carbohydrates. If, however, both the diabetic and the healthy individual receive the same food with such restriction of carbohydrates as to render the diabetic free from glycosuria, both will probably store the same amount of glycogen. The diabetic patient in the severe stage always passes in the urine glucose derived from both the carbohydrates and the proteids of the food, and from this cause alone he possesses but a limited power of storing glycogen. In the severe stage, however, this power is besides weakened by the acidosis, or the presence in the blood of diacetic acid and β-oxybutyric acid.

At the same time that the amount of glycogen is diminished in the liver and in the muscles in cases of diabetes, it is increased in other parts and elements of the organism. Gabritschewski found much more marked reaction for glycogen in the leukocytes of diabetic blood than in those of normal blood; Minkowski observed the same fact in pus (0.83 per cent. in diabetics as against 0.23 per cent. in nondiabetics). The leukocytes partly have their own independent economy and store much glycogen from a hyperglycemic medium. The brain, in which glycogen is not normally found, contains this substance in cases of diabetes (see above). Ehrlich first demonstrated the deposition of glycogen in the epithelial elements of the kidneys. Leube found it twice in diabetic urine.*

The enormously important questions with regard to the metabolism of glycogen, and with regard to the origin and significance of the glucose in the liver, have given rise to a variety of opinions and have been the subject of much controversy. The technical difficulties in solving these problems experimentally are very great, and the human obstinacy in defending *per fas* and *nefas* a position once taken is still greater. Even to-day three different main currents of opinion may be recognized as represented by the names of Claude Bernard, Pavy, and Seegen. At present we are justified

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* Glycogen is besides found (in cases of diabetes) in the lungs, in the testicles (Grohe), pancreas, spleen (Abeles), in the heart, and in the cartilages (v. Mering, Ewald).

in saying that the theory advocated by Bernard has proved to be much the strongest, and that the vast amount of work performed since the fundamental discoveries of this great French physiologist and experimenter has tended to strengthen the opinion that if he has not demonstrated the whole truth he has certainly demonstrated the essential points of it. Pavy's theory, denying entirely the physiologic formation of glucose in the liver and its presence for purposes of vital power in the blood, almost everywhere belongs to the past. Seegen, who denies that the glucose of the liver and of the blood (whose vital importance for the organism he acknowledges) is formed from glycogen, and who considers it to be formed from proteids and from fat, has gained comparatively few adherents to this last view, in which he deviates from Claude Bernard.

Claude Bernard, in 1877, summed up his views on these subjects, his theory, confirmed and enlarged by later investigations, being as follows: The liver forms glycogen from (a part of) the carbohydrates and the proteids of the food, and afterward, from this glycogen, under the influence of a ferment and under the vasomotor regulation of the nervous system, forms glucose, which, according to the needs of the organism, it delivers to the blood, of which glucose is a most important ingredient. For the production of vital force the glucose is then oxidized in the tissues into carbonic acid and water. Recent investigations, leaving many questions as to the fate of glucose for solution in the future, seem to confirm Bernard's opinion that the glucose is led to complete combustion through the molecular structure of lactic acid (Kausch, Lang), and make it probable that another intermediate station between the glucose and its ultimate products, carbonic acid and water, is represented by the molecule of glycuronic acid (Weintraud). It has been proved and is universally accepted that fat is produced from the superfluous carbohydrates, and the seat of this process is believed to be the liver.

Of late, some persons, who may be considered authorities, have so far adopted Seegen's theory as to believe that, with a deficiency of proteids and carbohydrates, fat may give rise to the formation of glucose. It seems to me that the facts that plead for such a theory are much weaker than those that plead against it (see below).

The diastatic ferment in the liver, like all ferments not consisting of organisms, presents many mysterious points; Dastre goes

so far as to call it hypothetic. All attempts to isolate it—chiefly by precipitating it with alcohol after having extracted it from the liver with glycerin—have failed. Tiegl believes that it arises from the products of the disintegration of the red blood-corpuscles, while many believe it to be fixed to the living liver-cells.*

In a decoction of the liver and in the precipitate thrown down by absolute alcohol from such a decoction again dissolved in water, glucose is formed at ordinary temperature, which is not the case with a solution of pure glycogen (Schwiening). Bernard believed the variations in the production of glucose to depend on variations in the circulation, and these on nervous, vasomotor influences. Bial, who considers the diastatic ferment of the liver identical with the diastatic ferment of the muscles, believes both to belong to and depend on the lymph. The diastatic ferment in the liver and in the blood changes starch and dextrin and glycogen, not into maltose, but into glucose, and also converts maltose into glucose. In the embryo and in the new-born child these effects, which vary in different species of animals, are quite weak. Sodium carbonate and bicarbonate retard the effect of the diastatic ferment on glycogen (Gans).

The sugar in the liver has been produced in substance by Külz, has been proved to be glucose, and is present in the liver during life to the amount of from 0.2 to 0.5 per cent. (Bernard, Seegen).

After some knowledge on these subjects had been gained through earlier investigations, Claude Bernard, late in the forties, proved the constant presence of sugar in the blood, independently of the kind of food taken, and showed that it must be looked for shortly after the blood is obtained, as it soon decomposes. He showed that the sugar of the blood is formed in the liver, which always contains some, and that a piece of liver from which the sugar has been removed by washing soon again becomes sacchariferous. He explained this by the continued activity of the diastatic ferment constantly producing sugar, which increases when not removed by the circulation. When Pavy afterward considered this process to take place exclusively after death, Bernard (as Dalton, Seegen, and others have done after him) showed that the liver during life also contained sugar, the quantity of which he (by somewhat too low an estimate) placed at 0.24 per cent.

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*Arthus and Hubner, however, have shown that a solution of fluorin (1 : 100), which destroys cellular life, does not prevent the formation of glucose in pieces of liver. Schwiening believes that the proteids play some special rôle in the formation of glucose in the liver.

Nearly ten years afterward Claude Bernard and Hensen discovered the glycogen, determined its nature, and proved that it could be formed both from proteids and from carbohydrates. Bernard showed also that, if the liver is separated from the circulation, the sugar disappears from the blood—a fact afterward corroborated by Bock and Hoffmann and by v. Mering. Bernard found, moreover, that the veins issuing from the liver and the inferior vena cava usually contain more sugar than the portal vein. On finding more sugar in the inferior vena cava than in the carotid artery, he first concluded that the sugar is consumed in the lungs, but, always ready to be corrected by facts, he, after Chauveau's investigations, and after having himself found more sugar in the arteries than in the collateral veins, expressed the opinion that this consumption takes place in the tissues of the whole organism. Bernard showed that the sugar of the blood usually undergoes only slight variations in quantity, that it is somewhat increased after generous meals, that it gradually diminishes on starvation and in the febrile state, and that it disappears from the blood outside the organism in about twenty-four hours. Finally, Bernard found glycosuria after lesions of the brain in the floor of the fourth ventricle, made investigations concerning hyperglycemia in diabetes, and showed that glycosuria in the dog begins when the sugar in the blood reaches from 0.25 to 0.30 per cent.

At about the same time Lehmann found traces of sugar in the portal vein, and determinable quantities of it in the veins issuing from the liver (horse).

C. Schmidt, in 1850, without a knowledge of the results of Bernard's investigations, found sugar in the blood of cows, dogs, and cats.

Chauveau, partly alone and partly in conjunction with Kaufmann, has, since 1856, contributed more than any one else to the confirmation of Bernard's theories. After extensive and numerous experiments he came to the conclusion that the sugar in the blood is derived from the liver, that it is always present, and even after long-continued starvation does not entirely disappear ; that the arteries contain more sugar than the collateral veins, and that all divisions of the circulatory system contain about the same amount, except the veins issuing from the liver and the inferior vena cava, which are more saccharifer-ous, and the portal vein, which (except after the ingestion of large amounts of carbohydrates) is less saccharifer ous than other vessels.

Subsequently, Böhm and Hoffmann, Bock and Hoffmann, Bleile, Külz, Lusk, v. Mering, Ewald, Otto, Barral, Lépine, and others made investigations which have corroborated Bernard's results.

Pavy, one of Bernard's own disciples, began at the close of the fifties his opposition to this greatest of French experimenters. Pavy found that the blood from the right heart of a living dog contained much less sugar than after death—an observation that is certainly correct, and is dependent on the fact that when the circulation gradually ceases, the districts next to the liver, where the formation of sugar continues even some time after death, become more saccharifer ous. Pavy found also that bits of liver obtained from living animals and thrown into boiling water or subjected to freezing contained only small quantities of sugar, while, when exposed to ordinary temperature, they contained much larger quantities. This is also true, partly, perhaps, because the

liver-cells of living animals produce, and the dead liver-cells do not produce, sugar, and partly because excessive temperatures diminish the influence of the diastatic ferment. Pavy concluded from these observations that the production of sugar in the liver is a portmortem phenomenon, and that in life the sugar passes through the liver only under pathologic conditions, as in diabetes or after certain lesions, probably in consequence of a vasomotor neurosis which leads to congestion of the liver with blood that has not entirely lost its arterial qualities. This sugar, then, may come from the glucose formed normally by ingested carbohydrates or from the glycogen, which customarily produces fat. Even Pavy has been forced to acknowledge the presence of sugar in the blood under ordinary conditions, but he believes it to be there only in insignificant traces and for no physiologic purpose, admitted, as it were, by some defect in the functions of the liver, escaping again through the kidneys as a trace of sugar in the urine. Pavy's views have now only historic and personal interest, and are strenuously opposed even in Great Britain (*e. g.*, by Dr. Noel Paton [1898]). For many years, however, they exercised considerable influence. Among Pavy's adherents were Schiff, Meissner, Ritter, MacDonnell, and (as late as 1876) Lussanna.

Seegen also was at first an adherent of this view. Then having found (with Kratschmer) that diastatic ferment in saliva and in the pancreatic juice does not change glycogen into glucose, but into another saccharid, which Musculus and v. Mering showed to be maltose, and finding in the liver no other substance capable of saccharifying the glycogen, he began to doubt that it was the source of the glucose. In a series of experiments he sought and believed that he had found that the glucose must be derived from other substances than glycogen. He found the glucose to increase in bits of liver before the glycogen began to decrease. Investigations on this subject, however, by Böhm and Hoffmann, Girard, Chittenden and Lambert, Bial, Butte, and Montuori have not corroborated Seegen's results. Seegen, by various experiments, for which I must refer to his own works, believed also that he had proved the formation of glucose in the liver from peptone, a process which Lépine considers to take place throughout the whole organism. Hofmeister, Chittenden, Lambert, Neumeister, and Bial have also on this point arrayed themselves against Seegen, and arrived at other conclusions. Seegen believed, further, that he had found in 70 cases the blood of the hepatic veins always more sacchariferous than the blood of the portal vein, and he somewhat irrationally considered this a proof of the correctness of his views. In this also he has powerful opponents; both Bernard's and v. Mering's observations tend to show that after the ingestion of large amounts of carbohydrates the portal vein may contain a much higher percentage (up to 0.4 per cent.) than the hepatic veins or the inferior vena cava.

It must be remembered that we here have usually to do with small differences. Max Mosse found 0.107 per cent. in the hepatic veins and 0.093 per cent. in the femoral artery, which, according to Seegen, contains only slightly more than the portal vein. Mosse and others are in all probability right when they maintain that the high percentage of glucose sometimes found in the blood just coming from the liver is partly due to the sufferings of the animal

during the experiment. Seegen finally remarks that, while glycogen is driven out of the liver by starvation, the sugar of the blood remains in unchanged quantity. This is decidedly wrong. Claude Bernard, Böhm and Hoffmann, and Otto all have shown that prolonged starvation does decrease, though slowly, the sugar of the blood; and, on the other hand, Külz has shown that even starvation for twenty days does not fully free either liver or muscles from glycogen. Seegen, however, is determined to adhere to his opinion that glycogen does not form glucose, but fat, and that the liver for purposes of vital energy produces glucose from fat and proteids. At the same time that Seegen denies the formation of glucose from the glycogen of the liver he accepts such a formation from the glycogen of the muscles. This surely appears a rather far-fetched theory, and the presumed facts on which it is based have not been established, nor would they necessarily lead to Seegen's conclusions even if they were so; but, according to the strongest evidence, some of them are false. Naturalists will not, without convincing proofs, believe that nature should form exclusively fat from carbohydrates, and at the same time and in the same organ should form carbohydrates from fat; and even those who believe that fat may form glucose under certain circumstances are far from accepting Seegen's views, which now, like Pavy's, may be considered to be a matter of history.

We now have acquired a right to consider the liver as the main sugar-producing organ of the body, and to look upon the sugar of the liver, which is identical with the sugar of the blood, as derived from the glycogen. We have seen that the sugar of the blood usually is most abundant in the vessels leaving the liver, and that it decreases and disappears if the liver is cut off from the circulation. We have seen also that, when the sugar increases in portions of liver, there is a corresponding decrease in glycogen. This fact may be demonstrated experimentally even during life by irritation of the celiac plexus or the sympathetic nerves of the liver, which produces an immediate increase in the amount of sugar with a corresponding decrease in the amount of glycogen (Chauveau, Cavazzani and Butte, Morat and Dufour). Marcuse has lately shown that the diabetes that is constantly caused also in frogs by extirpation of the pancreas is prevented by previous extirpation of the liver. Finally, we know that phloridzin, which causes the sugar of the blood to pass into the urine without hyperglycemia in consequence of changes in the kidneys, and causes a constant and rapid reproduction of glucose, decreases the glycogen, and that diabetes following the extirpation of the pancreas, with the consequent enormous losses of glucose, has the same effect.

Generally, glycogen is believed to represent fixed, stored-up potential energy, which, whenever it is found, may be changed into glucose, representing potential energy in solution ready to be transformed into vital force.

So far, so good; but what about the important questions that next present themselves?

Does all transformation into vital force necessarily pass through the molecular structure of glucose, or may proteids and fat be used unchanged for this purpose?

Can glucose be formed from proteids anywhere else than in the liver?

Can glucose be formed at all from fat?

Can carbohydrates and, perhaps, fat contribute to a possible synthetic formation of proteids?

Where and how are the molecules of fat attacked and disintegrated?

It appears to me, unfortunately unable to form an opinion on these subjects, but, from the researches of others, that we can at present not give much more definitive answers to these questions than we could in the beginning of the last decad of the nineteenth century.

Chauveau has recently formulated his own conclusions from extensive researches on the transformation of force within the organism. These conclusions, in a somewhat abbreviated form, are as follows:

1. All vital force within the organism is produced by oxidation.

2. The potential energy is always in the ultimate stage represented by carbohydrates.

3. During starvation carbohydrates are constantly formed also by a rudimentary oxidation of fats.

4. Oxidation of proteids never directly contributes to the production of vital force; or, in other words, mechanical work does not increase the amount of nitrogen in the urine.

Unfortunately, there are still various opinions with regard to each of these conclusions. Munk, Zuntz, and others think it still doubtful that all vital force is produced by oxidation. We know, especially from the researches of Zuntz, that mechanical work in some way may be sustained by fat and by proteids, as well as by

carbohydrates, and Newton Heyneman's experiments prove also, by the figures of the respiratory quotient, that the kind of food chiefly ingested, be it proteids, fat, or carbohydrates, is also chiefly used for the production of mechanical force.

The power of the organism to produce carbohydrates from fats is exceedingly doubtful. Something may be said in favor of the existence of such a power, but it seems to me that still much more may be said against it. The chief reason—apart from the much opposed results of Seegen's experiments—for believing in the formation of glycogen or glucose from fats depends on the highly uncertain theory that muscles can not use fats as fuel for their work. It has been demonstrated that with a scanty supply of carbohydrates the quantity of proteids and carbohydrates consumed does not always cover the expense of the mechanical work performed. The formation of carbohydrates from fats in vegetable cells constitutes absolutely no reason for admitting such a formation in animal cells. Any one who has at all occupied himself with the physiology of plants knows what an enormous metabolic difference there is between animals and plants. The clinician, who constantly finds that he may increase the butter in the food of his diabetic patients to any ingestible quantity in any stage of diabetes and under any diet, without any perceptible increase of the amount of glucose in the urine, will have strong doubts as to the formation of carbohydrates from fats even with a deficient supply of carbohydrates ; and, however much it may be repeated from some quarters that the sugar of the blood remains at par during feeding with fats alone, Seegen's* own figures show that the sugar of the blood, after having diminished during starvation continues to do so during subsequent feeding exclusively on fats. Von Mering, Moritz and Praussnitz, Cremer and Ritter, and now (1898) Kumagawa and Miura alike consider that during phloridzin-poisoning, with its enormous loss of glucose, fats do not give rise to carbohydrates.

Chauveau has been led to his conclusions as to the ability of the organism to produce carbohydrates from fats chiefly by his own and by Regnault's and

* Among authorities now living, so far as I know, only Seegen, v. Noorden, Bunge, Chauveau and Kaufmann, and Weiss accept the formation of carbohydrates from fats in man.

Reiset's investigations on the marmot. This animal, when subjected to starvation in summer, dies after the loss of between 95 per cent. and 97 per cent. of its fat, and then has scarcely any carbohydrate at all left in liver, muscles, or blood. After hibernation the marmot has used up its fat, but the blood still contains glucose and the liver and muscles contain glycogen. Chauveau asks how this could be, after such a time of continued abstinence from food, with considerable expenditure for heat and circulation, if the carbohydrates (glycogen and glucose) had not been formed from fat. Then Regnault and Reiset had observed that the marmot may, during its sleep in hibernation, *increase* in weight, and that it consumes considerably more oxygen than it expires in carbonic acid, and Chauveau thinks that the fat has been changed into glucose by oxidation according to the following equation:

$$\underset{\text{Stearin.}}{2C_{57}H_{110}O_6} + 67O_2 = \underset{\text{Glucose.}}{16C_6H_{12}O_6} + \underset{\text{Carbonic Acid.}}{18CO_2} + \underset{\text{Water.}}{14H_2O}.$$

The question whether proteids directly produce vital force is not to be answered at present. Voit, Brietske, Fick and Wislicenus, and others found no increase in the nitrogen of the urine after mechanical work. Pavy, Flint, Parkes, Argutinsky, Oppenheim, and others arrived at opposite results, and Zuntz, too, after his beautiful researches, has formed the opinion that proteids (and fats) may directly contribute to the formation of vital force.

Finally, it is not impossible that a part of the proteids so utilized is derived from carbohydrates. Pflüger, Schenk, and others admit a synthetic formation of proteids, as a station on the way to the final production of vital force, to which formation carbohydrates may contribute part of the nonnitrogenous constituents. So long as we do not know more than we do at present of the fate of the fats, we can not absolutely deny its participation in such a synthesis of proteids.

Until further information is forthcoming it must be admitted that proteids may form proteids, fats, and carbohydrates, that carbohydrates may form carbohydrates and fats, but that fats are not positively known to form anything but fat. On the other hand, we have no right to deny positively the formation under some circumstances of carbohydrates from fat; still less have we a right to deny the synthesis of proteids, in which both carbohydrates and fats may participate. . . .

The sugar of the blood is proved to be glucose, and is found in the serum.

The quantity of sugar in the blood varies normally from 0.10 to 0.15 per cent., and it may, perhaps, sometimes slightly exceed these limits in either direction. The veins contain somewhat less than the collateral arteries. The portal vein, except after the ingestion of large amounts of carbohydrate, contains less and the hepatic veins contain more than do other vascular areas. Unlike the glycogen of the liver, which varies enormously under different dietetic conditions, the amount of sugar in the blood normally undergoes but comparatively slight variations. It increases somewhat after the ingestion of large amounts of carbohydrate (Claude Bernard, v. Mering) and after copious hemorrhage (Edel, Schenk), and decreases during continued starvation (Bernard, Bock and Hoffmann, Otto, Seegen, Chauveau), during the febrile state, after extirpation of the liver, and as a result of poisoning with phloridzin. The quantity of sugar in the blood is about half of the quantity of fibrin, and the amount is not small considering that the sugar is being constantly produced and constantly consumed. Seegen calculates that a human being produces and consumes about 10 grams of glucose per kilogram of bodily weight in twenty-four hours. A German, Anglo-Saxon, or Scandinavian of ordinary size thus manufactures and uses up between 700 and 800 grams.

The sugar of the blood is consumed in the different tissues of the organism, but chiefly in the muscles; and by its oxidation into carbonic acid and water it forms the organism's largest, but probably not its only, source of vital power.

The sugar of the blood causes reduction of copper- and bismuth-solutions; undergoes fermentation, with the generation of alcohol, carbonic acid, etc.; forms with potassium a combination, out of which it may be driven by carbonic acid (Seegen, Ludwig, Abeles); deflects the ray of polarized light to the right (Ewald); and yields glycosazone with phenyl-hydrazin-chlorate and sodium acetate (Pickhardt). Thus, there is no doubt that it is glucose. To this rule there may, however, be rare exceptions; it seems probable that in cases in which the sugar in the urine is another saccharid—*e. g.*, levulose—the sugar of the blood is also constituted by this saccharid.

Otto proved the sugar of the blood to be contained in the serum by introducing in Hoppe-Seyler's equation for the valuation of blood-corpuscles from the quantity of plasma and fibrin (in two cases) the figures of the sugar instead of the figures of the fibrin, arriving at nearly the same figures as Hoppe-Seyler's equation gave. Calculating with the aid of Hoppe-Seyler's equation,

he found in one case 64.65 per cent. of plasma and 35.35 per cent. of red blood-corpuscles; and with his own equation he found the corresponding figures to be 64.29 and 35.71. In a second case the analogous figures were 67.88 and 32.12, and 67.96 and 32.04. The figures representing fibrin and sugar were as follows:

Cases.	Blood.		Plasma.	
	Fibrin.	Sugar.	Fibrin.	Sugar.
1, ...	0.205 per cent.	0.116 per cent.	0.317 per cent.	0.182 per cent.
2, ...	0.311 "	0.123 "	0.458 "	0.181 "

Naunyn states the normal quantity of sugar in the blood as about 0.1 per cent. —rather somewhat below (from 0.08 to 0.09) than above this figure; Bernard found between 0.09 and 0.117 per cent.; Seegen, between 0.12 and 0.19, and as an average in ten cases, nearly 0.17 per cent.; Otto, nearly 0.12 per cent.; v. Mering (in the serum), between 0.13 and 0.14 per cent.; Frerichs, between 0.12 and 0.30 (!!!) per cent. All of these figures refer to man. In the rabbit Otto found between 0.09 and 0.11 per cent.; Barral, in the dog, between 0.08 and 0.17 per cent.; Otto, in the dog, 0.11 per cent. The highest of these figures include not only the sugar, but all reducing-substances in the blood (kreatinin, uric acid, etc.), and thus represent too high a value for the glucose. Otto corrected this error, which, besides, shows a wrong relation between the quantity of sugar in the arteries and that in the veins, the reducing, nonsaccharine substances being present in greater quantity in the veins than in the arteries. Otto found in the dog, in blood from the femoral artery, a reduction before fermentation of 0.160 per cent., and after fermentation of 0.034 per cent., the amount of glucose thus equaling 0.126 per cent.; in blood from the femoral vein of the same dog a reduction before fermentation of 0.158 per cent., and after fermentation of 0.039 per cent., the amount of glucose thus equaling 0.119 per cent. (The blood was taken simultaneously from both vessels.) After hemorrhage the reduction is increased. Otto considered this to be an effect of the increase of nonsaccharine reducing-substances. Bernard had mentioned this increase as due to the presence of an increased amount of glucose, and Schenk,* in opposition to Otto, maintains that the whole increase is due to the presence of glucose.

The excess of glucose in the arteries over that in the veins is small; according to Otto, the proportion is 12 : 11; according to Barral, 100 : 92.7. As already mentioned, the hepatic veins generally contain most, and the portal vein least sugar of all vessels. The *great* difference, however, that has so often been found is *in part* the effect of a marked increase in the production of sugar in the liver from nervous causes during the experiment. Mosse, who arranged his experiments with a view to the elimination of this influence, found only

* "Pflüger's Archiv," 1894.

0.107 per cent. of glucose in the hepatic veins; the portal vein rarely contains less than 0.08 or 0.09 per cent. After the ingestion of large amounts of carbohydrate the portal vein may contain as much as 0.4 per cent., and much more than the hepatic veins (v. Mering).

The accompanying table, showing the results of Seegen's experiments, illustrates the influence of diet on the amount of glycogen in the liver and the amount of glucose in the blood. The figures representing the amount of glucose in the hepatic veins probably are much too high, from the influence of the experiment on the nerves; and all the figures relating to glucose in reality represent both glucose and other reducing-substances. Nevertheless, I consider the *relations* of this conscientious experimenter's figures to be of great value. The observations were made upon dogs that had been subjected to starvation for eight days, and were then fed exclusively on one of the several kinds of food named. I would call attention to the most important fact that both glucose and glycogen reach their lowest figures when the period of preliminary starvation is followed by a period in which the only food is fat.

Food.	Glucose.			Glycogen in Liver.
	Carotid.	Portal Vein.	Hepatic Vein.	
None,	0.157 per cent.	0.147 per cent.	0.269 per cent.	1.67 per cent.
Fat,	0.128 "	0.114 "	0.217 "	0.93 "
Muscle,	0.155 "	0.141 "	0.281 "	3.7 "
Starch,	0.165 "	0.147 "	0.261 "	6.0 "
Cane-sugar,	0.165 "	0.186 "	0.265 "	9.4 "
Cane-sugar and dextrin,	0.176 "	0.258 "	0.327 "	12.0 "

Chauveau and Kaufmann, in 1886, brought to light important facts in connection with the consumption of glucose in the muscles. They determined the amount of both carbonic acid and glucose in the blood from the masseter muscle and from the parotid gland, having previously made a corresponding analysis of the blood in the carotid. This artery supplies the muscle and the gland with about the same amount of blood, which in both is about three times as large during functional activity as during repose. During functional activity the muscle consumed about 5½ times as much glucose as the gland and produced about five times as much carbonic acid. The muscle in exercise produced about 3½ times as much carbonic acid as in repose, and also consumed about 3½ times as much glucose. With the gland, the figures during functional activity and in repose were as 87 : 60 with regard to the production of carbonic acid, and as 90 : 70 with regard to the consumption of glucose.

Quinquaud found from 0.12 to 0.15 per cent. of glucose in the femoral vein before, but only 0.07 per cent. after strong faradization.

As soon as the sugar in the blood reaches a certain amount, which Claude Bernard found to be about 0.25 per cent. in the dog,

it begins to pass over into the urine. Lépine, immediately after the beginning of the glycosuria in diabetic dogs (following extirpation of the pancreas), found between 0.19 and 0.24 per cent. of glucose in the blood. Seegen's figures indicate that glycosuria in man may exist with less glycemia than 0.20 per cent. Still, there seems to be a certain interval between the ordinary glycemia, which only rarely exceeds 0.15 per cent., and the decided hyperglycemia, in connection with which glycosuria begins. Thus, we find glycosuria often absent in states that bring about hyperglycemia—*e. g.*, asphyxia. Carcinoma is usually (Freund), though not constantly (Matrai), attended with hyperglycemia, but is often found without glycosuria. In cases of simple glycosuria only the highest degrees of glycemia give rise to glycosuria, which appears for only a short part of the day some time after meals. In cases of diabetes there is always hyperglycemia in the severe and often in the light stage. It rarely exceeds 0.4 per cent., but much higher figures are occasionally reached. Pavy found 0.57 and Hoppe-Seyler 0.9 per cent. of glucose in the blood. Investigations have proved that the glycosuria bears no fixed relation to hyperglycemia (Seegen, Lépine, and others). Seegen found 3.8 per cent. of sugar in the urine and 0.182 per cent. in the blood; and afterward, in the same (mild) case, 0.6 per cent. in the urine and 0.181 per cent. in the blood. In a severe case during the observance of a strict diet he found 0.6 per cent. in the urine and 0.19 per cent. in the blood. We thus see that the hyperglycemia, even with considerable glycosuria, may be quite moderate. Still, the hyperglycemia constitutes the real "*nocens*"—the sugar in the urine, which alone we are generally able to observe, is of small account. A moderate hyperglycemia, however, is certainly capable of only a moderate noxious influence. We are terrified on finding a glycosuria of 3.8 per cent. in a patient, but should be much less alarmed if told at the same time that it resulted from a hyperglycemia of only 0.18 per cent. Every one understands at once that if it is normal for the blood to contain 0.12 per cent., or even 0.15 per cent. of glucose, it does not constitute a very great danger for it to contain 0.18 per cent. of glucose.

I now arrive at that much-discussed question whether hyperglycemia and glycosuria—*i. e.*, diabetes mellitus—arise from an in-

creased production or from a decreased consumption of sugar, or from both of these causes.

The first essential difference in metabolism between the normal and the diabetic individual is met with in the liver, which exhibits a decreased capability of storing glycogen. The opinion is held by many that this deficiency of forming glycogen—which may afterward be used for producing fat, or, in case of need, may be left to the blood as glucose—is the immediate cause of diabetes. The liver is incapable either of keeping the formed glycogen in that state or of transforming enough of the glucose derived from the food into glycogen, and thus it produces or permits too large quantities of glucose to escape into the circulation. Claude Bernard believed the increased production of sugar in the liver to be a result of hyperemia and of the action of the diastatic ferment in the blood in attacking the glycogen too vigorously—"*l'augmentation de rapidité de la circulation du foie accroît la glycemie.*"

Others—*e. g.*, Zimmer—sought to find the root of the evil in the muscles and in an impaired consumption of the sugar of the blood. When in these latter days it was discovered that extirpation of the pancreas causes diabetes, and that extirpation of the thyroid gland causes myxedema, Brown-Séquard formulated the theory of an "internal" secretion of the glands in addition to that which had hitherto alone been observed. The profession, as already mentioned, for a large part adopted the view that the pancreas, through an internal secretion, sends into the blood some substance necessary to the combustion and the utilization of the sugar.

Claude Bernard was familiar with this "glycolytic ferment," or, as Nommès calls it, the "glycolysine." It is this ferment that drives the sugar out of the extravasated blood in about twenty-four hours. Bernard used acetic acid, carbolic acid, or sodium sulphate to prevent or retard this disappearance. Lépine has proposed as a unit of glycolytic power the relative quantity of sugar that disappears from the blood in one hour at a temperature of 38° C. (100.4° F.). The normal unit is about twenty per cent. of the whole amount. According to Lépine and Barral, the glycolytic power—which seems to be subject to great variations within the normal—is quite low at a temperature of 15° C. (66° F.), but it increases then for a while with the higher temperature, and is very

strong at 40° C. (104° F.). At 52° C. (125.6° F.) it suddenly decreases, and is annihilated at 54° C. (129.2° F.). Lépine and his disciples have made extensive researches upon the glycolytic ferment, which, according to that observer, is partly, but not exclusively, formed in the pancreas, and is delivered to the blood and the lymph; it is, further, chiefly, but not exclusively, fixed in the white blood-corpuscles. Spitzer found the glycolysis effected both by the red and the white blood-corpuscles. The process is one of oxidation, oxygen being taken up and carbonic acid produced (Kraus, Spitzer). Barral found that oxygen and ozone slightly increase, while rarefied air, carbonic acid, and carbon monoxid diminish the glycolytic power. Acidity also lessens and finally annihilates the glycolytic power. This is also the effect of antipyrin (Lépine and Barral, Brouardel and Loye), of sodium carbonate, of morphin, and of valerian (Butte). Colenbrander made the observation that the glycolysis is destroyed by the extract of leeches. Curare augments it somewhat (Butte). The glycolysis is about as energetic after as before defibrination (Dastre).

Lépine considers that there is a certain alternation between the "internal" secretion (of the glycolytic ferment) and the external secretion (of the pancreatic juice) in the pancreas. By irritation of the peripheral stump of the pneumogastric nerve Lépine caused increased secretion of pancreatic juice, and found that at the same time the blood from the pancreatic vein had almost entirely lost its glycolytic power, which afterward returned, when the external secretion had moderated.

After ligation of the pancreatic duct the glycolytic ferment in the blood is increased, probably as a result of pressure on the glandular cells in consequence of stasis.

In cases of diabetes the glycolytic ferment in the blood is markedly diminished, according to Lépine and many others; therefore less sugar is consumed in the tissues, and hyperglycemia, with its various consequences—*i. e.*, diabetes—arises.

Lépine and Metroz* found that in normal blood—at 37° C. (98.6° F.)—the sugar had decreased, as a result of glycolysis, from 0.13 per cent. to 0.10 per cent.; *i. e.*, the blood had lost

* "Compt. Rend.," 1893.

23 per cent. of its sugar. In diabetic blood under the same circumstances the glycolysis may bring down the sugar from 0.32 to 0.29 per cent., and the loss amounts to less than 10 per cent. Not only the relative, but also the absolute, loss of sugar is smaller in diabetic than in normal blood; but relative loss is the one to be taken into consideration. Lépine and Metroz have found that a liter of normal blood customarily loses in the course of an hour about 0.20 gram of sugar, but that an addition of glucose to this same blood may cause the loss, under otherwise the same circumstances, to amount to 0.60 gram.

Lépine observed chyle from the thoracic duct of a normal dog injected in the veins of a diabetic dog diminish for a short time the glycosuria. Lépine and Barral, by adding such chyle to a solution of glucose in water, also produced "glycolysis," with loss of glucose. They also found the normal difference between arterial and venous blood decreased in diabetes. By driving the blood through the extirpated kidney of a dog in Jacoby's apparatus they proved that loss of sugar takes place in the tissues independently of nervous influences.* For the details of the extensive researches of Lépine and his disciples I must refer to his own treatises.

Hédon also, by a series of investigations, has tried to establish a defective glycolysis in cases of diabetes and to exclude an increased production of sugar in the liver. He maintains that on separating the liver from the circulation the sugar disappears (by glycolysis) from normal, but not from diabetic, blood. Minkowski submits that this last fact may depend upon an abnormal transformation into glucose of the glycogen of the muscles. For other results of Hédon's researches also I must refer to the original communications.

Several experimenters, and especially Minkowski, have come to other conclusions than those of Lépine. Minkowski found the glycolysis in the blood of a diabetic dog to be quite normal, and he was not able to reduce the glycosuria by injections of glycolytic ferment or of pancreatic extract; he points out that the experiments with Jacoby's apparatus do not exclude postmortem changes—*Qui vivra, verra!*

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* Barral, "Sucre du Sang," Paris, 1890.

Lépine also mentions a "*pouvoir sacchariferant*" of the blood. While the "*pouvoir glycolytique*" ceases at 54° C. (129.2° F.), the saccharification, which is effected in the serum, is at its best at from 56° to 58° C. (132.8° to 136.4° F.), and gives rise to the production of about one gram of sugar to the kilogram of blood. The material for this production of glucose is, according to Lépine (*vide* Seegen), left by peptones. The "*pouvoir sacchariferant*," like the "*pouvoir glycolytique*," is increased by acute, but reduced by slow, asphyxia.

Lépine, while laying the greatest stress on reduced "glycolysis" and diminished consumption of sugar as a cause of diabetes, prudently does not deny an increased production of glucose as an additional cause. It is interesting to note Kaufmann's plea * for the view at which he and Chauveau have arrived as a result of numerous experiments. The production of sugar is, according to Kaufmann, like the oxidation in the lungs, a regulative function of *one* organ. The consumption of sugar, on the other hand, is a common quality of the different tissues, which consume sugar in order to be able to perform their functions, but which do not perform their functions for the purpose of consuming sugar. When a deviation from the normal takes place, it is more reasonable to look for the cause in the organ among whose functions is the production and distribution of sugar—*i. e.*, the liver—than in those organs that have only indirectly anything to do with the sugar. In hibernating animals, in spite of their comparatively profound muscular repose, one does not find hyperglycemia but hypoglycemia, and only when they return to muscular activity does the sugar in the blood reach its full amount. In this instance production is seen to depend on consumption. Chauveau and Kaufmann, in 1893, demonstrated the fact that the sugar increases in organs, especially in muscles, when they are occupied in their functions. By administering large amounts of glucose or by injections of glucose into the portal vein one may induce a glycosuria that manifestly has nothing to do with diminished consumption, but with the overstraining of the liver's capability of transforming and storing glucose in the form of glycogen. This capability is reduced in cirrhosis of the liver; this

* "Sem. Méd.," January 16, 1895.

is the cause of the frequency of glycosuria in connection with that disease. Kaufmann further calls attention to Dastre's view that in cases of asphyctic glycosuria the asphyctic blood causes an abnormally large production of sugar in the liver by stimulating the organ to increased activity. In the course of glycosuria due to other poisons (curare, morphin, and anesthetics in general) there is certainly a reduction in oxidation and in consumption; but the glycosuria is not caused by this, being often developed during the stage of excitement, before the decrease of oxidation and consumption; under these conditions also the glycosuria results from increased production. After Bernard's puncture, with the development of glycosuria the consumption of sugar is normal (Chauveau). In the course of glycosuria from irritation of peripheral nerves the animals are much excited and consumption is increased. After section of the spinal cord between the last cervical and the first dorsal vertebra Bernard found (after a transitory hyperglycemia from the operation *per se*), in spite of the lameness and reduced consumption, no hyperglycemia, but a decided *hypoglycemia*. The lowered temperature in cases of severe diabetes does not depend on the diabetes, but on the marasmus.

Chauveau and Kaufmann * accept a *combined* activity of the liver and the pancreas for the regulation of the glucose—economy of the organism, each organ having an inhibitory and a stimulating nervous center influencing its secretion. The medulla oblongata contains a stimulating center for the pancreas and an inhibitory center for the liver.† When the stimulating center for the pancreas becomes active, the internal secretion of the pancreas increases and stimulates the inhibitory center for the liver; this secretion has at the same time an inhibitory influence on the stimulating center for the liver located in the cervical part of the spinal cord above the fourth cervical vertebra. The production of glucose in the liver is thus diminished by a twofold influence.

Chauveau and Kaufmann, besides, accept an inhibitory influence

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* "Comptes rend.," 1893–1897.

† The inhibitory center for the liver transmits its impulses through the "rami communicantes" of the first four pairs of cervical nerves. Its stimulating center transmits its impulses through the "rami communicantes" below the first four pairs down to the sixth dorsal vertebra.

from the stimulating center for the pancreas on the whole general metabolism—the "histolysis" in the tissues." * This histolysis, they further state, results in the bringing to the blood certain substances, which are again carried to the liver and there transformed into glycogen and glucose. The same influence of the pancreas that otherwise inhibits the production of glucose in the liver thus also diminishes its supply of carbohydrates.

A section through the spinal cord between the atlas and the occipital bone separates the liver from its inhibitory centers and delivers its stimulating center in the upper cervical cord from its antagonist; at the same time it separates the pancreas from its stimulating center and cuts off communication between the cerebral centers and the sympathetic nervous system (inferior cervical ganglion), which executes the impulses transmitted from the cerebral centers. The internal secretion of the pancreas does not cease, but it is considerably diminished, and the effect of the operation is a hyperemia, quite distinct from, and less pronounced than that which follows total extirpation of the pancreas. Bernard's puncture on the floor of the fourth ventricle has the same effect, in consequence—according to Chauveau and Kaufmann—not of stimulation, but of a paralyzing effect on the nervous center of excitation for the internal secretion of the pancreas.†

Section through the cord below (or behind) the fourth cervical vertebra, and between this and the sixth thoracic vertebra, leaves the communication between the cerebral stimulating center for the pancreas and the cerebral inhibitory center for the liver, but cuts off the stimulating center for the liver, and the effect is not hyperglycemia, but distinct hypoglycemia. Sections below the sixth thoracic vertebra have no influence on the amount of sugar of the blood.

If the pancreas is extirpated *after* section of the cord between

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* I fear that it is impossible to bring this part of Chauveau's and Kaufmann's theories in accordance with the established facts concerning the metabolism of diabetic patients.

† Kaufmann later, after cutting all the nerves of the liver, found that hyperglycemia still follows Bernard's puncture, and he therefore also accepts a direct influence, outside of the nervous system, of the internal secretion of the pancreas on the liver. This internal secretion and its inhibitory influence on the liver are diminished by the paralyzing influence of the puncture on the stimulating center for the pancreas.

the fourth cervical and the sixth thoracic vertebra, diabetes does not develop, but the hypoglycemia continues, the stimulating center for the formation of glucose in the liver being cut off. If, however, the pancreas is first extirpated, and the same section is made after the beginning of the diabetes, hyperglycemia and glycosuria continue. Chauveau and Kaufmann explain this by a certain autonomy on the part of the sympathetic centers in the abdominal cavity, which continue to exercise stimulating functions after these have once been assumed.

For the same reason hypoglycemia continues if the cord is first severed between the fourth cervical and the sixth thoracic vertebra and section of the medulla oblongata above the atlas is made afterward. For the same reason hyperglycemia continues after section of the medulla above the atlas, if later the cord is severed between the fourth cervical and the sixth thoracic vertebra.

After publication of the foregoing results Kaufmann * came to the conclusion, from further experiments, that Lépine's observations concerning diminished "glycolysis" on the part of the blood after total extirpation of the pancreas are correct. Kaufmann, too, has found (in dogs) diabetic after such extirpation, a reduction of "glycolysis" from 1 to 0.77, or even to 0.68, and a normal or even slightly decreased production of sugar. He maintains his previously expressed views, so far as they are not directly affected by Lépine's and his own observations on the effect of extirpation of the pancreas on glycolysis. He accepts two secretions on the part of the pancreas: one, the well-known external secretion, among whose functions is the production of glucose from the ingested carbohydrates; and the other, the recently discovered internal secretion, among whose functions is the production both of a glycolytic ferment and of a substance possessing an inhibitory influence upon the production of glucose in the liver. Kaufmann thus adopts at present the view that will probably in the future be universally accepted. He believes that diabetes mellitus may arise from an increased production of glucose in the liver or from a decreased consumption of glucose in the tissues, especially in the muscles, or from both of these causes in combination.

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* "Comptes rend. hebd. Soc. de Biologie," 1896.

The results of Chauveau's and of Kaufmann's experiments tend to make a pathologic unit of all varieties of decreased power of assimilating carbohydrates. The hypothesis of the two distinguished French physiologists must, however, be confirmed by a vast amount of experimental work before anything can be considered settled. For the details of Kaufmann's numerous and laborious experiments I must refer to his own works.

The clinician certainly sees more manifestly the increased production than the decreased consumption of glucose in cases of diabetes. A child of 20 kilograms bodily weight requires 800 calories in twenty-four hours. A diabetic child of equal weight may produce one kilogram of glucose, representing 3692 calories, in the same time, or so enormously much more vital force than is needed or can be consumed that such a production under normal conditions is not possible.

As long as we know so little of the laws governing the activity of the pancreas and of the liver, or are uncertain with regard to the details of the regulatory nervous influence; as long as the formation of carbohydrates from fats is a mystery and the conditions for the formation of fats from carbohydrates are unknown; as long as the molecular conditions necessary for the ultimate oxidation are not clearer than they are at present, so long shall we, even if we accept recent views on the increased production of sugar and on decreased "glycolysis" in cases of diabetes, be unable to form any detailed or clear opinions on the immediate cause or causes of diabetes, and we shall do well to abstain from too much speculation on the subject and to wait for further conclusions until experimental pathology has provided us with the necessary amount of established facts.

The normal human being after ingestion of carbohydrates other than glucose excretes no glucose in determinable quantities in the urine. This fact was first proved by Worm-Müller, and I have repeatedly verified the correctness of the observation so far as starch, cane-sugar, and levulose are concerned. After the ingestion of enormous amounts of rice by healthy individuals the urine causes no reduction that can be removed by fermentation. My own experience has been only with isolated instances in which large amounts of carbohydrate have been taken. But healthy Chinese, who live almost exclusively on rice, exhibit no glycosuria. After

the ingestion of large amounts of the different disaccharids or monosaccharids, a comparatively insignificant part of the ingested saccharid appears in the urine in unchanged form. My own numerous experiments have yielded in all essential respects the same results as Worm-Müller's. After the ingestion of 250 grams of cane-sugar, Worm-Müller found 1.81 grams of cane-sugar in the urine; after the ingestion of 50 grams of cane-sugar, he found 0.1 gram of the same disaccharid in the urine, but not a trace of glucose. The ingestion of 200 grams of lactose was followed by the excretion of 1.68 grams of lactose; 100 grams of lactose by the mouth yielded 0.32 gram of lactose in the urine. After the ingestion of large amounts of honey, which is a mixture of levulose and glucose, Worm-Müller found only glucose in the urine. Levulose, however, obeys the same laws as other saccharids. After the ingestion of 150 grams of crystallized levulose by a normal individual, I found a small quantity of reducing and fermenting substance in the urine; and by doubling the dose I was able to demonstrate that the urine contained no saccharid other than levulose, and to observe the difference in levogyration at different temperatures peculiar to this saccharid.

Miura has lately observed that the ingestion of large amounts of different saccharids by healthy individuals is followed by the appearance in the urine of small quantities of these saccharids exclusively in unchanged form. Maltose yielded maltosuria; levulose, levulosuria; lactose, lactosuria. Miura found also that the ingestion of even enormous amounts of starch by healthy persons is followed by the appearance of no abnormal or unusual substance in the urine.

When taken in large amounts, glucose, like other saccharids, appears in some degree unchanged in the urine in normal as well as in diabetic persons. Normal individuals, however, are usually able to assimilate considerable amounts of glucose without exhibiting glycosuria. Worm-Müller found, in the urine of a person whom he accepted as normal, 0.47 gram of glucose after the ingestion of only 50 grams of the same monosaccharid. I am inclined to believe that in this experiment Worm-Müller happened to come across a person with the common, but decidedly pathologic, weakening of the power of assimilation found especially often in brain-

workers with some degree of neurasthenia. A perfectly normal person can usually take, on an empty stomach or after a light meal, at least 100 grams of glucose without consequent glycosuria. To again assure myself of this fact, I had, shortly before this manuscript left my hands, each of fifteen soldiers in Stockholm take in my presence, at 10 A. M., 100 grams of glucose,* a few hours after a light breakfast. Not one of them afterward excreted sufficient glucose in the urine to cause any reaction with Nylander's solution of bismuth. Two days afterward I gave 200 grams of glucose in water to each of ten soldiers ; neither after this amount was there in any case sufficient glucose in the urine to yield a distinct reaction with Nylander's solution after four minutes of boiling.

In other instances 200 grams, and sometimes, though rarely, even 100 grams of glucose cause, in apparently healthy persons, some slight glycosuria.

Moritz mentions that large amounts of cane-sugar cause in normal individuals an excretion of cane-sugar and of glucose. I maintain that when glucose appears in the urine after the ingestion of cane-sugar the individuals in question are not normal.†

De Jong, after some experiments with lactose, came to the conclusion that large amounts cause in normal men an excretion of lactose and of a comparatively small amount of fermentable saccharid. This is contrary to the observations of Worm-Müller, Miura, and others, and I doubt that the individual in question was normal.

A large number of observations have taught me to conclude that any person who exhibits glycosuria after the ingestion of large amounts of rice suffers from a deficient, distinctly pathologic power

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* Five of the soldiers received 100 grams of perfectly pure glucose ; all the others were given "technical" glucose, which contains some dextrin. The urine was secured nearly three hours after the ingestion of the sugar. The excretion of the saccharid is, in the large majority of cases, ended, or nearly ended, after that length of time. The diuretic influence of large amounts of glucose is often apparent, even when there is no glycosuria.

† I wish again to call attention to the fact that no conclusions can be drawn with regard to the details of metabolism in one species of vertebrates from the results of observations made upon another species. Seegen found cane-sugar, glucose, and levulose in the urine of dogs after the ingestion of large amounts of cane-sugar, and Rubner found cane-sugar and glucose. Budge also found glucose in the urine of dogs after the ingestion of large amounts of cane-sugar, but not in man. As to starch, Hofmeister mentions that the ingestion of even enormous amounts causes no glycosuria in the normal dog.

of assimilating carbohydrates. To me, such an individual is either distinctly diabetic or in danger of becoming so. The appearance of glucose in the urine, together with unchanged cane-sugar, after the ingestion of large amounts of cane-sugar is a less serious manifestation, but it is not normal, and it takes place in individuals who will daily, under ordinary circumstances, show some glycosuria. The smaller the proportion of glucose and the greater that of cane-sugar in the urine under such circumstances, the more nearly is the patient in a normal condition. There are individuals who may take from 200 to 300 grams of cane-sugar without excreting determinable quantities of glucose,—but only some cane-sugar,—and who still do not possess perfectly normal powers of assimilation, but present glycosuria up to 0.05 or 0.1 or 0.15 per cent. for a short while after every dinner of mixed food.

In cases of diabetes the ingestion of large amounts of carbohydrate, continued for any considerable length of time, always causes glycosuria; and the more pronounced the glycosuria, the more advanced the glycosuric dystrophy. Generally, no other saccharid is then found in the urine than glucose. This is always the case after ever so large doses of the polysaccharid starch. But after *very large* amounts of disaccharids, or of other monosaccharids than glucose, there will appear, even in cases of severe diabetes, together with a large quantity of glucose, a slight quantity of the ingested monosaccharid or disaccharid unchanged. This is also the case in dogs diabetic after extirpation of the pancreas. Minkowski found, after administration of 100 grams of levulose, 98.3 grams of glucose and 2.2 grams of levulose in the urine of such a dog. Administration of 200 grams of levulose yielded 105.6 grams of glucose and 15.6 grams of levulose in the urine.

The addition of proteids to a certain portion of carbohydrate increases the glycosuria in all stages of the glycosuric dystrophy. Many persons who are able to take large amounts of saccharids without the development of glycosuria, often excrete small quantities of glucose after rich meals of mixed character; and in cases of both light and severe diabetes, a portion of meat given with a certain amount of carbohydrate increases the resultant glycosuria.

There is only a gradual difference between the different stages of diabetes as to the power of assimilating carbohydrates. All dia-

betics have this in common, that they lose a part of the ingested and digested carbohydrates during a prolonged, abundant supply thereof; on this single symptom is built the whole dystrophic group of diabetes mellitus. All cases and stages of diabetes also have this in common: that they utilize a part of the ingested and digested carbohydrates. For the slight deficiency in the power of assimilation that causes a simple glycosuria, only an insignificant part of the ingested carbohydrates again appears in the urine as glucose; the individual may eat 300 grams of starch and excrete one gram of glucose in the twenty-four hours. In a case of mild diabetes the patient sometimes may receive sixty grams of starch without exhibiting glycosuria, and after long abstinence from carbohydrates he may even take large amounts of cane-sugar without manifesting any appreciable degree of glycosuria. Even in the worst cases, however, the physician, if he has the courage, in spite of the danger of coma, to put his patient on an exclusively animal diet until the glycosuria reaches a certain fixed degree for the twenty-four hours, will find that the patient, when again allowed a certain quantity of starch, will excrete a smaller excess above the former quantity of glucose than corresponds to the digested part of the ingested portion of starch. It seems that only after extirpation of the pancreas in dogs the power of assimilating carbohydrates may sometimes be for a short while completely destroyed (Minkowski); but even in these cases a certain amount of starch is usually assimilated.*

Almost all of the glucose eliminated from the blood in cases of diabetes passes into the urine. The saliva, the tears, and the sweat are generally free from glucose, though it has sometimes been found in these in fractions of one per cent.† It is sometimes found

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* A dog, after extirpation of its pancreas, received 151 grams of starch, of which 64.8 grams were found in the feces and—not including small quantities possibly lost in the intestines by fermentation—86.2 grams were digested. The urine contained 99.2 grams of glucose and 12.22 grams of nitrogen. The sugar formed from proteids, compared to the nitrogen derived from them, bears a ratio as of 2.8 : 1, so that 34.21 grams of glucose must have been derived from proteids and 64.99 grams from the ingested starch. A considerable part of the starch—of which 54 grams correspond to 60 grams of glucose—had manifestly been utilized.

† Toralbi mentions a case of "salivary diabetes" in a hysteric woman, without glucose, but with a large amount of oxalates in the urine and one per cent of glucose in the saliva.

in serous fluids; from 0.14 to 0.27 per cent. in ascites (Letulle, Naunyn), 0.5 per cent. in a pleuritic exudate (Foster), etc. Bussenius found 0.25 per cent. in the sputa.

The greatest amount of glucose to the kilogram of bodily weight that can be taken without the development of glycosuria represents what Hofmeister calls the limit of assimilation. This limit varies in different patients, and also varies in the same patient at different times. All of those influences that are known to cause diabetes or glycosuria, of course, lower the limit of assimilation. Excesses and emotions cause glycosuria in normal individuals and increase it in diabetics. Starvation or underfeeding has a bad influence in this direction; this was discovered by Claude Bernard and has been elaborately studied by Hofmeister (see Glycosurias). Muscular activity within certain limits heightens the limit of assimilation (Bouchardat, Zimmer, Külz, v. Mering); massage has the same effect (Finkler and Brockhaus). Fatigue, however, has a contrary effect, and after long marches or after journeys in railway cars the diabetic patient often exhibits for several days a lower power of assimilation than under ordinary circumstances. Külz made an observation which can be easily verified—viz., the limit of assimilation is often higher early than late in the day. A most important fact (see below) is this: that the limit of assimilation is higher after the observance for some time of a strict diet and absence of hyperglycemia and glycosuria. Opium, syzygium jambulanum, arsenic, etc., often increase the limit of assimilation; in other cases these drugs have no effect whatever. In the course of careful experiments with phenacetin, which a physician recommended for increasing the power of assimilation, I was able repeatedly to demonstrate an increased glycosuria. Lépine and his disciples have lately given an explanation of the fact that the same agent may have quite contrary effects in different cases; it increases both the production and the consumption of glucose, so that its effect on the limit of assimilation depends on the relative state of production and consumption in the case. The best remedies, of course, are those that decrease production and increase consumption. Alcohol in small doses increases, in large doses diminishes, the power of assimilation. Fever decidedly increases this power. Finally, the limit of assimilation often

slowly sinks, from unknown causes, in consequence of the progressive nature of the glycosuric dystrophy.

The limit of assimilation varies also in the same individual from unknown causes. Worm-Müller gives a striking instance of this: V. C., previously mentioned, received 50 grams of glucose before breakfast, and excreted 0.47 gram in the urine during the next three hours. At another time, under the same circumstances, the subject received 100 grams without the development of any glycosuria whatever. On a third occasion glycosuria appeared six hours after the ingestion of 100 grams of glucose (rare !), and continued for three and one-half hours, during which time 1.85 grams of glucose were excreted.

Shortly before death and in advanced marantic states, the glycosuria, *ceteris paribus*, diminishes—not by reason of an increased power of assimilation, but on account of impaired digestion and the retardation of all the metabolic processes. The reason why glycosuria diminishes in cases of cirrhosis of the kidneys remains to be explained.

Glycosuria following the ingestion of carbohydrates in cases of diabetes (and after large amounts of glucose in any person) begins, in the enormous majority of cases at least, within the first hour, and generally a distinct reaction can be found after half an hour. Bread and well-cooked rice seem to cause glycosuria almost as quickly as pure glucose. The larger part of the glucose in the urine has often been excreted at the end of the first hour; the curve afterward sinks, and after from three to six hours the urine in mild cases is again free from glucose. In cases of simple glycosuria the whole excretion may not continue for more than an hour, beginning about half an hour and often ending an hour and a half after the meal. Even with a free diet the mild cases of true diabetes often exhibit, some hours after a meal, no glycosuria, and the majority of such patients present no glycosuria in the morning before the first meal. This is, therefore, the worst time for testing whether or not an individual is free from diabetes.

My patient, T., suffered from simple glycosuria, and with a perfectly free diet, including an abundant supply of carbohydrates, excreted about 2 grams of glucose in twenty-four hours. Between 9.30 and 10 A. M. he was free from

glycosuria, and drank 300 grams of cane-sugar in 1000 cu. cm. of water, excreting afterward as follows :

At 10.30	A. M.	130	cu. cm.	of urine of	1.030	specific gravity	and containing 0.2 per cent. of sugar.
At 11	"	95	"	"	1.006	"	containing 0.1 per cent. of sugar.
At 11.30	"	145	"	"	1.004	"	containing about 0.07 per cent. of sugar.
At 12	M.	36	"	"	1.018	"	containing 0.15 per cent. of sugar.
At 12.30	P. M.	24	"	"	x	"	containing somewhat more than 0.1 per cent. of sugar.
At 1	"	21	"	"	x	"	containing less than 0.1 per cent. of sugar.
At 1.30	"	26	"	"	x	"	containing traces.
At 2	"	x	"	"	x	"	containing faint trace.
At 2.30	"	the urine did not contain as much as 0.01 per cent. of glucose.					

The figures here given as representing sugar were obtained by polarization, and thus refer to the mixture of glucose and cane-sugar in the urine. The figures are, besides, all somewhat too low, the levogyration of glycuronic acids not being taken into account.

A medical student, X., rang me up on the telephone, and in a trembling voice asked if he might pay me a visit at once; and I, having had several times before a similar experience, at once suspected that he had passed glucose in his urine. The ingestion of 250 grams of cane-sugar caused him to vomit after half an hour. The urine, however, passed a few minutes later contained cane-sugar but no glucose, and reduced after, but not before, boiling with some sulphuric acid. On the next day X. had better luck, and was able to retain 200 grams of cane-sugar. About two and a quarter hours afterward he passed 100 cu. cm. of urine, with a specific gravity of 1.022, and which, before boiling with some sulphuric acid, reduced as a solution of glucose of 0.33 per cent.; but after "inversion" (of the excreted cane-sugar) it reduced as a solution of glucose of 0.55 per cent. In the next sample of urine, passed three and a half hours after the cane-sugar had been taken, there was no appreciable amount either of glucose or of cane-sugar.

I consider X. more nearly a case of true diabetes than he would be if he had passed only cane-sugar and no glucose; but he is better off than he would be with greater glycosuria and less saccharosuria.

Külz made it a rule to give the patient the allowed daily quantity of starch at *one* meal, believing that it induced a greater degree of glycosuria if given in several portions at different times. The result, however, depends on circumstances. If the patient's limit (or power) of assimilation is small as compared with the allowed

quantity of carbohydrates, this quantity given in several doses may occasion the presence of more glucose in the urine than when given at one time; but if the amount allowed is small as compared with the power of assimilation, it may induce less glycosuria by being given in divided portions than when given at once. This is manifest both from Külz's figures and from mere reasoning as soon as the patient can take any quantity of carbohydrates without the development of glycosuria.

Külz, in addition to many other services, also rendered that of teaching us that different kinds of carbohydrate are assimilated in different degree by diabetics.

Starch induces greater glycosuria than any other article of food—greater even than pure glucose. The formula of starch is $C_6H_{10}O_5$; that of glucose, $C_6H_{12}O_6$. By taking up water, starch will form glucose: $C_6H_{10}O_5 + H_2O = C_6H_{12}O_6$. The atomic weights being for C = 12, H = 1, and for O = 16, the foregoing equation yields $12.6+1.10+16.5+1.2+16=12.6+1.12+16.6$, or $162 + 18 = 180$. In other words, 162 grams of starch, by taking up 18 grams of water, will form 180 grams of glucose; or 9 grams of starch + 1 gram of water will form 10 grams of glucose.

Cane-sugar is a disaccharid of glucose and levulose. Glucose causes marked glycosuria in cases of diabetes; levulose, much less. Thus, cane-sugar causes less marked glycosuria than starch or glucose.

Lactose is easily partly changed by fermentation in the bowel into lactic acid, which does not give rise to glycosuria, but often causes diarrhea, in consequence of which more than usual of the ingested saccharid passes off in the feces. In so far, however, as neither the one nor the other occurs, lactose seems to give rise to about as marked a degree of glycosuria as does glucose itself. Külz's patient, F. S., after the ingestion of 100 grams of glucose, excreted 8.9 grams of glucose; and after 100 grams of lactose, excreted 9 grams of glucose.* Fr. Voit, in a severe case, saw 100 grams of lactose increase the glycosuria by 49 grams.

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* After five weeks of abstinence from carbohydrates the power of assimilation had increased, and 100 grams of lactose gave rise to the excretion of only 4.1 grams of glucose. The glycosuria lasted about three and one-half hours, and the larger part of the glucose was excreted within the first hour.

Galactose also gives rise to quite a considerable degree of glycosuria. Fr. Voit saw the glycosuria increased by 70 grams in a severe case, after the ingestion of 100 grams of galactose.

Külz has published a report stating that the polysaccharid inulin and the monosaccharid levulose, which are related chemically in the same way as starch and glucose, are completely assimilated by diabetics. As soon as the price of levulose made this substance of practical value for such a purpose I began to use it in cases of diabetes; in severe cases with pronounced autophagia and loss of weight to lessen the daily nutritive deficit, and in mild cases as a substitute for cane-sugar. I found levulose of great value in checking the loss of weight in severe cases, and I believe it has a powerful effect in warding off the coma for a time. I constantly found that levulose increases the glycosuria in severe cases, and that large amounts in mild cases also cause glycosuria,* though more of levulose than of other saccharids is assimilated.

Inulin, a polysaccharid, is found in unusually large quantities in the tubers of *Helianthus tuberosus*, which is sometimes used for food in Europe and America, and is known under the name of Jerusalem artichokes (topinambour). Boiled with diluted acid it yields levulose. It is better assimilated by diabetics than starch, though, like levulose, it decidedly increases the glycosuria.

Inosite does not give rise to glycosuria, even when given in large amounts, as in young string-beans (Külz). Inosite is, however, not a saccharid, and it is not considered as belonging to the carbohydrates. Maquenne believes it to be hexahydroxyl-benzol.

[As is well known, inosite is found in many parts of the human organism, and is often present in the urine in conjunction with polyuria, with diabetes mellitus or insipidus, and with cirrhosis of the kidney. Sometimes glycosuria is succeeded by inosituria. In a case of diabetes, Vahl saw the glucose disappear and polyuria continue, and observed an excretion of from eighteen to twenty grams of inosite in twenty-four hours.]

Mannite, which is a hexatomic alcohol, causes, according to

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* Gruber, Hale White, Haycroft, Heyse, Klemperer, Minkowski, Palma, and others have had a similar experience. In the severe stage Palma found that 100 grams of levulose increased the glycosuria by 60.49 grams.

Külz, no glycosuria in any stage of diabetes, and normally appears in the urine in only small quantities. It may be used by diabetics as a mild aperient.

Other saccharids than glucose are also found in the urine, both in normal and in abnormal states. Lactose, as has already been mentioned, normally occurs in the urine of mothers during lactation and in that of sucking children. Levulose has several times been found in cases that have presented otherwise more or less the clinical image of diabetes mellitus, and the same may perhaps be true of maltose. Laios, found by Leo with glucose in a case of severe diabetes, may possibly be a saccharid, but it is as yet very little known.

Gorup-Besanez mentions levulosuria. Zimmer and Czapek have described a case of diabetes with as much as 2.2 per cent. of levulose, excreted with some glucose. Röhmann and Wolf saw a case with urine that turned the ray of polarized light to the right as much as a 1.6 per cent. solution of glucose, but reduced as a 4.3 per cent. solution of glucose. It contained in addition to glucose a reducing-substance that turned the ray of polarized light to the left, was decomposed by fermentation, and was thus in all probability levulose. Seegen, in 1884, treated in Carlsbad a case of pure levulosuria. In the following year Seegen had left the place and the patient came under my treatment, as she did also in 1893 and in 1896. Both Seegen and Külz have published the case, which clinically is more similar to one of simple glycosuria than to one of true diabetes. As it presents a peculiar interest, I briefly describe it herewith:

Mrs. F., a Jewess, born in 1837, knew of nothing else of anamnestic interest than that her mother had suffered from obesity and probably from diabetes, the thirst being remarkable during the latter part of life. The patient herself was always rheumatic, and since childhood had from time to time been troubled by furuncles. She sometimes suffered from dryness of the mouth and from increased thirst. At no time, however, had there been distinct polyuria, although there was marked pollakiuria.

The patient was a pronounced neurasthenic with a number of the usual symptoms. She suffered from right-sided sciatica. The knee-jerks were somewhat weakened. A sample of the mixed urine for twenty-four hours slightly reduced Fehling's solution. After an abundant dinner, with much carbohydrate, there was a deviation to the left of the ray of polarized light of 0.3° (with Hoppe-Seyler's instrument), which disappeared for the greater part after fermentation, when the reduction was almost entirely gone.

In 1893, nine years afterward, the excretion did not amount to more than 0.3 per cent. at the utmost, and it was not possible to decide with certainty whether or not some glucose was mixed with the levulose.

In the summer of 1896 the patient again visited Carlsbad, being otherwise

in about the same state as eleven years before, *i. e.*, in fairly good health, suffering only from some neurasthenic symptoms and from sciatica on one side. The excretion of sugar, however, was larger, and in some samples reached almost two per cent. The urine contained no albumin. After removing the saccharid by fermentation I found only a slight and uncertain reducing effect on the part of the urine, but a deviation of the ray of polarized light about 0.15° to the left. This undoubtedly arose from combined glycuronic acids, and it disappeared after precipitation with ammonia and lead acetate. This deviation taken into consideration, quantitative determinations of the saccharid, very carefully performed by methods of polarization and reduction, perfectly agreed in results, and I concluded that the urine contained no other saccharid than levulose. The quantity of levulose was large enough to enable me to observe distinctly the decrease in the deviation of the ray of polarized light at higher temperature peculiar to solutions of this substance.

Seegen, who had the patient under his care in 1884, then found 3.2 per cent. of levulose. Mauthner, who analyzed another specimen of the urine, found 1.59 per cent. of levulose. The results of polarization and reduction agreed, and the urine contained no other saccharid than levulose in appreciable quantity.

Külz, in 1886, wrote to the patient asking for five liters of her urine, and found that the urine fermented slowly but completely on addition of yeast, forming alcohol and carbonic acid; that it had a sweet taste on concentration; and that with phenylhydrazin chlorate and sodium acetate it yielded an osazone that melted at 205° C. (401° F.), and had the formula $C_6H_{12}O_6$. It yielded also Selivanoff's reaction and turned the ray of polarized light to the left. This would have assured an ordinary person of the identity of the saccharid with levulose. Külz found also that levulose in "absolutely pure, hard crystals" dissolved in water was again precipitated by lead acetate, and that the saccharid in the urine of Mrs. F. was precipitated by this salt only on addition of ammonia—a difference that, as he himself, with all his doubts, remarked, might well depend on the different solvent mediums.

Le Nobel mentions a case of *maltosuria* in a diabetic patient of sixty-one years, whose digestion of fat was much impaired. Von Ackeren found maltosuria in a case of carcinoma of the pancreas, and Wedenski possibly also saw such a case. Further investigations seem necessary, especially in view of the fact that extirpation of the pancreas causes in dogs only glycosuria.

Laios, found by Leo in association with glucose in three severe cases of diabetes, reduced (less than glucose), turned the ray of polarized light to the left, yielded an osazone with Fischer's test, but did not ferment and had no sweet taste.

If there has been much to say with regard to the fate of carbohydrates in normal and diabetic organisms, we may state in comparatively few words what is necessary with regard to the fats, however important an item they constitute in the dietary of a diabetic patient. We know of no *direct* changes in the metabolism of fat in cases of diabetes.

We have seen that fat does not increase the glycogen in the liver or elsewhere. We also know that it does not increase the glycosuria in any cases of diabetes.

The absorption of fat, as has already been mentioned, is, in most cases of diabetes, normal. Fat is decomposed, as usual, by the bile and the pancreatic juice into triglycerid, free fatty acids, and soaps. In the chyle it is again found almost exclusively as neutral fat, and is stored in the liver and in the muscles. We have seen that its fate afterward is unknown, and that there are various opinions, differing from the one expressed by Nasse, who believes that it is utilized and oxidized exclusively in the liver, to which the fat would have to return when once stored anywhere else.

Two qualities of fat—its high caloric value and that of not increasing the hyperglycemia—make it an excellent food for diabetics. Unfortunately, it is impossible to utilize practically to the full extent what might theoretically be expected from this kind of food. Fat can be tolerated only in quantities that are far below the caloric needs of the organism. Then fat does not protect the proteids of the organism as powerfully as carbohydrates do.

The circumstance that the same number of calories given in the form of carbohydrates diminish the consumption of proteids much more than an equal number of calories in the form of fat has been demonstrated by Voit, who was able to reduce the excreted nitrogen with 15 per cent. by the administration of carbohydrates, but only with 9 per cent. by the administration of fat.

I insert the following table, compiled from Kaiser's researches :

Time.	Daily Food in Grams.			Calories.	Nitrogen in Urine and Feces.	Gain or Loss.
	Nitrogen.	Fat.	Carbohydrate.			
I. Four days, . .	21.18	71.65	338.2	2593	20.15	+1.03
II. Three days,	21.53	217.9	0.	2577	24.51	—3.05
III. Three days, .	21.10	70.37	338.2	2581	20.17	+0.93

The most curious fact, that the nitrogen in the urine is sometimes increased by the ingestion of fat, has several times been observed, in contradistinction to the power of conserving proteid, which certainly belongs to some extent to fat. Voit believes that this happens only with a small supply of proteids and a large

supply of fat, but Weintraud's tables do not seem to corroborate this view. Voit attributes to the fat two qualities with opposite results: It has the well-known effect of conserving proteids; but, on the other hand, it has a tendency to increase the circulating proteids. Weintraud refers to an analogous phenomenon in one of Nasse's experiments: A dog receives a certain quantity of phenol, excretes part of it unchanged and oxidizes the remainder to hydrochinon; with a larger supply of fat the unchanged phenol decreases and the hydrochinon increases. Nasse considers that the oxidation of fat produces free atoms of oxygen. Still, we do not know how this is done, and we stand before a most curious enigma. I should find it interesting to know how the diaceturia and the glycosuria resulting from proteids in a severe case of diabetes are influenced by a larger supply of fat, when fat increases the nitrogen of the urine.

An ordinary civilized person can not eat more than a certain limited quantity of fat,* and—worse luck for the diabetic patients!—it is not meat, but bread and potatoes (*i. e.*, carbohydrates), that help him to eat more. A comparatively limited allowance of bread—viz., from 80 to 100 grams a day—markedly increases the capability of eating a good deal of fat; but even then patients generally can not take more than 200 or 250 grams of this in the twenty-four hours † without nausea and digestive disturbances.

The formation of fat within the organism in cases of diabetes is impaired by the passing off in the urine of a part of the carbohydrates of the food which otherwise might form fat. In the severe stage a deficit arises in a like manner in the formation of fat from proteids, which may occur in different ways, but which certainly takes place in consequence of the intermediate formation of glycogen. It is, by the way, possible that a better knowledge of the details of the formation of fat from carbohydrates and from pro-

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* The Arctic nationalities are capable of devouring large quantities of fat. In 1868 I traveled through Lapland with no other company than a Lap for a servant. I was on one occasion about to throw away quite a quantity of butter which began to be rancid. The Lap protested against this waste, and, on permission, devoured the whole amount at once without the addition of bread or of anything else.

† The ordinary articles of food containing the largest percentage of fat are as follows:

Butter,	with about	84.4	per cent.	of	fat	and from	0.1	to 0.5	per cent.	of carbohydrate.
Olive-oil,	"	99	"	"	"		0.x	"	"	
Lard,	"	76	"	"	"		0.	"	"	
Rich cheese,	"	30.5	"	"	"		1.5	"	"	

"Lipanin" is olive-oil with about six per cent. of free fatty acid, and is said to taste better and be easier of digestion than neutral olive oil.

teids in the normal organism would contribute to a solution of some of the many mysteries of diabetes. A consideration of the formation of fat within the diabetic organism leads me to discuss the close connection that, notwithstanding the restriction of this formation, undoubtedly exists between adiposity and diabetes, and also the connection of both of these dystrophies with the gouty dystrophy. It would be pleasant and convenient to be able to indicate the nature of this connection by saying that the deficient power of oxidizing fat goes hand in hand with a deficient power of oxidizing carbohydrates, and that both these deficiencies are closely related to the deficient power of oxidizing proteids. But, with all the weakness of our present position, with our exceedingly imperfect knowledge of the pathogenesis of each of the three dystrophies, we now know enough to understand how premature it would be to indicate in such a manner the deep mystery of the relation referred to. The worst diabetic can oxidize fat and other substances in enormous quantities. The theories lately emanating from Germany in this connection belong, in all their ingenuity, in the domain of pure speculation.

Since the end of the 18th century physicians now and then have observed that the blood exhibits a grayish color in cases of severe diabetes, and this color has been found to be due to the presence of an increased quantity of fat in minute particles. *Diabetic lipemia* has reached as high as 11.7 per cent. in man (Lecanu) and 12.3 per cent. in the dog (D. Gerhardt). It is known that the customary 0.2 or 0.3 per cent. of fat in the blood may normally increase enormously after digestion. Still, there seems to be no doubt that some diabetes, like tuberculosis and alcoholism, sometimes causes the appearance of a still larger quantity of fat in the blood, a true *hyperlipemia*, and, sometimes, though only in rare cases, a consequent *lipuria*. This may be a phenomenon connected with the toxic, "protoplasmatic" disintegration of proteids; but at present our knowledge of the matter is restricted to what I have already mentioned.

Alcohol must not be left out of consideration in a discussion of human food. It has high caloric value; a gram yields seven calories gross. When large amounts are taken, about ninety per cent. of

these calories are utilized (Strassman); when the amounts are small, probably more is utilized (Hirschfeld). These calories are, however, not of high quality; Miura has shown that alcohol protects the proteids much less than the same caloric amount of carbohydrates, and less even, it seems, than the same caloric amount of fat. In large amounts it acts as a protoplasmic poison, with a well-known deleterious influence in various respects, and in such amounts lessens the power of assimilation both in cases of diabetes and under other conditions. In most cases ¼ of a gram of pure alcohol per kilogram of bodily weight is a fair allowance a day; double this amount is never to be exceeded for habitual use. Even in these amounts alcohol ought always to be taken *much* diluted, to avoid irritation of the mucous membranes and of other structures. In this condition and in the doses stated it will do no harm and some good, especially to diabetics. It economizes fat, and if any one, after taking from twenty to thirty grams of alcohol a day, suddenly observes absolute abstinence, he will always, *ceteris paribus*, lose in bodily weight. In such amounts alcohol does not lessen, but rather increases, the power of assimilating carbohydrates (Külz). If recent investigations (of Hirschfeld) have not corroborated the claims for alcohol that it facilitates the absorption of fat, there can be no doubt about its value in small amounts in facilitating the *ingestion* of larger quantities of fat and in increasing the appetite in general. The many and terrible sins that mankind has committed with alcohol ought not to make us blind to its real and most important advantages. There are at present in this country (Sweden), as there have always been, a great many drunkards, who ruin themselves with alcohol, and a great many cranks with an unwise and blind passion for total abstinence.

As a faulty metabolism of carbohydrates distinguishes the mild stage of diabetes from a normal condition, so a faulty metabolism of proteids distinguishes the severe stage from both the mild stage and the normal condition. Unfortunately, a host of questions, that can not at present be answered, present themselves with regard to the fate of proteids both in the normal and in the diabetic organism. We do not know much more than that proteids may form proteids,

fat, and carbohydrates.* The differences with regard to processes both of disintegration and of synthesis between different kinds of proteids, especially between the simpler proteids and those of a more complicated molecular constitution, the proteids *sensu strictiori* (nucleins, mucins), the metabolic differences between the various tissues, the successive molecular steps on the way to complete oxidation, etc., are, for the greater part, unknown.

Our next most important task will be to become better acquainted with the conditions of production and consumption of the three substances, acetone, diacetic acid, and β-oxybutyric acid, in cases of diabetes. We have good general and special reasons for considering them to be momentarily present even in healthy organisms, though the β-oxybutyric acid, the mother-substance of the others, is normally quickly converted into diacetic acid, this acid into acetone, and acetone into carbonic acid and water. I shall return to this subject later.

The difference in the metabolism of the proteids between the mild and the severe stage of diabetes begins in the liver. I have stated that if in the mild stage the carbohydrates are restricted below the patient's limit of assimilation, the formation of glycogen in the liver in great probability takes place just as it does in a normal individual *upon the same diet.* In cases of severe diabetes, however, the formation of glycogen is restricted under all dietetic conditions, and even a part of the products of proteids passes off in the urine as glucose.

The details of the formation of carbohydrates from proteids are not known. We do not know if all the glucose derived from proteids must first become glycogen, but we have good reason for believing that there is no such necessity and that proteids can

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* The formation of proteids from peptones and albuminoids need not detain us, and we have already spoken of the formation of carbohydrates from proteids. There is still some slight doubt whether proteids can or can not form fat directly and without first forming glycogen, notwithstanding the cellular manifestations in regressive metamorphosis or after certain poisons, the formation of the acid of palmitin (Salkowski) and other productions after death (Salkowski, Lehmann), the supposed formation of fat from proteids in larvæ (Hofmann), the abundant formation of milk even with an exclusive diet of meat in bitches (Subbotin, Voit, Kemmerich), and the disappearance in the organism of carbon with a similar diet (Pettenkofer and Voit, E. Voit).

directly form other carbohydrates than glycogen. Hammarsten isolated (from the pancreas, the liver, and the mammary gland) a nucleo-proteid which, when boiled with a diluted mineral, yielded a reducing substance that was proved to be a pentose. Hammarsten admits the separation of a molecule of carbohydrate from the proteids of a more complicated structure (nucleins, mucins). Pavy considers the proteids glucosids that, boiled with diluted acids, yield saccharids and proteids of less complicated structure, and has produced carbohydrates from the albumen of eggs and from fibrin. Kravkow's researches have led to similar conclusions with regard to some kinds of proteids. Kassel produced formic acid and levulinic acid by the action of sulphuric acid on nuclein. Levulinic acid has always shown itself as a derivative of carbohydrates.

It is the presence of derivatives of proteids in the urine that distinguishes severe from mild diabetes. The glucose in severe cases is partly derived from proteids; the acetone, the diacetic acid, and the β-oxybutyric acid in such cases are believed to be derived exclusively from proteids.

If in a case in the mild stage the carbohydrates of the food are restricted below the patient's limit of assimilation his urine, as is well known, remains free from glucose *and does not, so far as we know at present, differ from the urine of a normal person living on the same diet.*

For practical reasons I here deviate from the straight line of exposition to show the truth of this last assertion.

Among certain derivatives of proteids in the urine in the mild stage we are chiefly interested in urea, uric acid, and acetone (the diacetic and β-oxybutyric acids belong exclusively to the severe stage).

Acetone was first discovered in a case of severe diabetes. It is undoubtedly increased in such cases. Engel found 2.8 grams, which is a rare figure. In normal individuals the daily excretion is only about 0.01 gram (v. Jaksch); but it is often increased in children, whose breath, by the way, sometimes under apparently normal conditions smells of acetone. It is increased also with lactosuria during lactation, being probably derived from casein (Guckelberg, v. Jaksch), and after the ingestion of certain poisons, during starvation, in febrile states, in eclampsia and epilepsy, lyssa,

cachexia, disturbances of digestion, and mental diseases. It is normally increased when carbohydrates are excluded from the diet and with a purely animal diet. Von Jaksch states that in some mild cases of diabetes it does not occur in larger quantities than in normal individuals using the same food, and Hirschberg's researches point to a similar result. At present it is not *proved* that there is any increase of acetone at all in the mild stage of diabetes, and, even in that event, it is not known under what circumstances or in what class of cases (see below).

As to urea, it is now known that in the large majority of cases of diabetes it is not present in the urine in larger quantities than in normal individuals under the same dietetic conditions. Only in the very severe cases with the toxic or protoplasmic disintegration of tissues is the patient supposed to excrete more urea than a normal person upon the same food.

The quantity of uric acid, about which only the newest analytic methods give reliable information, varies greatly in normal individuals. Naunyn and Riess, by a method of their own, found from 0.16 to 1.05 grams; Külz, by the same method, from 0.06 to 0.76 gram; Bouchardat, more than three grams; Hartz, in six cases of diabetes, found at the utmost between 1.5 and 2 grams of uric acid in the urine in twenty-four hours. Neither from these, nor from Bischofswerder's, nor any other researches can it be concluded that a greater or lesser excretion of uric acid takes place in diabetics than in normal individuals. To gain some notion of the difference between normal individuals and diabetics in this respect, it would be necessary to compare a large number from each of the two classes under the same dietetic conditions, and especially with the same quantity of ingested nucleins. On account of the absence or presence of sediment, and on no better basis than "uroscopy," it has been said that uric acid is diminished in the severe stage and increased in the mild stage of diabetes. Some writers have also (since 1855) spoken of a "*diabetes alternans*," with alternation in the excretion of large quantities of uric acid and of glucose (Claude Bernard, Bouchardat, Brogniart, Budde, Coignard, Charcot, Ebstein). I am far from certain that such an alternation takes place, and I am pretty certain that its existence has never been proved. As is well known, the sediment is by no means an adequate expression of the quantity of uric acid

present. A urine containing a greater amount of uric acid may keep the whole amount in solution, while another urine containing less uric acid may present a part of it in the form of a sediment. In mild gouty cases of diabetes the urine often contains considerable sediment. All that can at present be safely asserted is that a marked sediment of uric acid indicates a mild case of diabetes, and that such a sediment is absent from the pale greenish-yellow urine of severe cases.

Kreatin was found by Winogradoff in small quantities and by Senator in large quantities in diabetic urine (up to two grams a day). From their researches, and from those of Bunge and St. Johnson, we infer that kreatin and kreatinin are in most cases of diabetes (and apart from toxic disintegration of tissue), under the same dietetic conditions, to be found in the urine in the same quantity as in normal urine.

In mild cases the amount of ammonia does not exceed that which may be found normally with an abundant supply of proteids. Only in severe cases with "acidosis" does it attain large proportions, and it may equal as much as twelve grams in twenty-four hours—solely because the acids have a greater affinity for it than they have for urea.

Boedeker found in diabetic urine a substance that he called alkapton, but which is found also in the urine of normal children and of other nondiabetic persons. In some instances the substance found may possibly have been pyrocatechin. It is also represented by uroleucin and glycosuric acid, and is otherwise known as homogentisinic acid. It can not be said to bear any special relation to diabetes; according to Baumann and Walkow, it is formed in the bowel under the influence of certain microorganisms.

Hippuric acid has been found in diabetic urine (from 0.1 to 1 gram) by Lehmann; it is found also in normal urine, and is increased in febrile states, in diseases of the liver, and in neuroses. It arises in the course of the putrefaction of proteids, and may be found equally apart from as with diabetes, whenever putrefactive processes are taking place.

The low fatty acids (formic, acetic, butyric, propionic) are but rarely found in diabetic urine recently passed (v. Jaksch); they are

sometimes found in normal urine and, according to Rumpf, they are present in normal quantities in mild, but in increased quantities (up to ten grams) in severe cases. Purely diabetic lipaciduria is a feature exclusively of such cases.

Lipuria is sometimes found in normal persons after the ingestion of large amounts of fat, and is found in association with the most widely different pathologic conditions, chiefly after the taking of certain poisons and in cachectic or marantic states. Purely diabetic lipuria, like purely diabetic lipaciduria, is a feature of severe cases.

Lactic acid in its two slightly different modifications may occur in the urine in cases of diabetes. Minkowski in a severe case found the levogyrate acid in the blood; Rumpf in a similar case found it in the urine. We have already seen that lactaciduria is a common phenomenon in conjunction with glycosuria after some poisons; it has also been found in cases of acute yellow atrophy of the liver. Colasanti and Moscatelli found lactic acid in small quantities in the urine of soldiers after forced marches. We are at present too little acquainted with the conditions for the appearance of lactic acid in the urine to decide its relation to diabetes. Still, it seems certain that it may appear under other conditions.

We undoubtedly find in cases of diabetes—especially, as it seems to me, in mild cases—an increased amount of oxalic acid in the urine. I have sometimes seen quite an enormous number of the small crystals of calcium oxalate in cases of simple glycosuria, when an abundant supply of carbohydrates has given rise to only a trace of glucose in the mixed urine. I am much more inclined to accept (with Prout) an alternation between oxaluria and glycosuria in certain cases than an alternating excretion of glucose and uric acid. Fürbringer saw oxaluria and oxaloptysis in a diabetic patient. There are many records of oxaluria in cases of diabetes, and it may exist without being discovered by the microscope, the calcium oxalate being kept in solution by the acid phosphates, which are often present in large quantities in the urine of diabetic patients eating much meat. Apart from alimentary and normal oxaluria and the "symptomatic" oxaluria associated with some other diseases and pathologic states, and apart from diabetic oxaluria, there is a form known as (Cantani's) idiopathic oxaluria with its neurasthenic and

slight dystrophic symptoms. This idiopathic glycosuria is probably identical with the oxaluria found in neurasthenic individuals with or without glycosuria. On the other hand, and so far as is known at present, there are many cases of glycosuria or diabetes without oxaluria.

The abundant ingestion of proteids in cases of diabetes, often associated with habitual constipation and protracted retention of the feces in the bowels, causes an increase in the products of putrefaction. We thus find sulphuric acid combined with aromatic alcohols (phenol, indoxyl, etc.) and the combined glycuronic acids increased. The sulphuric acid in the sulphates is also increased by the customary abundant amount of animal food; but we have no reason to believe that in mild cases of diabetes, and apart from toxic disintegration, the whole amount is more greatly increased than it would be under similar circumstances in nondiabetic individuals. The total acidity, too, is often increased in cases of diabetes, as Dérignac and others have noted, but in mild cases only from the causes just mentioned. In severe cases the diacetic and β-oxybutyric and other acids contribute to the increase of the total acidity.

Phosphaturia will be considered later.

Inosite is found in cases of diabetes, but also in all states attended with polyuria. Reichardt's dextrin was found in the urine in a case of mild diabetes, but it is not known whether or not it has any connection with diabetes. The same is true with regard to Leube's glycogen, which may perhaps be identical with Reichardt's dextrin. Lemaire's isomaltose is not well known, and Wedenski found in normal urine something that may be maltose. Gum or achrooglycogen is also found in normal urine (Landwehr, Wedenski, Amann).

Külz and T. Vogel found pentoses (from 0.25 to 0.43 gram a day) in cases of severe diabetes. The test for phenylhydrazin in normal urine also yields some crystals of osazone, which melt at 165° C. (329° F.), and which probably are pentoses (E. Holmgren).

Leon Kalm found urobilin absent in two *severe* cases of diabetes. Vogel and Neubauer mention this absence in normal urine.

M. Ch. Ulrich has come to the conclusion that leucin and tyrosin are present in normal urine, but absent in cases of severe diabetes. (The crystals seen by Roque, Devie, and Hugonenq in the liver,

then, could not have been leucin and tyrosin.) Whether the two substances are present in or absent from the urine in mild cases of diabetes is not known.

In severe cases of diabetes the diastatic and the peptic ferment have been found to be increased in the urine (Hoffmann, Stadelmann, Leo, and others). Lépine found no increase of the diastatic ferment, and nothing is known of such an increase in mild cases.

Albic found diabetic urine strongly toxic (from ptomains, diamins, etc.). Neubauer and Vogel mention that diabetic urine apart from cachexia is not more toxic than other urine, which indicates that the increase of toxic substances is a feature of severe cases exclusively.

From the foregoing brief exposition it may be concluded that we do not at present know of any pathologic substance that is invariably present in the urine in mild cases of diabetes.*

Traube's definition of severe diabetes is the best even to-day: A state that is attended with excretion of glucose in the urine, even when carbohydrates are excluded from the food, and when a pure diet of proteids (and of fat) is observed. It will be understood that this does not mean that severe diabetes is, while light diabetes is not, attended with the *production* of carbohydrates from proteids; it having been proved long ago that proteids give rise to glycogen and thus indirectly (and perhaps also directly) to glucose, in all organisms, diabetic in any stage, or nondiabetic. In the mild stage, however, the patient, while losing (some of) the glucose derived from carbohydrates, has the power of assimilating at least all of the glucose derived from proteids. In the severe stage, though the patient always retains the capability of utilizing a part of the glucose derived from carbohydrates, he has lost the power of utilizing all of the glucose derived from proteids.

On this point, again, we find that mild and severe diabetes are only stages of the same dystrophy, and that there are intermediate states representing the gradual transition from the one to the other. There are patients who, when carbohydrates are excluded from the food, present no glycosuria with a certain daily supply of proteids,

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* The substances whose connection with mild diabetes it seems most interesting to investigate are acetone, oxalic, glycuronic, and lactic acids.

but who again excrete glucose if the amount of proteids is increased, though carbohydrates are still excluded (Naunyn, Lichtheim, Troye, Weintraud).

I wish, however, to insist most forcibly that the hyperglycemia and the glycosuria resulting from proteids do *not* constitute the most important metabolic difference between the mild and the severe stage of diabetes. The main and all-important difference between mild and severe diabetes is the production in the latter of certain acid toxins in the blood and in the urine.

This brings us again to a consideration of that most interesting trio already touched upon: acetone, diacetic acid, and β-oxybutyric acid.* The latter two substances, and especially the last, are important factors in the acid diathesis, the "acidosis," existing in cases of severe, but not of mild, diabetes.

All three substances, free from nitrogen as they are, originate in proteids, and seem to appear as soon as the organism, from some cause or other, attacks its own proteid tissues; they all three appear during starvation, and in the course of different states producing inanition.

Though there is little doubt as to the intimate connection of the three substances as representing different stations on the way to complete oxidation of molecules derived from proteids, the reason *why* the course of oxidation is interrupted in cases of severe diabetes and in some other states will probably continue for a long while to be a puzzle to every student of diabetes. There are good reasons for believing that the same disintegrated proteids as alone give rise to glucose in the urine in cases of severe diabetes also give rise to β-oxybutyric acid and its derivatives, diacetic acid and acetone. The curves representing the glucose derived from proteids and the β-oxybutyric acid show unmistakable parallelism (Naunyn). Any one that follows a case of diabetes in its development through the mild into the severe stage will gain the positive impression of a

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* Acetone [C_3H_6O] is a watery, strong-smelling, neutral liquid, boiling at 56.5° C. (133.7° F.).

Diacetic acid [$C_4H_6O_3$] is a thick, colorless, hygroscopic liquid, which is decomposed into carbonic acid and water at a temperature below 100° C. (212° F.).

β-oxybutyric acid is a colorless liquid of the consistency of syrup, which by oxidation easily yields acetone. Boiled with acid water, it yields α-crotonic acid and water.

parallelism between the glycosuria due to proteids on the one hand, and the three substances named on the other. The patient in the distinctly mild stage can usually take some carbohydrate without the development of glycosuria. During this state there is no β-oxybutyric acid and no diacetic acid in the urine so long as the patient utilizes a sufficient amount of calories in his food, and there is under these conditions no more acetone than in the urine of a normal person using the same kind of food (see below). As the dystrophy advances, the amount of acetone in the urine probably increases before either of the acids has made its appearance. There is at present some uncertainty as to the exact place in the development of the glycosuric dystrophy where this happens (see below). So long as the patient, with exclusion of carbohydrates from the food, becomes free from glycosuria, he presents no diaceturia with a sufficient supply of calories. After some time, however, in slowly developing cases,—generally some years after the beginning of the diabetes,—the patient, even during a period of exclusion from the food of carbohydrates, exhibits a distinct, though slight, glycosuria. At this stage the physician finds for the first time Gerhardt's reaction in the urine with ferric chlorid, though he has taken care to provide his patient with an adequate supply of calories. There is now also an increased amount of acetone in the urine, and there is a faint odor of this substance on the patient's breath. The urine contains no β-oxybutyric acid. The patient is likely to lose flesh, but he is only in the first part of the severe stage, and he is often able to maintain his weight. There is a possibility that this can be effected only by some increase in the amount of fat covering a loss of proteid. As the dystrophy advances the glycosuria due to proteids increases, and *pari passu* Gerhardt's reaction deepens in intensity until it gives rise to a dark bluish-red color, the breath smells more and more strongly of acetone, and autophagy becomes more and more manifest. Long before these last symptoms become extreme, but, in slowly developing cases, often a considerable time after the transition from the mild to the severe stage, the physician, after having removed the glucose from the urine by fermentation, and after having removed other levogyrate substances than β-oxybutyric acid (combined glycuronic acids) by precipitation with ammonia and lead acetate, still finds a distinct

levogyration in the polarimeter. He can afterward observe how the β-oxybutyric acid increases in quantity as the case advances in the severe stage.

It has generally been accepted that when β-oxybutyric acid, the mother-substance of diacetic acid and acetone,* appears in the urine, these latter substances are certain also to be present. It has also been quite generally accepted that β-oxybutyric acid is present only in urine that yields a marked Gerhardt's reaction, or, in other words, in urine that contains a considerable amount of diacetic acid. In general, the rule holds good that when one finds the β-oxybutyric acid,—which undoubtedly denotes a more advanced period in the severe stage and a greater autophagy than either of the two other substances,—these are also to be found. It also seems certain that when diacetic acid is found, which is not rarely the case when no β-oxybutyric acid is present, acetone is usually found in an abnormally increased quantity. The appearance of the latter substance is a less grave phenomenon than that of diacetic acid, and this, again, is less grave than that of β-oxybutyric acid. It seems certain, however, that the quantitative relations of the three substances are not fixed, and that one can not, from the quantity of one, reach a conclusion as to the quantity of either of the others. It is especially worth remembering that the common idea with regard to a necessarily pronounced Gerhardt's reaction in all urine containing β-oxybutyric acid is a false one. I have several times found an unmistakable amount of β-oxybutyric acid in urine that has not yielded with the solution of ferric chlorid the dark bluish-red color of considerable quantities of diacetic acid, but only a light, transparent red. Naunyn and Albertoni have made analogous observations. I find in Neubauer and Vogel's last edition a note (after Stadelmann?) that β-oxybutyric acid may be present without any diacetic acid at all. This certainly is not a common occurrence.

Gerhardt's reaction, if pronounced, indicates constant danger of coma. If the reaction is absent or only faint, this seems to indicate the absence of any considerable quantity of β-oxybutyric

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* Minkowski demonstrated the relation of β-oxybutyric acid as the mother-substance of diacetic acid and acetone. By administering β-oxybutyric acid to diabetic dogs he caused the appearance or the increase of both of the other substances in the urine.

acid, and, unless the general state is extremely bad, there is then no immediate danger of coma. What the actual conditions are in those extremely rare cases in which a strong acidosis has been found as a result of the presence of some other acid than β-oxybutyric (and diacetic) acid, I do not know.

The β-oxybutyric acid in the urine of the three substances under consideration alone reaches large amounts. One hundred grams in twenty-four hours is not very rare ; seventy grams is not uncommon. Külz found 226 grams in one case. The relation between the quantity of β-oxybutyric acid in the blood and the quantity in the urine is not clearly known. Hugonenq found 0.427 per cent. in the blood and 0.448 per cent. in the urine. In the enormous majority of cases the acid diathesis—the "acidosis," as Naunyn calls it—are determined chiefly by the amount of β-oxybutyric acid. This danger is also, and to a great extent, determined by the general state. The same amount of acid which one patient is able to endure for months may kill another in a few hours. As soon as the urine for twenty-four hours contains as much as twenty grams of β-oxybutyric acid there may be danger of coma.*

Diacetic acid is found throughout the whole of the severe stage and, as a mere diabetic phenomenon, not in the mild stage at all. If a healthy person be given an exclusive diet of proteids or of proteids and fat, no diaceturia arises so long as a sufficiently large number of calories for the nutritive balance is ingested ; but the ingestion of a sufficient supply of calories without carbohydrate in the food is a difficult task. A deficit readily arises, of which from 83 to 93 per cent. is covered by the consumption of the patient's own fat, while the remainder is furnished by that of his own proteids (Lusk, Miura, v. Noorden). With this kind of disintegration of the latter diaceturia begins and Gerhardt's reaction with the urine will appear. In this manner diaceturia will arise in cases of mild diabetes, just as it does in cases of ulcer of the stomach or of appendicitis or of seasickness in the progress of more or less pronounced starvation. Unless the starvation is very severe, however, the solu-

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* This danger can also be estimated by the amount of ammonia excreted. As soon as the quantity reaches 1.5 grams in twenty-four hours the acidosis is sufficient, in conjunction with a greatly enfeebled general state, to produce coma.

tion of ferric chlorid will not cause the typical purple or bluish-red color to appear in the urine. When the ferric chlorid falls drop by drop into the urine, it becomes surrounded by a red zone ; when the phosphates of iron afterward sink, the liquid above has a brownish-red, sherry color.

Even in the worst cases the diacetic acid in the urine hardly ever reaches twenty grams in the twenty-four hours, and, though it must be considered as contributing to the acidosis and to the coma, it is far less efficient in this respect than the β-oxybutyric acid.

It is an important circumstance that, so far as I have been able to ascertain, the whole severe stage of diabetes, *per se* and apart from other causes, is attended with diaceturia. Whenever I see a frank Gerhardt's reaction with the urine of a patient receiving an abundant supply of calories with his food,—which generally presupposes a certain amount of carbohydrate,—I know at once that an exclusive diet on meat and fat will not remove the glucose from his urine. On the other hand, the absence of diacetic acid from the urine almost invariably indicates that the case is still in the mild stage, and that a number of days * of abstinence from carbohydrates will cause the sugar to disappear from the urine. There are, however, exceptions to this rule. Also with regard to diaceturia, it is known that there are individuals living on the borderland between the mild and the severe stage of diabetes. I have seen patients who, with an abundant supply of mixed food, presented a large quantity of the glucose in the urine, but no diacetic acid, and who, with an exclusive but quite adequate supply of meat and fat, continued to excrete a small amount of glucose, and then also exhibited slight diaceturia. I take it that these individuals are able with an abundant supply of carbohydrates to protect their own proteids from the disintegration that at once gives rise to both glycosuria and diaceturia ; all the glucose excreted with such a diet being derived from carbohydrates. When carbohydrates are strongly diminished or excluded, the glycosuria due to them ceases, but the patient is no longer able to protect his own proteids, the fat being

* The length of the period of abstinence from carbohydrates for the necessary removal of the glucose from the urine varies according to the patient's power of assimilation, and probably, also, according to the storage of glycogen and to other causes of an unknown nature.

less efficient for this purpose than carbohydrates. He excretes only a small quantity of glucose, but this is now derived from the disintegration of his own proteids, and the diacetic acid has the same origin.

The difficulty of demonstrating the presence of acetone in the urine, and the still greater difficulty of determining the quantity produced in twenty-four hours,* have given rise to much uncertainty with regard to many important points connected with this substance. It is not known in what cases of diabetes acetone, as a mere diabetic phenomenon, is abnormally increased. Unlike diacetic and β-oxybutyric acids, acetone is also found, though only in small quantities, in normal urine. It is certain that in a great many cases of fully developed but mild diabetes there is no increase of acetone with an abundant supply of carbohydrate. Von Jaksch found only the normal, small quantity of acetone in cases with an excretion of from 250 to 300 grams of glucose. On the other hand, it seems probable that an increased amount of acetone may appear in the urine in mild cases. One may sometimes perceive a faint but distinct odor of acetone on the breath of patients in the mild stage, even when they seem to be receiving a supply of calories sufficient for the maintenance of the nutritive equilibrium. When any person, diabetic or not, excludes carbohydrates from his food and lives on meat and fat, the amount of acetone in the urine always increases (Hirschberg and others). This occurs more readily in diabetics than in healthy individuals (Rosenfeld), but even in healthy individuals it may cause an excretion of 0.7 gram in the twenty-four hours. The addition to the food of sixty grams of glucose or of starch causes the acetonuria to disappear.† The excretion of acetone in the urine is certainly of smaller significance than the excretion of diacetic or of β-oxybutyric acid. If, with a sufficient supply of calories from a mixed diet, including a fair amount of carbohydrates, acetonuria exists at all in the mild stage, this certainly must occur in cases not far from the boundary between this and the severe stage.

It is a most important fact that the whole trio of acetone, diacetic

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* Acetone being constantly exhaled through the lungs, the determination of the quantity excreted necessitates an analysis of the expired air.

† Mannite in considerable amounts also causes acetonuria to disappear (Hirschberg).

acid, and β-oxybutyric acid seem to be more easily produced with an exclusive diet of fat and proteids than when carbohydrate is added. Dr. D. Gerhardt (see Naunyn) has observed that the same insufficient supply of calories in the diet causes the appearance of more β-oxybutyric acid in the urine if made up of proteids and fat alone than if derived from a mixed diet, consisting in part of carbohydrates. Hirschberg has proved the analogous fact with regard to acetone, and the same is probably true also of diacetic acid. It is a common phenomenon that Gerhardt's reaction perceptibly increases in diabetic urine when the patient is deprived of carbohydrates and is put on a strict animal diet.

Free fatty acids (formic, acetic, butyric, propionic, valerianic), which in normal urine scarcely reach 0.01 gram in the twenty-four hours, may in cases of severe diabetes be present in tenfold quantity (Rumpf). These acids are derivatives of proteids, and the diabetic *aciduria*, as has been already mentioned, is a feature of the severe stage.

The whole amount of acids—acetic, β-oxybutyric, fatty acids, lactic acid, oxalic acid, phosphoric acid, sulphuric acid (in the sulphates and combined)—may reach a large quantity, and in the course of twenty-four hours equal forty or fifty grams of concentrated sulphuric acid.

The acid diathesis, the acidosis, causes an increase of ammonia in the blood and the urine in cases of severe diabetes, and the quantity in the urine, which normally is about 0.7 gram for twenty-four hours, may reach the enormous amount of twelve grams in cases of diabetes (Stadelmann). This shows the great variation in the individual ability to bear up under the acidosis and to resist its comatose influence ; even 1.5 grams of ammonia constitute a warning of coma, and two grams are often quite a distinct forerunner of it.

When in a severe case of diabetes the carbohydrates are restricted or are excluded, autophagy and loss of bodily weight increase ; glycosuria and generally polyuria diminish ; the urine, even when diluted to its previous volume, yields a more pronounced Gerhardt's reaction, from the presence of an increased amount of diacetic acid ; and the polarimeter shows some increase in the excretion of β-oxybutyric acid. Sometimes, in cases that had previously

been free from albuminuria, one also finds that with the strict diet the urine begins to contain a small amount of albumin, probably from the effect of the acid toxins on the kidneys.

There are in the literature, and especially from those who defend exclusion of carbohydrates, even in the severe stage, reports of a decrease of diaceturia with such a dietetic change. Thus, Troye * relates the case of a patient who, with mixed diet, excreted 658 grams of glucose and a moderate amount of diacetic acid in more than nine liters of urine in the twenty-four hours, but who, after five days of a strict diet, excreted a normal amount of urine, free from diacetic acid, but containing twenty-seven grams of glucose. Such a statement is so contradictory to all of my experience that I can only conclude that there must be some mistake.

Stokvis seems to consider the occasional appearance of albumin in the urine after the exclusion of the carbohydrates from the diet as resulting from the decrease in the quantity of urine, so that a trace, previously undiscoverable, becomes appreciable with Heller's nitric-acid test. Even after diluting the urine to its previous volume one finds sometimes, with a marked restriction of carbohydrates, a trace of albumin that did not appear previously.

Azoturia † in cases of diabetes has been much spoken of. An increased amount of nitrogen may appear constantly in the urine in cases of diabetes from two entirely different causes. There may be an *alimentary azoturia* and a *protoplasmic* or *toxic azoturia.*

Alimentary azoturia of diabetes is easy to understand, and is the only increased excretion of nitrogen in the mild stage. The diabetic patient either ingests much less carbohydrate with his food or he again loses part of it in his urine, and he must make up for this by the ingestion of a larger amount of fat and proteids. The larger supply of proteids to a diabetic as to a healthy person necessarily leads to a larger excretion of nitrogen. This excretion may be temporarily increased in consequence of marked polydipsia and polyuria, which *per se* may for the moment increase the nitrogen in the urine. During somewhat longer periods, however, with sufficient food, the amount of nitrogen excreted in a case of diabetes in the mild stage does not exceed the amount of nitrogen ingested.

The second variety of diabetic azoturia, *toxic* or *protoplasmic azo-*

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* "Archiv für experim. Path. und Pharm.," 1890.

† Among one hundred cases Bouchard found forty-seven with an ordinarily large amount of nitrogen in the urine, forty with an increased amount, and thirteen with a diminished amount. Such figures are not worth much, if they do not cover a considerable length of time.

turia, is a feature of the severe stage exclusively; but it has not yet been quite decided whether it occurs in all or only in advanced cases of this stage. Toxic azoturia, however, was known to Bernard, and was subsequently studied by Voit and Pettenkofer, Külz, v. Mering and Minkowski, Chauveau and Kaufmann, Gley, Thiroloix, and others. It is believed to be caused by the toxins, and chiefly by the acid toxins, in the blood, and their disintegrating influence on protoplasm. The most marked effect of this kind undoubtedly is caused by β-oxybutyric acid. For my part, I am inclined to believe that some toxic disintegration of protoplasm takes place throughout the whole of the severe stage, and that there is a slight toxic azoturia even in cases in which the β-oxybutyric acid has not yet shown itself, a purely diabetic diaceturia being already a sign of toxic or protoplasmic disintegration. It will be no easy matter, however, to demonstrate in such cases a constant excess of nitrogen-excretion over nitrogen-ingestion. This seems to me, however, to have been fully done in dogs after total extirpation of the pancreas, and I consider unsustained the doubt remaining in some minds as to the very existence of a diabetic toxic disintegration of tissue and the consequent azoturia.

During coma the products of metabolism in the urine generally decrease. Münzer and Strasser, however, observed the nitrogen increase.

The present views on diabetic azoturia have been gradually developed by the labors of Mosler, Boecker, Thierfelder, Uhle, Reich, Rosenstein, Haughton, and Gäthgens (1853–1866), and within more recent years by the researches of Külz, Kratschmer, Pettenkofer and Voit, Frerichs, Lusk, Fr. Voit, Minkowski, v. Mering, v. Noorden, Weintraud, Borchert and Finkelstein, Gley, Thiroloix, and others.

The enormous amounts of animal food consumed by some diabetic patients sometimes cause the appearance of large quantities of nitrogen in the urine. Leube found 150 grams, Fürbringer 163 grams of urea, and I found eighty grams of *nitrogen* (equal to 171 grams of urea; from 13 to 16 per cent. of the nitrogen, however, belongs to other substances) in twenty-four hours. Such figures are rare, but large quantities of nitrogen in the urine are common in cases of diabetes. This fact favored the opinion that every diabetic patient excreted more nitrogen than he ingested, an opinion which for a long time prevailed, though the very analyses on which it was founded and the mathematic absurdities to which it leads, considering the average duration of life in mild cases of diabetes, ought to have led quickly to more rational views.

It is evident that if a diabetic and a healthy individual ingest the same

number of calories with their food, and the diabetic again loses a certain amount of them in the form of glucose in his urine, the food that is barely sufficient for the healthy individual will not be sufficient for the diabetic, and the latter will cover the deficit by expending a part of his own fat and a smaller part of his own proteids. He will then decrease in bodily weight, and his urine will contain more nitrogen than has been ingested and digested. The same would happen with the healthy individual if from his food were removed the number of calories represented by glucose in the diabetic's urine. If, however, both individuals received the same amount of calories with a diet that permits the diabetic to utilize the whole amount, he will not, in the mild stage, excrete more nitrogen than the healthy individual.

In the severe stage toxic disintegration of protoplasm is *a priori* not improbable, and it seems almost impossible to explain the results of recent most laborious investigations without admitting its occurrence.

It is not at all certain that even all of the common toxins in cases of diabetes are known at present, though those that are amply explain the comatose syndrome. Then, just as there are instances in which levulose appears in the urine instead of the customary saccharid, glucose, there may be exceptional products of metabolism. In fact, the more one studies diabetes, the more will he be prepared for surprises. We must, therefore, not entirely close our minds against the possibility of correct observation in Rupstein's (1874) and Külz's (1875) cases of diabetes in which alcohol was excreted in the urine. It is impossible to presume, in either case, the occurrence of fermentation in the bladder, and there scarcely remains any other way of explaining the formation of alcohol than by accepting Rupstein's theory of an oxidation of diacetic acid. Külz, who was about as skeptical as any right-minded person is justified in being, considered that the large amount of alcohol in the urine was proved in the case that he published. Still, he did not observe it himself; but Dr. Guckelberg, an assistant of Liebig's, performed the analytic work. The patient died (in coma) in 1869, shortly after exhibiting symptoms of alcoholic intoxication, but before the reactions of the substances chiefly concerned were as well known as they are now; and incipient diabetic coma may sometimes resemble alcoholic intoxication.

The diabetic patient using an abundance of animal food ingests a large amount of salts. Lean meat contains about 0.70 per cent. of phosphoric acid, and *diabetic phosphaturia* may be four times as marked as the normal phosphaturia. Whatever future researches may have to add to our present views on the functions and influence of mineral salts in the organism, the question that chiefly interests us here is whether or not the component salts of the bones are found in the urine in cases of severe diabetes in larger quantities than can be explained by the quantity of salts ingested plus the protoplasmic disintegration of the soft cellular tissues almost universally admitted as taking place in such cases. Calcium and magnesium phosphate

and the other salts that enter into the constitution of the bones are excreted in such large amounts in some cases of severe diabetes that many writers in explanation suggest the existence of *osteomalacia* as a result either of the acidosis or of trophoneurotic influences. The question has not yet been decided, and Dr. E. Tenbaum's recent researches only prove what an enormous amount of elaborate work will be required for its solution.

The water streaming constantly through the organism, with most important functions and effects (of which there is yet much to learn), is generally increased in cases of diabetes. Even normally the figures are large. About sixty-three per cent. of the human body consists of water. A man of ordinary size ingests about 2.5 or 3 liters daily,* and excretes an equal amount. About one-third of the whole excretion passes through the lungs and the skin, and the greater part of the remainder is eliminated with the excreta and feces, chiefly in the urine, and only a comparatively small part in other excretions. In cases of diabetes the increased ingestion of water causes chiefly an increase in the amount of urine. The elimination through lungs and the skin is usually diminished, partly on account of atrophy of the latter, partly on account of the increased amount of sugar in the blood, which retains the water more firmly than normally.

Ever since 1580 some persons, in their amazement at the enormous quantity of urine sometimes passed in cases of diabetes, have held the curious notion that a diabetic patient may pass more urine than he ingests water, and even Gäthgens, in 1886, believed that he had proved this astounding fact, which could scarcely be explained otherwise than upon the theory that a diabetic patient, like concentrated sulphuric acid, attracts to himself the water in the air. This would have to be done by the so-called "negative insensible perspiration"—one of the most amusing products of speculative science. [The positive insensible perspiration is obtained by weighing a person at the beginning and at the end of the experiment, by adding the weight of the ingested water to the first and of the excreted water to the last figure; the difference between the two sums then represents the "insensible perspiration."] Burger, Nasse, Külz, and Engelmann have put an end to all these fanciful theories by showing that during somewhat extended periods no more water is excreted in cases of diabetes than is ingested. The insensible perspiration in severe cases is undoubtedly diminished.

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* According to Forster, from 2200 to 3500 cu. cm.

A diabetic needs in general the same amount of digested and utilized calories as a normal individual. This was proved by Pettenkofer and Voit,* and has been corroborated by Fr. Voit, Weintraud, Pautz, Borchert and Finkelstein, and other investigators.

According to Rubner, a normal man requires in twenty-four hours per kilogram of bodily weight :

In repose, ...	32.9 calories.†	With moderate work, . . .	41 calories.
With light work,‡ . .	34.9 "	With severe work, ...	48 "

The thin individual, richer in cells, requires more calories than the fat one, with more comparatively inactive adipose tissue. The growing child, with a larger bodily surface compared to its weight, requires more than a developed person.

One gram of	carbohydrate	represents	gross	4.1	calories,	net	3.8.§
" "	fat	"	"	9.3	"	"	8.4.
" "	proteids	"	"	4.1	"	"	3.2.

The figures for the gross value are Rubner's, those for the net value are v. Rechenberg's, who estimated the average loss from the amount of the ingested (but undigested) food in the feces. This loss usually is not greater in diabetics than in normal individuals, but it is probably somewhat smaller than it was in v. Rechenberg's weavers, who doubtless received rather coarse food.

The alcohol represents gross seven calories, and the net value may, in view of the small daily doses, be put practically at the same

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* The learned Professors Pettenkofer and Voit, however splendid their life's work, unfortunately were sometimes a little absent-minded. Thus, when in 1867 they made their observations upon an unusually small diabetic Teuton, weighing only 54 kilograms, they at first overlooked the fact that he could not be expected to eat as much and to consume as much oxygen and produce as much carbonic acid as an ordinary Teuton; and from the low figures they gained the impression that the metabolism was decreased. In relation to the bodily weight, however, their man consumed a perfectly normal amount of calories,—34.5 calories per kilogram of bodily weight in twenty-four hours, during repose, in the apparatus used. All subsequent figures, correctly interpreted, lead to the same result. (Livierato's researches can not be considered satisfactory.)

† I always mean great calories, viz., the amount of heat required to raise the temperature of one kilogram of water 1° C.

‡ Only mechanic (and chemic) work entails expenditure of force. Nature is too generous to charge us for our poor intellectual work.

§ Rubner's figures are :

4.116 calories for	starch.	3.877 calories for	lactose.
3.959 "	cane-sugar.	3.692 "	glucose.

figure. The levulose, an important alimentary item in cases of diabetes, represents about 3.7 calories gross, and nearly as much net, the amount taken being almost entirely absorbed.

It must be borne in mind that the isodynamic law is to be accepted with some reservation, and that different kinds of food are not interchangeable with regard to the number of calories they represent. The same number of calories derived from carbohydrates are more efficient in protecting the proteids of the organism than the calories derived from fats, and the latter rank higher in this respect than the calories derived from alcohol. Then, it seems to me that diabetics, especially when subjected to rigorous restriction of carbohydrates, sometimes, though unfortunately only for a short while, apart from the calories lost by glycosuria, consume an amazingly large amount of calories. I have seen the value utilized reach nearly one hundred calories per kilogram of bodily weight in twenty-four hours. The toxic disintegration of protoplasm in severe cases explains this phenomenon in part. In other part it may be explained by the increased work necessary for the mere transformation of other molecular structures into glucose. Still, I do not feel at all certain that we know at present in every detail how to estimate dietic values for our diabetic patients.

To estimate the caloric value of a patient's food we must weigh all that he ingests and obtain the net value of the total. So far as proteids are concerned, we can take the easier way of determining the nitrogen in the urine. Albumin consisting of sixteen per cent. nitrogen, the ingested and digested albumin can be determined in grams by multiplying the number of grams of nitrogen in the urine by $\frac{100}{16}$ (= 6.25). (We then presume that practically all of the nitrogen has, as usual, been ingested in the form of proteids, and we take no account of the toxic disintegration of the tissues, which is a feature only of severe cases, and usually gives rise to the appearance of comparatively small amounts of nitrogen in the urine, and which can not be determined without an immense amount of analytic work.) In using this mode of calculation we must, of course, value each gram of proteid at 4.1 calories. From the final sum of calories derived from proteids, fats, carbohydrates, and alcohol we then subtract the number of calories lost in the urine in the form of glucose, valued at 3.7 calories per gram.

Mr. R. has drunk 0.5 liter of milk with 17.5 grams of proteid, 18 grams of fat, and 24 grams of lactose; which represent in calories $17.5 \times 3.2 + 18 \times 8.4 + 24 \times 3.8 = 298.4$. He had had 650 grams of raw meat, with about 20 per cent. of proteids and 6.5 per cent. of fats and a net value of $416 + 354.9 = 770.9$ calories. Four eggs may be considered as representing 280 calories. Two hundred grams of butter (with 1.6 grams of proteid, 166 grams of fat, and 0.4 grams of carbohydrate) represent 1394.6 calories; 100 grams of rye-bread, 209.84 calories; 50 grams of rich cheese yielded 13 grams of proteids + 15 grams of fat + 1.25 grams of carbohydrate = 172.2 calories. Sixty grams of American whisky represent about 219 calories. No account was taken of some tomatoes and some "sauerkraut." If I am correct in my calculations—and of this I am not certain—R. received $298.4 + 770.9 + 280 + 1304.6 + 209.84 + 172.3 + 219 = 3345$. Mr. R., again, lost 51.8 calories in 14 grams of glucose in the urine, and thus really received only 3263.2—*i. e.*, a trifle more than 40.3 calories per kilogram of his bodily weight, which was 82 and was increasing.

Mr. L. had excreted 31 grams of nitrogen, and had thus utilized $62.5 \times 31 = 193.75$ grams of proteid, or $4.1 \times 193.75 = 793.3$ calories. About 180 grams of fat had yielded, net, 1512 calories. Ninety grams of white bread had yielded 179.18 calories. Twenty grams of alcohol had yielded 140 calories. The man had lost 32 grams of glucose, or 118.4 calories. He had thus utilized $2624.48 - 118.4 = 2506.08$ calories. He weighed 68 kilograms, had received over 36.8 per kilogram, did not perform much work, and increased in weight.

These calculations, however, are troublesome, and will not be undertaken in addition to the strain of practical work. It is easy, however, to remember that soft, white bread usually yields about twice as many calories as its own weight in grams; that an egg represents about 70 or 75 calories; that raw, lean meat yields a somewhat larger, raw, lean fish a somewhat smaller, number of calories than its own weight in grams; that butter yields about 7 calories per gram, and alcohol also 7 calories per gram. All of these figures represent the net value, and are all that the practitioner need bear in mind when confronted with the important task of informing his patient as to the necessary amount of food to be ingested.

The oxygen consumed and the carbonic acid generated in cases of diabetes equal normal quantities. Except what is represented by the glucose in his urine and by diabetic toxins, the diabetic patient oxidizes his food, especially the sometimes enormous quantities of fat, as a normal person does, just as he oxidizes organic acids (Strauss), or lactates (Weintraud), or benzol (v. Nencki and Sieber), etc. The normal consumption of oxygen varies from 3 to 4.5

cu. cm., and is, on the average, 3.81 cu. cm. per kilogram of bodily weight in the minute. The amount of carbonic acid excreted, estimated on the same basis, varies from 2.5 to 3.5 cu. cm., and is, on the average, 3.08 cu. cm. The figures that Leo * and others have found in cases of diabetes correspond exactly with these figures.

Since Reignault's and Reiset's classic researches it has been known that the relation between the oxygen consumed and the carbonic acid excreted varies somewhat, for evident chemic reasons, according to the nature of the food, so that the respiratory quotient, or $\frac{\text{produced } CO_2}{\text{consumed } O}$, during the ingestion of food consisting essentially of carbohydrates approaches the quantity 1. If proteids make up the greater part of the food, the figure is about 0.73. When large quantities of fat exclusively are taken, the quotient falls somewhat, and is about 0.70.† It is evident that the quotient in diabetes approaches in general the latter values, the patient not being able fully to utilize the digested carbohydrates,‡ and that it is the farther from the ordinary maximum value of 1 the less carbohydrate oxidized, whether this arises from restriction of supply or from a low limit of the power of assimilation. Laves' and Weintraud's researches show, however, that a diabetic patient on an exclusive diet of meat and fat has the same respiratory quotient as a normal person on the same

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* "Zeitschr. f. klin. Med.," Berlin, 1891, Supplement.

† Laulanié found that in starvation both the respiratory quotient and the production of heat are at their lowest. With an exclusive supply of meat (muscles) both the production of heat and the respiratory quotient increase. Both figures in the latter become higher, but the increase in the amount of carbonic acid excreted is rather greater than that of the oxygen excreted. The quotient, however, still remains comparatively small. With an almost exclusive supply of carbohydrates the quotient increases considerably and may exceed the figure 1. The thermic curve follows the curve of the absorption of oxygen. A considerable part of the carbonic acid is produced without the generation of heat by the transformation of carbohydrate into fat.

‡ Laves and Weintraud, from the results of their investigations, have reached the conclusions that in cases of diabetes the ingested carbohydrates, even apart from what is lost as glucose in the urine, do not give rise to the production of fully as much carbonic acid as in normal individuals, probably because a larger part of the carbohydrates remains in cases of diabetes at a lower point of oxidation; *e. g.*, as oxalic acid instead of forming water and carbonic acid.

Henriot, Magnus-Levy, and Bleibtreu also found that with an abundant and exclusive supply of carbohydrates the amount of carbonic acid excreted may attain a higher figure than the amount of oxygen consumed, so that the respiratory quotient exceeds the figure 1, and may even reach 1.3.

diet, and Leo's figures of this quotient make it evident that even in very severe cases of diabetes with a mixed diet a part of the carbohydrates must have been utilized and then excreted as carbonic acid.

CHAPTER VIII.—INVESTIGATION OF A CASE OF DIABETES.

It is the duty of every physician to test his patient's urine for sugar. This investigation alone enables us to detect a simple, but rarely insignificant, habitual glycosuria, and the presence of sugar in the urine may be the one distinctive symptom of a mild but true diabetes.

In making this test two most important points must be observed. In testing there should be used, systematically, a sample of the urine likely to contain the maximum, or nearly the maximum, percentage of sugar excreted during the twenty-four hours, and the test should be so performed as to reveal the minimum distinctly pathologic quantity of glucose in the urine.

There are, as we have seen, a great many individuals with a lowered power of assimilating carbohydrates who secrete glucose only for short periods in the day, some time after meals, and then only in small quantities. Even true diabetics in the mild stage are often, even apart from diet, free from glycosuria for some parts of the twenty-four hours, especially in the morning before the first meal.

The first and most important rule is, therefore, never to use for a test a specimen of urine passed when the patient's stomach is empty, before the first meal of the day.

The best means of deciding from a single examination of the urine whether a person is normal or not in this respect is furnished by a sample passed an hour after the end of the dinner. In cases of simple glycosuria the excretion at this time is, with rare exceptions, near its maximum. The bladder should be emptied just before the meal, which ought to be a mixed and abundant one, including

meat, fat, bread, potatoes, rice, and sweets, but not any considerable quantity of alcoholic liquors.

The patient must be in his ordinary state; the sample of urine ought not to be taken during any illness or indisposition or after violent emotion or excess of any kind.

For the purpose of revealing with certainty the presence of pathologic traces of glucose, the practitioner will do well to use constantly two different reduction-tests, and to verify the saccharine nature of the reducing-substance by the fermentation-test whenever doubt exists. The best reagents known for this purpose are Nylander's solution of bismuth and Trommer's test, used in a somewhat modified way with Fehling's solution of copper.*

The test with Nylander's solution is the easiest to perform and to observe. A tube is filled one-fourth or one-third with urine, and one-tenth or one-fifth as much of Nylander's solution is added, the mixture being boiled for four or five minutes. It is important to boil for the full length of time. Under these conditions urine containing at least some tenths of a per cent. of glucose will be rendered more or less opaque and black; urine containing only 0.02 or 0.03 per cent. will assume a somewhat brownish color, in consequence of admixture of the reduced bismuth with the flakes of phosphates, etc. Urine containing no sugar, or less than 0.02 per cent., will, except in rare cases, maintain its transparency and its yellow color;† the latter will perhaps be somewhat deepened.

Trommer's test, as is known, has undergone many modifications, and may be performed in several different ways. I have adopted Worm-Müller's modification in part, and like to combine it with the decoloration of the urine by filtering it through well-pulverized and

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* Both of these tests are much easier and quicker of performance than Fischer's test, and are, when only hundredths of a per cent. of glucose are concerned, at least as reliable. Fischer's test, as is well known, consists in heating (over a water-bath) for about half an hour about fifty parts of urine, to which have been added one part of phenylhydrazin chlorate and two parts of sodium acetate; the characteristic yellow crystals of glycosazone form in cooling. Even when pure phenylhydrazin is used the test—which also yields similar crystals with other saccharids than glucose—yields, when 0.02 per cent. or smaller quantities of glucose are present, imperfect crystals, not with certainty to be distinguished from similar formations due to pentoses (E. Holmgren) or glycuronic acids (except by their melting at 205° C.—401° F.) (Thierfelder, Geyer).

† Apart from the white flakes of the phosphates.

well-washed animal charcoal. In one tube I put a few cubic centimeters of the urine and in another about the same amount of Fehling's solution. The latter is then diluted with two or three times its volume of water, and the contents of both tubes are simultaneously heated to boiling. As soon as they are fairly boiling I let them cool for twenty-five seconds, the temperature falling to 70° or 75° C. (158° or 167° F.).* I then slowly pour the urine into the other tube ; reduction will take place within five or ten minutes if the urine contain at least 0.01 or 0.02 per cent. of glucose. By following Worm-Müller's directions closely, and especially by determining experimentally the best possible quantitative relations between the solution and the urine, one may somewhat improve the test, which, however, performed in the manner just described, is delicate enough for practical purposes and consumes but a short time.

I sometimes perform the test by passing not too small a quantity of urine through animal charcoal on the filter, then washing the charcoal with a small quantity of water, diluting one volume of Fehling's solution with two or three volumes of this water, and heating to the boiling-point.

In whatever manner the reduction-test is performed, it is *absolutely* necessary, in cases at all doubtful, to verify the saccharine quality of the reducing-substances by the fermentation-test. To this end a small piece of yeast is placed in a tube almost filled with urine, which is permitted to stand at ordinary room-temperature or in a somewhat warmer place. If after fermentation the reducing-substance has disappeared or diminished, it may be concluded that it was glucose or levulose or maltose, of which saccharids glucose is very common in urine and the two others are extremely rare.

By omitting the fermentation-test and by trusting only to reduction-tests, one incurs great danger of increasing, in his own mind or in the literature, the large number of cases of false glycosurias.

Referring for further particulars to the special manuals, I would here only

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* Worm-Müller found that though the sugar reduces more readily at a higher temperature than 70° or 75° C. (158° or 167° F.), a reduction at this higher temperature is easily brought about by other substances than glucose. At a lower temperature than 70° C. (158° F.) the test is less delicate.

The decoloration of the urine, which was first practised by Claude Bernard, was adopted by Seegen as a modification of Trommer's test, for the purpose of eliminating the reducing uric acid and substances that prevent the cupric oxid from being precipitated.

recapitulate that glucose reduces Fehling's, Nylander's, and Barfoed's* solutions, turns the ray of polarized light to the right, and is readily and completely decomposed into alcohol, carbonic acid, etc., by the influence of common yeast and of saccharomyces apiculatus. Its crystals of osazone melt at 205° C. (401° F.).

Uric acid and kreatinin, which are present normally and constantly in the urine, cause reduction, but do not undergo fermentation.

Many of the combined glycuronic acids, some of which are present in normal urine (in combination with indoxyl, skatoxyl, phenol, etc.), also cause reduction. After the ingestion of chloral there may, with or without glucose, be quite a considerable reduction from the presence of urochloral acid (= trichlorethyl-glycuronic acid). The combined glycuronic acids do not undergo fermentation, and turn the ray of polarized light to the left.† One may remove the combined glycuronic acids from the urine with ammonia and lead-acetate.

Many substances besides may be responsible for the presence in the urine of nonsaccharine reducing-substances, some of which probably are combined glycuronic acids. Other substances, such as benzoic, salicylic, oxalic, prussic, and mineral acids, turpentine, different phenols, morphium, copaiba, glycerin, kairin, sulphonal, trional, arsenic, caustic alkali, etc., may cause true glycosuria. Rhubarb, senna, eucalyptus, large doses of quinin, also cause a reaction with Nylander's solution similar to that caused by glucose.

Alkapton reduces Fehling's solution, but not the solution of bismuth. It does not deflect the ray of polarized light, and it does not undergo fermentation. Urine containing alkapton presents, after some time, a brown, almost a black, color.

The disaccharid maltose, which probably sometimes occurs in urine, is, like glucose, attacked by common yeast; but it reduces Fehling's solution only two-thirds as much as glucose, and it turns the polarized light three times as much to the right. Unlike glucose, maltose does *not* reduce Barfoed's solution, which is, however, reduced to some extent by other substances present in all urine.

Levulose causes about as much reduction as glucose, and is quite readily attacked by common yeast; but it turns the ray of polarized light to the left, and its osazone melts at 190° C. (374° F.).

Lactose turns the ray of polarized light to the right and reduces Nylander's and Fehling's solutions. It does not reduce Barfoed's solution, which, unfortunately, with regard to urine, does not help us much, as other substances (than saccharids), that are constantly present in urine, cause its reduction; but lactose, though it undergoes lactic-acid fermentation or alcoholic fermentation with other fungi, does not ferment at all with saccharomyces apiculatus, and ferments with common yeast only when it has been inverted into its two monosaccharids, glucose and galactose, which both ferment.

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* Barfoed's solution is a solution of from 0.5 to 4 per cent. copper-acetate with one per cent. of free acetic acid. It is not reduced by lactose or maltose.

† Glycuronic acid *per se* turns the ray to the right, but it is never present in urine.

The inversion is likely to take place spontaneously after some time. Lactosazone melts at 200° C. (392° F.).

Galactose is not under ordinary circumstances to be expected in urine, but may be present after the ingestion of large amounts of galactose, and arises (with glucose) when lactose is boiled with diluted mineral acids. It reduces somewhat less, but turns the ray of polarized light more strongly to the right than glucose. Its osazone melts at 193° C. (379° F.). Laios (found by Leo in 1887) reduces, but does not ferment.

Pentoses reduce, but do not deflect the ray of polarized light and do not ferment. They are found both in diabetic and in normal urine.

The substance found in urine after the ingestion of turpentine reduces and ferments, but it does not deflect the ray of polarized light (Vetlesen).

Animal gum turns the ray of polarized light to the right, but does not ferment. It forms a compound with the copper of Fehling's solution, which is precipitated in whitish-blue flakes.

If after a generous mixed meal the urine contains no glucose as determined by the tests named, a distinctly pathologic deficiency in the power of assimilation is excluded.

Some who have occupied themselves a good deal with similar researches may feel some doubt as to the correctness of this assertion. May not, they will probably urge, a simple glycosuria, or even a "periodic" or an "alternating" diabetes, or a very mild common diabetes after abstinence from carbohydrates continued for some time, withstand such a trial without the appearance of glucose in the urine? To this I would answer that even in such cases the urine will, an hour after a generous *mixed* meal, yield to the tests named evidence of the presence of at least a trace of glucose. I have found this to be the case even in individuals who have been capable of taking large portions of rice or cane-sugar without the development of glycosuria. Escape from detection in any stage of the glycosuric dystrophy under the circumstances named will at all events be exceedingly rare.

If after a generous mixed meal the urine contains a considerable quantity (several per cent.) of sugar, the secretion is undoubtedly that of a diabetic individual.

My next step—never to be omitted—will then be to submit the urine to Gerhardt's test for diacetic acid. This is done in a moment. I almost fill an ordinary test-tube with urine and add six or eight drops of a solution of ferric chlorid. If the urine, with the patient in his customary state and with a good supply of calories in his food, turns a red, or, still more, if it turns a dark bluish-red color, the patient is, without doubt, in the severe stage of diabetes. It is then unnecessary, and, besides, it would incur danger of coma, to exclude carbohydrates from the patient's food.

If Gerhardt's reaction is wanting or indistinct, I may, without danger, so far as possible exclude carbohydrates from the diet for several days or a couple of weeks. If during this *régime* the urine becomes free from glucose, the patient is in the mild stage; but if sugar appears, he has entered upon the severe stage of diabetes.

Having ascertained that the patient is in the mild stage of diabetes, it must be determined how much carbohydrate he is capable of taking without the development of glycosuria. For practical purposes this is best done by allowing the patient, in addition to generous animal food, a certain amount of the kind of bread that he prefers. In doing this I may either, after absolute exclusion of bread, permit larger and larger amounts until glycosuria appears, or diminish the amount after a more generous supply until the glycosuria ceases; and it is not an entirely indifferent matter which of these plans I select. With exclusion of carbohydrates or restriction of them below his power of assimilation the patient increases this power, and thus, by progressing from small to larger amounts, I may find a higher power of assimilation than by pursuing the opposite course. If I am anxious in a case not to give the patient more carbohydrates than he can take continually without the development of glycosuria, I proceed from amounts of carbohydrate that are beyond his power of assimilation, and decrease them until glycosuria disappears. In either event I use for analytical purposes samples from the whole amount of urine collected during twenty-four hours.

If after a generous mixed meal I find only a small quantity of glucose in the urine, I must submit the case to further investigation before giving the dystrophy a name or forming a concrete opinion as to its nature. In this case, too, I always take for analysis a sample of the urine collected and measured during twenty-four hours, while the patient consumes with his daily food a rather large, determined amount of carbohydrates, represented by from 150 to 200 grams of bread and some potatoes, rice, macaroni, peas, and cane-sugar. The patient should observe this *régime* for a few days before collecting his urine for the test. If under such circumstances, and with the patient in his habitual state, *the mixed urine for twenty-four hours* contains a determinable amount of glucose, amounting at least to several tenths of a per cent., the case is

one of true, though it may be very mild, diabetes, and I am then generally able to find other purely diabetic symptoms besides glycosuria.

If an individual excretes for a short time after every generous mixed meal a determinable quantity of glucose, which in the urine passed at that time may occasionally reach perhaps even one per cent. or somewhat more, but which, in the whole amount of urine for the twenty-four hours, during a continued, abundant supply of carbohydrates, is present in scarcely more than traces, or, at all events, in less than several tenths of a per cent., the decision as to whether the case shall be called one of simple glycosuria or of light diabetes is to a certain extent a matter of opinion.

Still, continued investigation will elicit further information as to the patient's state and future prospects.

The patient, therefore, may be given, one morning for breakfast, exclusively, a large portion—*e. g.*, 200 grams—of dry rice, well cooked in milk or water. The urine is then collected for six or eight hours. Even in cases in which, after every generous mixed meal, glycosuria appears, the urine, after such an amount of rice, may remain perfectly free from glucose. I am then inclined to call the case one of simple glycosuria, which, especially in middle or advanced age, generally is of no noteworthy clinical importance. A recurring glycosuria after meals consisting exclusively of rice or bread, has, on the other hand, a deeper significance than the same phenomenon after generous mixed meals or after the ingestion of large amounts of cane-sugar, and I consider the designation diabetes in such a case better to represent the clinical condition and the prognostic aspect than that of simple glycosuria.

If after the ingestion of large quantities of rice the patient exhibits no glycosuria, I give him on another day 200 or 300 grams of cane-sugar, which is most easily taken dissolved in some mineral water containing free carbonic acid. An individual who, after the ingestion of large amounts of boiled rice, excretes glucose with his urine will also do so after the ingestion of large amounts of cane-sugar. It is quite possible, however, that a person in whom, after every dinner of mixed food, glycosuria appears may exhibit none after the ingestion of large amounts of cane-sugar, but only excrete some unchanged saccharose, as everybody without exception does under

the circumstances. In such a case the urine will not reduce Fehling's and Nylander's solutions before but only after being boiled with several drops of sulphuric acid. I then call the case one of simple glycosuria. In other cases the ingestion of a like amount of cane-sugar will be followed by the appearance in the urine of a mixture of cane-sugar and glucose, and I find more marked reduction after boiling with sulphuric acid than before, the difference representing the amount of cane-sugar that had passed through the organism unchanged.* Such a case always represents a weakened power of assimilation, and is either one of simple glycosuria or of diabetes. Referring to chapter II of this book, I am the more inclined to the milder name and the more favorable prognosis, the more unchanged cane-sugar and the less glucose the patient excretes.

It is also possible to test the power of assimilation by the administration of a large amount of glucose; only as all persons excrete glucose after the ingestion of very large amounts of this saccharid, the necessary quantity of which varies greatly even in the same individual under apparently similar conditions, and as under ordinary conditions such amounts of glucose are never taken, I prefer the other tests. From my own researches I will say that the development of glycosuria after the ingestion of 100 grams of glucose often denotes a weakened power of assimilation. In using ordinary "technical" glucose, mixed with dextrin, one ought to put the test-amount at least at 150 grams. Achard and Weil (1898) inject 10 cu. cm. of pure glucose *subcutaneously*, and consider the appearance of glycosuria after this pathologic. In a normal person, whose bodily weight unfortunately is not mentioned, Fritz Voit found (1896), after the subcutaneous injection of sixty grams of glucose, a trace of sugar in the urine; 100 grams given in the same manner caused a glycosuria of 2.6 grams. (Biedl, R. Kraus, and Pavy have made similar researches. If made in large numbers under different dietetic conditions, and with a determination of the bodily weight, experiments with subcutaneous injections may provide the means of finding some exact expression for the normal power of assimilation.) To decide immediately and after a single investigation the nature and the prognosis of a slight excretion of sugar, is, as may be understood from the foregoing, quite impossible. Neither does there at present exist any universal rule for the refusal or acceptance of an application for life-insurance in these

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* By boiling with diluted sulphuric acid the cane-sugar is "inverted" into a mixture of glucose and levulose. The former turning the ray of polarized light to the right, the latter to the left, polarization yields no information. Both saccharids, however, cause practically equal reduction (levulose $\frac{924}{1000}$ as much as glucose), and titration before and after boiling yields information as to the amount of glucose and the amount of cane-sugar excreted.

cases, and the physicians of insurance companies often decide the fate of such applications in a most summary way. Some examiners perform the analysis in the morning, when the patient's stomach contains no food, or without any information as to his diet. In this way many a diabetic in the mild stage secures life-insurance. On other occasions applications are refused on account of a slight and accidental excretion of sugar. The most rational manner of reaching a decision from a single investigation is, perhaps, to have the applicant partake of a large amount of rice with cane-sugar, and two hours afterward pass his urine for analysis. If such a specimen yields no distinct reaction for sugar, there is no reason, on a diabetic basis, for refusing the insurance; if the urine contains a slight amount of glucose, the insurance ought to be refused until more careful investigation shall settle the question as between simple glycosuria or mild diabetes, when insurance should be refused in the latter and accorded on higher premiums in the former case. Even with this test many persons who habitually excrete sugar after mixed meals would be accepted as first-class risks, and the same might happen in rare instances of true diabetes after prolonged abstinence from carbohydrates. It is perhaps possible to decide diagnostic questions quickly by Bremer's new tests, which are described immediately below, but which I have not yet had time to study.

Dr. Ludwig Bremer,* of St. Louis, has made the interesting and important discovery that diabetic blood (to the naked eye) and its red blood-corpuscles (microscopically) are colored differently from normal blood by certain dyes, whether there is or is not for the moment sufficient hyperglycemia to induce glycosuria. It is as yet not known at what stage in the development of glycosuric dystrophy this peculiarity of the blood first appears, but some of Bremer's cases were instances of glycosuria (according to his views †), and it seems that we have in this method a means also of detecting the glycosuric dystrophy in its incipiency.

Equal parts of saturated watery solutions of methylene-blue and eosin are mixed, and the precipitate that forms, and which is insoluble

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* "New York Med. Jour.," 1896.

† Dr. Bremer's views on other subjects differ widely from my own and from those held by most students of diabetes. When Dr. Bremer says: "It is a well-known fact that by means of dieting, *and by the administration of certain drugs* (antipyrin, calomel, and ammonium carbonate), the sugar can be made to temporarily greatly diminish or entirely disappear from the urine, even in cases of well-established and undoubted diabetes," or that "fasting is a tolerably certain means of freeing the urine from sugar," I can scarcely approve of his expressions, nor do I share his opinions. I do admit, however, that Dr. Bremer deserves great credit for his important discovery, which in some cases probably will constitute a valuable diagnostic means, and which may lead to a better knowledge of the diabetic changes in the red blood-corpuscles.

in water, but soluble in alcohol, is washed and dried on a filter. To this powder some methylene-blue (usually about one-sixth by weight) and some eosin (about one twenty-fourth by weight) are added. The whole forms a powder of reddish-brown color. Every time the test is to be made a fresh test-solution is to be prepared by dissolving from 0.025 to 0.05 gram of this powder in about 10 grams of dilute alcohol (1 : 3). A drop of blood from the finger of the patient is spread between two cover-glasses, which are then boiled over a water-bath for four minutes in equal parts of alcohol and ether, to fix the hemoglobin in the red blood-corpuscles, and transferred to the staining solution described for about the same length of time. After washing the cover-glasses in water, normal blood appears reddish-violet, while glycosuric or diabetic blood presents a sap-green or sometimes a bluish-green color.

In a later notice * Dr. Bremer has adopted a simpler method, spreading a drop of blood between the cover-glasses and exposing these for from six to ten minutes at a temperature of 135° C. (275° F.)—not below 129° C. (264.2° F.) nor above 140° C. (284° F.). The cover-slips are then placed for several minutes in a one per cent. solution of Congo-red or of methylene-blue, or Biebrich's or Ehrlich-Biondi's stain. The Congo-red colors diabetic blood but faintly or not at all, while it gives normal blood a bright red hue. Methylene-blue, which gives normal blood a violet color, gives diabetic blood a faint greenish or yellowish-green color. Biebrich's stain does not color normal blood, but makes diabetic blood a purple-red. Ehrlich-Biondi's stain makes diabetic blood orange and normal blood violet.

Dr. Williamson, of Manchester, with a capillary tube mixes twenty volumes of blood with forty volumes of water, forty volumes of a six per cent. solution of potassium hydrate, and one volume of a solution of methylene-blue (1 : 6000), and keeps the whole in boiling water for five minutes. In the presence of normal blood the mixture remains blue and afterward becomes greenish, while with diabetic blood the mixture turns a pale yellow.

Loewy and others found Bremer's and Williamson's tests valuable even when the diabetic patient's urine did not contain glucose.

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* "New York Med. Jour.," 1897.

Patients, however, submit much more readily to examination of their urine than to examination of their blood, and these tests are little likely ever to come into general practice. It is, therefore, of great importance that Dr. Bremer (1897) has published a method of performing a *color-test with the urine*. A small quantity of a powder consisting of three parts of gentian-violet and two parts of eosin is introduced into a tube almost filled with urine. Even at ordinary temperature, but more quickly on application of heat, diabetic urine assumes a deep violet, almost blue color; normal urine, a brownish-red color. This reaction, which appears whether the diabetic urine contains glucose or not, is explained by the solution of gentian-violet in diabetic but not in normal urine. In persons with simple glycosuria, but living on the boundary-line of diabetes, the urine presents a combination of the two colors.

I believe that these most interesting tests will, in combination with those hitherto employed, prove most valuable in cases of life-insurance and in cases of simulated diabetes (see below), and I intend, as soon as time permits, to devote a good deal of attention to Bremer's tests.

A medical practitioner's knowledge of a diabetic patient's urine must comprehend:

1. The quantity
2. The specific gravity
3. The quantity of glucose upon a determined supply of carbohydrates

} of the urine collected during twenty-four hours.

4. The absence or presence of Gerhardt's reaction and, if possible, of β-oxybutyric acid.
5. The absence or presence of albumin and of—
6. Structural elements from the kidneys.

To obtain information with regard to the excretion of urine for the twenty-four hours, it is necessary expressly and most distinctly to instruct the patient that he must collect every drop of urine in one vessel from, *e. g.*, 8 o'clock one morning until 8 o'clock the next morning. Any one but a physician would believe this task, or at least the full understanding of it, to be the easiest possible. In this, however, as in everything else, we often find painful illustrations of the correctness of Billroth's appropriate remark: In matters pertaining to the natural sciences the average man is quite stupid ("ganz dumm").

To take the specific gravity one must have at least two urometers, one graduated from 1.000 to 1.020, and another from 1.020 to 1.040. A specific gravity above 1.040 is rare. The fourth decimal must generally be taken

without any corresponding gradation on the urometer, which rarely is graduated to more than three decimals.

A practitioner who does not observe many diabetic patients generally possesses no polarimeter, and finds reduction by Fehling's solution (or like methods) too tedious a mode of determining the degree of glycosuria. For him Roberts' method, based upon the difference in the specific gravity of the urine before and after complete fermentation, is the easiest and best for determining the percentage of glucose present. A glass cylinder is almost filled with urine, the specific gravity taken to four decimals, about two grams of common yeast added, the yeast-cells somewhat evenly distributed through the liquid by stirring, and the cylinder, covered with a piece of glass, placed for fermentation if possible in a room with a temperature somewhat above the ordinary.* After two or three days it is ascertained with Nylander's or Fehling's solution that no determinable amount of glucose remains, and the specific gravity is again taken to four decimals. The latter figure is subtracted from that first obtained, and the difference is multiplied by a coefficient, which has been differently estimated and varies somewhat with the percentage of sugar, but which for practical purposes may, according to Lohnstein, be put at the constant 234. The results thus obtained scarcely differ from the correct ones by as much as 0.01 per cent., and they are sufficiently accurate for the purposes of the general practitioner. Thus:

Specific gravity before fermentation was 1.0345, and the
" " after " " 1.0165; the
Percentage of sugar is $0.0180 \times 234 = 4.86$.

Finally, I must again emphasize the necessity of performing Gerhardt's test, the easiest, the most important, and the most neglected of all. Into an ordinary test-tube nearly filled with urine, six, eight, or ten drops of a solution of ferric chlorid are poured; a red or a dark bluish-red color denotes the presence of diacetic acid. There is no method of quickly ascertaining the quantity. Oppler, of Breslau, adds the solution of ferric chlorid until the maximum intensity of color is reached; he then adds diluted hydrochloric acid until the color again disappears. From the quantity of hydrochloric acid necessary for this purpose an idea is gained as to the quantity of diacetic acid.

The practitioner who does not use a polarizing instrument can not determine the presence or the quantity of β-oxybutyric acid, which permits him to form a distinct opinion with regard to the danger of coma. There are some points apart from this best mode of estimating such a danger that it is important to observe. If the reaction with six or eight or ten drops of a solution of ferric chlorid in a test-tube almost filled with the patient's urine does not yield a true red, but only a brownish color, there is no considerable amount of β-oxybutyric acid present either in the urine or in the blood. If a distinct, but not pronounced, Gerhardt's reaction with a light red color appears, the amount of

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* The specific gravity of urine sinks about 0.001 with every increase of temperature of 3° C. (5.4° F.). To obviate the necessity of corrections and to avoid possible errors, it is best to determine the specific gravity in both instances at the same temperature.

β-oxybutyric acid present is not large, and, unless the patient's general state is very miserable, there will scarcely be any danger of coma. If the solution of ferric chlorid yields a deep, dark bluish-red, there is good reason to suspect the presence of a larger quantity of β-oxybutyric acid. The degree of danger of coma in such cases depends in large part upon the patient's general state. As has been already mentioned, one patient may go on for months excreting in the twenty-four hours many times as much β-oxybutyric acid as is excreted by another patient for only a short time before the fatal degree of poisoning is reached.

By the use of a polarimeter the task is much facilitated. After precipitating with ammonia and lead-acetate a sample of the mixed urine collected during twenty-four hours, and waiting for some time until the urine passes perfectly clear through the filter, the number of grams of the acid excreted in the twenty-four hours is easily determined by introducing the degree of levogyration into the formula, with the necessary correction for the dilution of the urine. As soon as this number reaches more than twenty in an adult, the "acidosis," operating in combination with a low state of general health, may threaten coma.

To demonstrate the presence of albumin there is no easier test than pouring nitric acid into a test-tube with a pipet beneath the urine. Even when only a trace of albumin is present, it then quickly shows as a thin, reddish-white layer immediately above the line of contact of the two liquids, below the less sharply defined, more grayish layer of urates, which often forms above it; care being taken when only one of the two layers is present not to mistake it for the other.

The quantity of albumin, which generally is small and often below one-half in a thousand, is most practically and enough accurately determined by means of Esbach's albuminimeter.

With the aid of a centrifuge the task of finding casts of the renal tubules is much facilitated, care being taken not to permit hyaline casts to escape detection, and in cases of severe diabetes to keep a sharp lookout for the numerous small casts described by Külz.

It is often worth the trouble to ascertain the patient's capability of ingesting and digesting proteids by determining—usually by Kjeldahl's method or by one of the many azotometers—the quantity of nitrogen excreted with the urine in twenty-four hours. By multiplying the number of grams of nitrogen by 6.25 the number of digested grams of proteids is learned, not taking into consideration the nitrogen possibly ingested with other substances than proteids and the nitrogen derived from toxic, protoplasmic disintegration, both of which, in most cases, only form "*une quantité négligeable*," and can not possibly be determined by the physician.

The general practitioner usually finding among his patients but a limited number of diabetics, as a rule does not, by analytic work, ascertain the changes in their nutritive state. On the other hand, he ought not to omit to follow these changes, even though in a somewhat crude but simple and practical manner. For this pur-

pose he may use *the scales*, the patient being weighed once a month, or, if necessary, once a week. In doing this the patient must necessarily take his weight at the same time of day and in the same dress, or, if convenient, without any clothes at all. It is evident that even if this is done the varying contents of the bowels and the bladder may give rise to error. Further, a less important gain of fat may cover and conceal a more important loss of proteids. However crude this method of following the patient's nutritive changes, it is of great practical importance, and, especially in two classes of cases, is not to be neglected by the conscientious physician. In severe cases it enables us to discover, and at once by all the means in our power to combat, any increase of the autophagy and rapid loss of weight, which often indicate the beginning of the end and the overwhelming danger of coma. In mild cases the scales enable us, during periods of marked restriction or exclusion of carbohydrates from the food, to control the loss of weight that usually occurs under such conditions, and which ought not to be too marked. A fat diabetic patient (in the mild stage) may—*ceteris paribus*—be permitted to lose more than a less fat patient, but no diabetic should be permitted to lose in a month more than a small percentage of his whole bodily weight. In the severe stage the physician should always do his best to prevent any loss of weight.

The remaining part of the investigation in a case of diabetes occupies comparatively little time. I will cursorily mention the points that strike me as most important.

In examining the patient as to his heredity one has especially to bear in mind diabetes mellitus and insipidus, gout, adiposity, and *all* neuroses (various forms of mental disease, neurasthenia, epilepsy, etc.), and exophthalmic goiter. In making inquiry as to mental diseases one must sometimes press the question in order to gain the necessary information ; an unintelligent, and sometimes even an intelligent, patient may, however, be irritated if the pressure be made too great. A satisfactory result is often more easily reached by asking as to symptoms rather than about names of diseases.

With regard to the patient's own life inquiry is made as to past diseases, especially gout, influenza, malaria, syphilis ; trauma, es-

pecially of the head; excessive intellectual work; powerful and permanent painful emotions; sexual excesses, natural or unnatural; deprivations; exposure; indulgence in alcohol, tobacco, or other intoxicants (morphin, cocain, chloral); gormandism; overindulgence in sweets; sedentary habits, etc.

If the diabetes has been discovered and treated before my own investigation, I never omit to ask whether the discovery was made from the sudden appearance of diabetic symptoms (thirst, polyuria, etc.) or whether the disease has developed slowly and has been discovered accidentally (life-insurance, etc.) or in consequence of some chronic diabetic complication affecting the skin, the eyes, the teeth, etc. The prognosis, as has already been mentioned, is far better when the development is slow than when the onset is sudden.

I likewise endeavor to secure information as to any loss of bodily weight, and attach much greater significance to this if it has begun before the diabetes was discovered and without any change of dietetic regimen, than if it began after a restriction of carbohydrates, which, if carried to anything like an extreme, is likely to cause loss of flesh in any person, diabetic or not.

I observe the patient's general appearance, complexion, manner of moving and of talking. I never omit to examine the cavity of the mouth, which, from the existence of alveolar pyorrhea and decay or loss of teeth, may afford evidence of diabetes of long standing, or from the typical, diabetic "crocodile" tongue, and a strong smell of acetone on the breath may show that the disease has entered upon the severe stage.

I first try to form an opinion as to the patient's mental state by my own observation, and afterward, prudently—*i. e.*, as kindly, interestedly, and delicately as possible—put direct questions about central nervous symptoms, especially depression and irritability. I pay particular attention in my examination to neurasthenic symptoms, whether revealed more directly through the nervous system or the organs of perception, circulation, digestion, and reproduction: Depression; irritability; sleeplessness; loss of memory or of capacity for intellectual work; vertigo, spontaneous or from a great depth; agoraphobia (rare); headache; hyperesthetic, dysesthetic, or paresthetic sensations (*casque neurasthenique*, *plaque sacrée*, and other rachialgic manifestations, formication, sense of heat or of cold,

shooting, "rheumatoid" pains, neuralgia, migraine); neuromuscular asthenia; cramps in the calves; neurasthenic asthenopia; hyperesthetic, ocular, or auditory manifestations; changes in taste and smell, etc.; pseudoangina pectoris—increased frequency of pulse; gastrointestinal disorders, with a capricious appetite; nervous nausea or vomiting; eructations, pains, flatulence (exceedingly common), sudden diarrheas, etc.; sexual weakness and impotency.

In cases of long standing or in cases complicated by gout I do not fail to look for symptoms of neuritis, and with a needle or a tube filled with hot water or the esthesimeter to test the sensibility, especially on the lower parts of the legs, where neuritic symptoms are more frequent and more intense.

I test the knee-jerks (the prepatellar reflexes) *à la* Jendrassik. The patient reclines upon a chair with his eyes closed, his legs bent at the knee-joint at an angle of about 110 degrees, the feet somewhat separated, and the whole sole on the floor. His hands are joined over his stomach, and he is told to relax the whole muscular system, especially the muscles of the legs, as much as possible. I place one hand near the knee, over the quadriceps femoris muscle, to feel the jerk, while with a small book in the other I try to elicit the reflex by striking a blow over the ligamentum patellæ. I am thus able to perceive by touch better than by sight the slightest contraction of the quadriceps femoris.

By physical investigation in the usual way I ascertain the size and the functional and valvular state of the heart, and I do not omit in forming an opinion as to this state to weigh the patient's statement with regard to his capacity for climbing, or any other energetic muscular activity which increases the demands on the heart. Palpation of the radial artery discloses the frequency, rhythm, and strength of the pulse; I try to detect any possible atheromatous rigidity of the radial, femoral, and temporal arteries.

In examining the lungs I direct attention especially to ascertaining the absence or presence of any incipient or advanced changes in the upper lobes.

I ask the patient about his appetite, the regularity of his bowels, etc. If there is any reason for presuming pancreatic disease, I request him to observe if the character of the stools indicates the presence of greater quantities of indigested fat than normal, and if

this is the case, I give my own special attention to the subject. I determine the size, the consistency, and the sensitiveness of the liver. In deciding as to the existence of incipient cirrhosis of the liver I attach great importance to any enlargement of the spleen, and sacrifice some time in carefully ascertaining the size of this organ. I seek information with regard to the presence of any symptoms of gall-stones, which are not rare in cases of diabetes.

I also inquire whether the patient has been troubled by pruritus or any local changes in the genitals.

I direct special attention to the eyes and look chiefly for cataract, myopia, premature presbyopia, retinitis, and inflammation of the optic nerve.

Simulation of diabetes is not rare in some European countries, and is generally attempted by persons who wish to secure exemption from military duty.

To contrive the fraud, the simulator either (1) eats a large quantity of glucose, usually in honey, or (2) introduces some saccharid in his urine within or without the bladder, or (3) takes a dose of phloridzin or of phloretin.

The ingestion of a large quantity of glucose is the shrewdest method. The consequent glycosuria, however, lasts only for a few hours, and then ceases when the supply is cut off. It is usually on the increase only for about an hour, and after this time the fraud can be discovered by giving a large portion of bread, and by observing that an hour later the glycosuria is on the wane instead of increasing.

Fraud has sometimes been attempted by injecting a solution of some saccharid into the bladder or by adding some saccharid to the urine outside the bladder. (See the case of Abeles and Hoffmann.*) In the latter case the fraud is detected by letting the simulator pass his urine under observation, or by withdrawing it directly from the bladder. In both cases detection is generally made easy by the simulator's ignorance of the different kinds of saccharids. Women scarcely ever know of any other sugar than the cane-sugar used in their household. Urine containing cane-sugar will not reduce Fehling's or Nylander's solutions before boiling with a dilute mineral acid, but will do so after this, and will turn the ray of polarized light to the right. The cane-sugar is generally added to the urine in amounts large enough to give it an exceedingly high specific gravity, which will immediately turn the physician's mind in the right direction. If the simulator has some knowledge of saccharids, the situation may be rendered more complicated. He may then contrive to get some really diabetic urine and inject it into his bladder; such a mode of simulation can only be detected by keeping the simulator under observation, or by subjecting his blood to Bremer's test. He is more likely, however, to use the glu-

* "Wiener med. Presse," 1876.

cose sold for technical purposes. This contains a good deal of dextrin which is strongly dextrogyrate, but does not reduce solutions of copper nor bismuth, and the fraud is detected by the polarimeter indicating a much higher percentage of glucose than do reduction-methods of estimation.

If simulation by means of phloridzin or phloretin is suspected, the urine should be tested with ferric chlorid for the brownish-violet color yielded by those substances—it being always borne in mind that a somewhat similar, but more reddish, color is caused (1) by diacetic acid in cases of severe diabetes, or when starvation is taking place, and (2) in any state of health by antipyrin, salicylic acid and its salts, kairin, thallin, chinanisol, and other substances. By cutting off the supply of phloridzin or phloretin for fully three days the glycosuria due to these poisons can be stopped.

If one is provided with the proper stains he will probably find in Bremer's method of diagnosticating diabetes (see above) an excellent means of detecting at once any simulation of diabetes in whatever manner it is attempted.

CHAPTER IX.—TREATMENT.

Some prophylactic measures may be taken against diabetes; this applies especially to members of families with a neuropathic, a gouty, or directly diabetic hereditary predisposition.

These measures are, in large part, exactly those that are rational in cases of nervous disposition. Children that begin life thus handicapped ought, still more than others, to be protected against fright and other emotions, overwork, and strains of all kind, fatiguing and enervating pleasures; and they should have all of the advantages to be derived from fresh air, bodily exercise, baths, early hours, and a systematic hygienic life. It is of paramount importance, after puberty, to guard such children against an abnormal or too early development of sexual activity. It is also an exceedingly important and fully rational, though often neglected, measure in the choice of a profession to direct such young persons to occupations in life that are less likely than others to develop neurotic tendencies. In this respect our descendants will certainly provide much more carefully than we do or even than we now would approve of doing.

It seems to me that something might also be done in the matter

of diet to diminish an inherited danger of future diabetes, though for my part I consider this item of diabetic prophylaxis to be much less efficient and important than antineurotic measures. It would certainly be most unwise to diminish a child's supply of bread, potatoes, and other more or less necessary articles of chiefly carbohydrate nature below fair daily portions; but nothing is lost, and perhaps something is gained, by a rigorous restriction of sweets and sugar in the food of such children. The custom prevalent in some countries of including beer and other liquors in the dietary of persons even below fifteen years of age might also well be avoided.

It not rarely happens that a diabetic patient asks his physician with regard to the advisability of marriage, often, I acknowledge, with a firm, though unconscious, resolution in this respect not to take advice that is opposed to his own inclinations. If a case of true diabetes sets in before the thirty-fifth or fortieth year, life will generally be short. Impotence and sterility threaten darkly, and pregnancy and maternal duties in woman, like sexual activity in man, often favor the development of the dystrophy. The mortality among children of diabetic parents, as has been mentioned, is enormously high, the constitutional inheritance a great handicap in life. It would be unwise for a physician to put all these facts distinctly before a patient who thinks of marrying, and who rarely is to be dissuaded from doing so, but these arguments must have a profound influence on the advice the physician will give. In severe cases of diabetes there are left but few of the customary reasons for marrying.

The great dangers for mother and child also ought to be taken into consideration in connection with pregnancy in diabetic women, and they may, under certain circumstances, justify artificial interruption of the pregnancy. Such a course in a case of simple glycosuria, or even in one of true but mild diabetes in otherwise fairly good condition, might justly be considered as malpractice, and the mere name of diabetes ought never to be made a safeguard for an operation of this kind. I should not hesitate, however, to give my vote in favor of interrupting the pregnancy in any case of diabetes

in the severe stage, or in any case in which the prospects of mother or child were gloomy.

There is but little to say outside of general rules with regard to the hygiene of diabetic patients.

The physician and his diabetic patient must never forget the small power of the latter to resist deleterious influences of all kinds. Diabetics are more likely than others to be affected by emotions of a depressing nature and to suffer more in consequence. Every physician who has seen much of these patients has learned how especially careful one must be not to irritate or in any way to frighten them, and he will adopt the rule of according to them, still more than to others, the patience and forbearance under all circumstances—which is not the lightest nor the least important of the many high duties of the medical profession. The necessity of avoiding all kinds of strains on his nervous system must be earnestly impressed upon the patient. He must, as far as possible, limit his intellectual activity not only below the level of overwork for a normal person but below the level of overwork for his own, usually limited, powers. He must be most moderate in sexual activity. He must forswear overuse of tobacco and alcohol, and it is still more important for him than for others not to fall into bad habits with morphin, cocain, somniferous drugs, etc. He ought to take as much exercise as he can take without fatigue. He must observe regular hours, with a large allowance of time for mental and bodily rest. His great sensitiveness to exposure, and the especially dangerous consequences of cold make it of paramount importance for him to be warmly dressed, and to wear, constantly, woolen underclothes. His whole mode of life must be thoroughly hygienic. If he lives in a rigorous climate, it is of great advantage to him to pass the coldest part of the year in some warmer place, observing there the same scrupulously hygienic regimen as at home.

The special duty of taking into earnest consideration the diabetic patient's mental sensitiveness begins at the moment the physician discovers the existence of any stage of the glycosuric dystrophy, and concerns the statements to be made to the patient on this subject.

If only a slight glycosuria, but no true diabetes, is found, it is in many cases wise to mention nothing about the matter to the patient. Individuals of great sensitiveness, especially if not highly intelligent, are often greatly affected by learning of the excretion of sugar in their urine, however slight and however accentuated by the physician its clinical insignificance. If the urine for twenty-four hours does not contain more than a trace of glucose (up to 0.05 per cent.) with an ordinary free diet, and the patient furnishes any ground for doubting his courage or judgment, other reasons than the existence of glycosuria can always be found for advising avoidance of the most objectionable kinds of food (sweets, dry fruits, rice, macaroni, peas, champagne, etc.).

If the case is one of true diabetes, it is generally necessary to inform the patient of this fact. In mild cases the physician then has the pleasant task of making the patient acquainted with many actual reasons for comfort and hope. In severe cases the physician, who alone can determine the nature and prognosis of the special case, will understand that, if prudence often is the better part of valor, discretion is often the better part of truthfulness. It is quite a satisfaction to know that downright lying is generally not necessary. The patient usually knows little else of diabetes than that a person may live with it for decades in fairly good health, and the physician will rather, by repeating this and other general facts, let the patient deceive himself than injure and torture him by stating the whole implacable truth.

On the whole, it is of great importance to arrange everything for the patient with a view of reminding him as little as possible of his own exceptional position.

For this reason I consider the "sanatoriums for diabetics," where the patient meets only brothers in misfortune, in many cases to be of doubtful advantage. The one indication that may arise for a sojourn of some weeks in such an institution is the period of absolute or of very rigid diet in the mild stage; it depends on circumstances whether the dietetic discipline is not even then acquired at too high a price.

The poor diabetic patient certainly derives some advantage from the hospital, where he may for some time enjoy a rational diet at moderate cost.

One of the diabetic's most frequent and most common nervous symptoms is *sleeplessness*. This is a trouble that often follows the

patient throughout his whole life, and it is of the utmost importance not to employ remedies that easily lead the patient into bad habits and may cause a much greater misfortune even than sleeplessness. We therefore, as far as possible, take refuge in simple and harmless remedies. We prescribe mental and physical rest during the last hours of the day. We recommend the system—already mentioned for its merits in other respects—of making the last meal of the day a light one, also for its better influence on the night's rest. A moderately warm bath at 35° or 36° C. (95° or 98.6° F.) before going to bed has a good effect in some cases. A hot foot-bath at this time and a wet, warm fomentation around the abdomen during the night are highly praised by some patients. In other cases I have found covering the head warmly at night—with a fur cap, for instance—a most efficient remedy for promoting sleep. The vibrations on the head, recommended by Charcot and others, have already been mentioned. I found Charcot's (or Gilles de la Tourette's) "*casque vibrant*" too weak, and have seen much better results from one of Zander's machines. One must sometimes try several of these simple remedies, and will often find one of them efficient when others have failed.

In the presence of severe exacerbations of insomnia and during mental disturbances we are sometimes forced to take refuge in narcotic, somniferous drugs. I prefer great economy in this, and I rarely give such remedies two nights in succession; neither do I use them for any length of time, if this can possibly be avoided. A large dose of the comparatively harmless bromids will diminish the necessary dose of other remedies. (I prefer sodium bromid to potassium bromid.) Among directly hypnotic remedies, I have, after many disappointments, returned to chloral hydrate or chloral-amid as the best and least objectionable. With all their drawbacks, these are decidedly better than the much-praised sulphonal and trional, both of which cause drowsiness on the next day, if taken in such doses as will cause sleep during the night, and both of which cut off the systolic apices on the pulse-curve. Among narcotic vegetable derivatives opium and extract of cannabis indica rank foremost. Neither morphin nor codein is ever to be used for this purpose. One may, for instance, give at one dose: sodium bromid, 2 gm.; chloral hydrate,

1.20 gm.; extract of cannabis indica, 0.05 gm.; or some similar formula.

In cases of severe diabetes, with a miserable general state and a distinct excretion of β-oxybutyric acid, our chief task must be as long as possible to prevent coma. The patient must with the greatest care be protected from injurious influences of all kinds. No mental or intellectual exertion, no exposure, no fatigue, no long journeys, no deviation from daily customs should be permitted. I add with the deepest conviction that the diet should not be made too rigid. The patient may have as much bread, green vegetables, and potatoes as he likes; several teaspoonfuls of levulose daily will help to keep him alive. It is of paramount importance to promote the excretion of toxins by favoring free diuresis. The patient is allowed to drink as much water as he chooses, and we especially recommend a generous daily supply of the customary alkaline table-waters, charged with free carbonic-acid gas. Strong acids ought not to be given; nor are large amounts of alkalies to be recommended for long periods; if large enough to decrease the acidosis considerably, they cause digestive troubles and have a weakening effect. It is also most important to keep the bowels open by means of massage, aperient drugs,* or by injections. The latter are advantageously performed with large quantities of tepid water and enough potassium permanganate to produce a faint violet color in the water.

Whenever there is a danger of coma, great care must be observed in the use of narcotic and somniferous remedies.

When the prodromes appear, or if headache and great lassitude raise suspicion of coma, rapid measures may still afford some respite. The patient is at once put to bed, receives a glass of brandy or of whisky, or a subcutaneous injection of ether, and is given enormous amounts of sodium bicarbonate in some water rich

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* I often give:

Pulveris aloes, }		
Pulveris rhei, }	āā 4	gm.
Extract. colocynth. comp.,	3	gm.
Extract. hyoscyamus,	1.50	gm. M.

Ft. pil. No. lx.

SIG.—One, two, or three pills at night.

The aperient effect of these pills usually follows in the morning.

in free carbonic acid. A moderate dose of digitalis or strophanthus may also be administered. The patient may also take a bath at a temperature of 38° or 39° C. (100.4° or 101.2° F.).

If matters have progressed still further,—if the respiration is dyspneic, the pulse inordinately frequent,—the same steps must be taken; except in exceedingly rare cases neither they nor any other means will effect more than a transitory and fallacious improvement. Under such circumstances the *alkaline solution may be injected into a vein*,* but this can not be considered necessary, as it presents few advantages over administration of large amounts of alkali by the mouth, and its effects are almost always of short duration. The intravenous injection of an alkaline solution requires, besides, elaborate contrivances, and is but rarely undertaken in private practice. Stadelmann used a concentrated solution of sodium bicarbonate and citric acid, and injected 150 cu. cm. three or four times a day. Others use solutions of a mixture of sodium chlorid, bicarbonate, phosphate, and sulphate. Lépine dissolves 7 grams of sodium chlorid and 10 grams of sodium bicarbonate in a liter of water; injects slowly, but within a short while, 2 liters (!!) of this solution at a temperature of 38° C. (100.4° F.) into a vein of the arm.

Whether the intravenous injection be performed or not, a concentrated solution of sodium bicarbonate in large doses should always be given by the mouth, and a subcutaneous injection of ether or caffein citrate may also be given.

The immediate effect of the alkaline venous injections, or of large doses of sodium bicarbonate by the mouth, is sometimes apparently favorable, and likely to inspire the inexperienced with the hope that the patient will return to his previous state before the onset of the symptoms of coma. In the large majority of cases this improvement will last only for a few hours or for a couple of days, and the physician will do well to prepare those interested for the patient's approaching death, however strongly the comatose symptoms have receded for the moment.

In treating a case of diabetes our first duty—apart from the

* The subcutaneous injection of large amounts of alkaline solution presents far greater inconveniences and dangers than advantages, and ought never be practised.

almost always hopeless task of removing the cause of the dystrophy —is to protect the patient from the inanition that threatens from the loss of glucose. Next in importance is the task of providing a sufficient number of calories in such food as to cause the least possible hyperglycemia and blood toxins, and counteract, as much as possible, the development of the diabetes. Dietetic prescriptions will thus always constitute an important part of the treatment, though they ought not, as is often the case, to make up the whole treatment.

The facts that ought to form the basis for our views on the dietary for a diabetic are as follows :

1. An individual performing some mechanical work needs from thirty-five to forty calories per kilogram of bodily weight in twenty-four hours to maintain his nutritive balance.

2. Proteids yield 3.2, fats 8.4, and carbohydrates 3.8 net calories per gram in healthy persons, and usually as much in diabetics— minus the loss from glucose in the urine following the ingestion of carbohydrates in the mild stage, and present with any diet during the severe stage, of the diabetic dystrophy.

3. Carbohydrates ingested in ordinary amounts cause in all cases of diabetes the distinctly, though only slightly, injurious hyperglycemia, which finds its expression in the, *per se*, almost indifferent glycosuria.

4. All diabetic patients, however, utilize some portion of ingested carbohydrates, and the calories thus gained contribute better than calories derived from fat to the protection of the organism's own proteids. Levulose is better utilized than any other yet known and fully acknowledged carbohydrate.

5. Restriction of carbohydrates in the food causes a decrease or a cessation of hyperglycemia and glycosuria, and, apart from other advantages, counteracts the development of the glycosuric dystrophy.

6. Fat, ingested in any quantity, does not cause hyperglycemia or glycosuria in any stage of diabetes.

7. Fat, however, in spite of its high caloric value, can not be ingested in any quantity that even remotely covers the expenses of the organism.

8. Still, fat can be ingested in much larger quantity with than without the ingestion of carbohydrates.

9. In cases of severe diabetes toxins arise in the blood that are far more injurious that the hyperglycemia.

10. These toxins are increased by exclusion or too rigid a restriction of carbohydrates from the food.

11. Normal human food—apart from water and salts—consists of proteid, fat, and carbohydrate, and permanent exclusion of carbohydrate from the diet can not be effected, because it prevents the supply of a sufficient quantity of calories and causes severe disturbances of the digestive functions.

12. Among articles of food rich in carbohydrate bread is most difficult to exclude.

A rational diet for a diabetic must be founded on *all* these facts; if too much importance be attached to dangers or to advantages of any special kind, the treatment necessarily will be defective.

An absolute diet—by which I mean a diet of meat and fat with the strictest possible exclusion of carbohydrates—can never be followed for periods of more than weeks, or, at the longest, of months. I consider the correctness of this opinion to be so universally acknowledged at the present time that it is unnecessary to spend more words on it.

It remains, then, to decide in which cases of diabetes it may be advantageous periodically to exclude carbohydrates* from the food.

This may advantageously be done in most cases within the mild diabetic stage. Even with robust individuals in that stage, however, I do not find it rational to prescribe, nor could I prevail upon the patient to submit to, longer periods of absolute diet than a month.

The advantages of the absolute diet in mild cases consist in the cessation of the hyperglycemia and its effects, the cessation in itself counteracting the progressive tendency of the diabetes and often increasing the power of assimilating carbohydrates.

The disadvantages of the absolute diet, even in mild cases, are,

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* Unfortunately for diabetics, bread is the kind of food that most people find it most difficult to spare. If any one should for a time live on only two of the three kinds of food,—meat, butter, and bread,—he would want first of all the bread and resign the butter. It is also known that large, fairly civilized populations chiefly (and up to more than 90 per cent. of the whole solid food) live on rice, but meat and fat nowhere constitute so large a part of the food, except among the few and low-ranking tribes in the Arctics.

unfortunately, very great. The patients with this diet often suffer from constipation, which is likely to give way only to diarrhea. They lose their appetite and are not able to ingest much fat or enough of any permitted food to maintain their nutritive balance ; they almost invariably lose flesh. The neurasthenic symptoms, rarely absent in cases of diabetes, are especially prone to be aggravated by the inanition. The mere absence of normal pleasure and satisfaction at meals also has, in many cases, an unfortunate effect on the patient's mental state.

It will generally be found that the patient will bear better the absolute diet, and derive greater advantages from it, the fatter and the less nervous he is. The state of the digestive organs and their power to support the absolute diet is also a most important and a most varying factor. It must also be remembered that there are in apparently quite similar cases great individual differences in the capability of supporting and in the general effects of the absolute diet. I have sometimes, even in mild cases of diabetes, found it wiser, after a signal failure, never to prescribe the absolute diet, from which some patients suffer exceedingly in their general state and well-being.

In the severe stage the advantages to be derived from the absolute diet are always much diminished. We can no longer free the patient from the hyperglycemia and its effects, and we can no longer materially increase his power of assimilating carbohydrates. The disadvantages arising from a rigid exclusion of carbohydrates are much greater than in the mild stage, and the increase of acetone, diacetic acid, and β-oxybutyric acid, inseparable from such a diet, also directly increases the danger of coma, which, besides, becomes greater by reason of the inanition itself, scarcely to be avoided upon exclusion of carbohydrates.

The rational application of these facts forbids the exclusion of carbohydrates in the distinctly severe stage of diabetes.

In determining the daily allowance of carbohydrates for a patient in the severe stage I must, however, distinguish between two classes of patients.

The first class consists of cases presenting diacetic acid but no β-oxybutyric acid in the urine. There is in these cases no danger of coma; but the patients generally have lost in bodily

weight, and are in a poor state of general health. An exclusion of carbohydrate seems to me, even in these cases, to do more harm than good, by decreasing their bodily weight and by exerting a bad influence on the general somatic and mental state. I customarily allow such patients from eighty to one hundred grams of carbohydrate in twenty-four hours; usually, at least half of this portion is taken in bread and the rest in vegetables of different kinds (see below).

The second class of severe cases consists of those in whose urine, in addition to diacetic acid, also β-oxybutyric acid is present: *i. e.*, cases in constant danger, more or less pronounced, of coma. Whenever I encounter a diabetic patient in the distinctly severe stage, I allow him a moderate daily amount of carbohydrates (eighty grams) until I have acquired definite information on this point. If after the removal of all sugar from the urine by fermentation, and of combined (levogyrate) glycuronic acids by precipitation with lead acetate and ammonia, I still find distinct levogyration, denoting the presence of β-oxybutyric acid and at the same time an advanced "acidosis" (in the blood), I am averse to any great restriction of carbohydrates. However absolutely I condemn an exclusion, if ever so short, of carbohydrates in these cases, I am willing to admit that the rational daily amount of carbohydrate is a matter open to discussion. Considerable experience, however, both of the effect of my own dietetic system and of that of other physicians, has forced me to the conclusion that I promote best the interests of such patients by allowing them a generous, if not an unlimited, amount of bread * and potatoes. I exclude from their dietary only such articles as contain much carbohydrate and at the same time can easily be spared (rice, macaroni, peas, dried or sweet fruits, sugar and sweets, champagne, beer, sweet wines and liquors, etc.). In these cases, if circumstances permit, I also use levulose, recommending it strongly as a substitute for cane-sugar. It invariably increases the glycosuria, but as invariably diminishes the autophagy and loss of weight, and I believe that it has in many of my own cases postponed the final issue.

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* In cases with advanced acidosis I allow at least one hundred grams of ordinary white bread a day.

If a patient in the advanced severe stage is, after some allowance of carbohydrate in his food, put on an exclusive animal régime, or only allowed a small daily amount of carbohydrate, he frequently is attacked and killed by coma within a few days.

"But," some one will say, "the absolute diet has also a diagnostic purpose; and how shall I ascertain the state of the patient's dystrophy without putting him on an exclusive animal diet, with a minimum of carbohydrate?" I have already answered this objection. If a diabetic patient on a mixed diet passes urine that does not yield a distinct Gerhardt's reaction (a wine-red color on addition of a solution of ferric chlorid), I may, without danger of coma, withdraw the carbohydrate. If the urine presents a distinct Gerhardt's reaction, the case is a severe one, and it would be a grave error to put him on an absolute diet.

In my opinion we must adopt the rule in all cases of diabetes, mild or severe, never, as a permanent dietetic rule, to put any maximum limit, any restriction, on the supply of meat or fat. There are cases on the borderland between mild and severe diabetes that with exclusion of carbohydrates and some restriction of meat present no glycosuria, and that with exclusion of carbohydrates, but with a larger supply of meat, excrete small quantities of glucose. A restriction of meat also in many other cases diminishes the glycosuria. The slight corresponding hyperglycemia, however, is an insignificant matter as compared with too much prescribing and, above all, with underfeeding. When one of Germany's greatest clinicians and best authorities on diabetes (Naunyn) recommends a maximum limit in the supply of meat,* even with an exclusion of carbohydrates,—which he also prescribes in cases in the severe stage,—with all my admiration for him personally and for his work, I can not follow him here. How could a patient who has to live exclusively on meat and fat avoid underfeeding if he is not permitted, even with regard to this poor food, to satisfy his appetite, which on this point affords more trustworthy indications than are sometimes given by learned and otherwise clever physicians?

The danger from underfeeding with exclusion or strong restric-

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* So far as I know, Rollo was the first to urge a restriction even of proteids in cases of diabetes. I have no doubt that this dietetic principle is at present on its last legs.

tion of carbohydrates is always imminent, and rather than restrict proteids and fat, we ought as much as possible to insure the patient against receiving too small amounts of both for the maintenance of his nutritive equilibrium. Even when we do our best, we shall find that a marked restriction of carbohydrates often necessarily results in some degree of starvation.

Let us consider the dietetic needs of a man of seventy-five kilograms of bodily weight who receives forty calories per kilogram in twenty-four hours, and how to meet those needs with different proportions of the three great classes of food. I shall, as far as possible, confine myself to round figures in making the whole amount of the daily supply reach about 3000 calories :

Case.	Proteid. Net Value, 3.2 Cal.	Fat. Net Value, 8.4 Cal.	Carbohydrate. Net Value, 3.8 Cal.	Sums of Calories.
No. 1	135 gm.	80 gm.	500 gm.	= 432 + 672 + 1900 = 3004
" 2	420 "	200 "	0 "	= 1344 + 1680 + 0 = 3024
" 3	120 "	285 "	60 "	= 384 + 2394 + 228 = 3006
" 4	700 "	65 "	60 "	= 2240 + 546 + 228 = 3014
" 5	185 "	260 "	60 "	= 592 + 2184 + 228 = 3004
" 6	225 "	245 "	60 "	= 720 + 2058 + 228 = 3006
" 7	250 "	235 "	60 "	= 800 + 1974 + 228 = 3002
" 8	345 "	200 "	60 "	= 1104 + 1680 + 228 = 3012
" 9	300 "	200 "	100 "	= 960 + 1680 + 380 = 3020
" 10	190 "	240 "	100 "	= 608 + 2016 + 380 = 3004

The first line in the table shows an arrangement that gives fifteen grams more of proteid and twenty-five grams more of fat with the same amount of carbohydrate than Voit's classic table. I have made the additions necessary to reach the 3000 calories to the proteids and to fat, because the patient, of his own choice, following only the dictates of taste, is much more likely to do this than to increase the amount of carbohydrate above 500 grams. Among Anglo-Saxon and Teutonic nations the free choice of proportions for 3000 calories would often increase the proteids to at least 150 grams, and the fat to an equally large or even larger amount.

The second line in the table shows at a glance how very difficult it is to obtain the 3000 calories without carbohydrate. If we put the fat at 200 grams,—which for many individuals represent the maximum possible of ingestion, and which are contained in about 240 grams of butter,—we must take 420 grams of proteid or nearly 1250 grams of cooked meat (free from fat). If we trust to the ability of the patient to take daily ten eggs, each of which shall contain fifty grams of food, we may decrease the meat by about 200 grams, and the butter by about fifty-four grams; but how many individuals are able to eat fully a kilogram of meat, nearly $\frac{1}{5}$ of a kilogram of butter, and ten eggs a day, even if the most expert chefs put their heads together to make the whole as palatable as possible?

The third and the fourth lines in the table only show that, even if I allow sixty grams, or the minimum of carbohydrate that is necessary in the long run, by increasing only the proteids or only the fat, I obtain perfectly impossible quantities of the one or the other.

The fifth, sixth, seventh, and eighth lines represent the possibilities of ingesting enough of proteids and fat in addition to the necessary minimum of carbohydrate; but we find that however the proportions of proteids and fat are arranged, the patient is likely to have before him a difficult task.

The ninth and tenth lines show how the patient's task is facilitated by allowing him a somewhat larger amount of carbohydrate. There are a great many persons of 75 kilograms of bodily weight who are able to keep themselves in a fair state of health by ingesting in the twenty-four hours 190 grams of proteids, 240 grams of fat, and 100 grams of carbohydrate, or about 2.5 grams of proteid and 3.2 grams of fat per kilogram bodily weight. The quantity of fat is rather large; in many cases it will be necessary to diminish this and to increase the amount of proteids to something more like the quantities given in the ninth column. But the more fat a diabetic can ingest, the better off he is, and a patient of 75 kilograms ought, if possible, not ingest less than 200 grams of it. The ninth and tenth lines show proportions that, especially in mild cases, will often be found in the long run to be the most advantageous. In very severe cases 100 grams of carbohydrate are, for a person of this weight, never too much, but often too little.

In this table I have not taken into consideration the loss of calories represented by the glucose in the urine. On the other hand, I have not taken into consideration the calories that may be gained by the use of a moderate amount of alcohol. If we put the caloric value of glucose at 3.7 per gram, we find that a patient that passes 50 grams of glucose in the twenty-four hours—a large amount in the mild stage with a daily supply of 100 grams of carbohydrate—loses 185 calories of what he has ingested and digested. This loss is not larger than the allowance of alcohol—equivalent to 7 calories per gram—that can be accorded to a person of 75 kilograms.

Rollo was the first, in the beginning of this century, to recommend an exclusive diet of meat and fat in cases of diabetes. He committed the error, afterterward repeated by others, of prescribing a restriction even of meat. In those days the laws of nutrition and the organism's imperative demands for a certain number of calories were not known, and importance was attached almost exclusively to a removal of the glycosuria. Rollo, however, in his practice did not carry out his theories with regard to an exclusively animal diet, which, according to his prescription, was adopted throughout Great Britain and its colonies, and soon spread to France and Germany. Wherever this system was introduced it proved unsatisfactory, from the consequent disturbances of digestion, its manifest insufficiency, and from the patient's invariable aversion. Opinions on this subject have since been much divided, and are so to some extent at the present time. Bouchardat (from 1842) contributed largely to the establishment of a better system with a mixed diet of ingestable quantities of meat and fat, and a restricted supply of starch, chiefly taken in the form of green vegetables and bread; he also allowed moderate quantities of alcohol. Meanwhile, Prout introduced gluten-bread and inaugurated the long series of breads made especially for diabetics.

The late distinguished Neapolitan physician, Cantani, was one of the most energetic advocates in our time of an absolute (animal) diet for cases of diabetes. He allowed only meat and fat, and as representatives of the latter he recommended olive oil and cod-liver oil. Butter was forbidden because it contains a trace of milk-sugar. Cantani later became somewhat more reasonable, and allowed butter and "*frutti di mare*," a dish composed of different small salt-water animals, some of which contain a considerable percentage of glycogen. It was his plan to enforce this diet for at least three months, and then gradually to make concessions toward a more mixed food. One gains quite a curious impression from reading Cantani's opinions with regard to the possibilities and the effects of the severe régime he prescribed. I suspect that some of his patients have, without his knowledge, smuggled not inconsiderable quantities of macaroni into their food. Cantani spent his life in Naples, with its heavenly nature and vile population, by whom a true word, to quote Swinburne, in "Peter Simple," seems to be spoken only by mistake.

An absolute diet in the severe stage of diabetes is now insisted upon strictly by Naunyn and his school. Even his justly honored name is not sufficient to sustain this position. The cases published by him and his disciples demonstrate what this régime is capable of effecting in the severe stage; the patients immediately after its inception being often delivered from their sufferings by death in coma.

It is a pleasure to know that the absolute diet has certainly never been observed, except for a very short time, by any one not kept under lock and key. A considerable experience with cases of diabetes in representatives of the best nations and of the best (*i. e.*, most educated, most intelligent, and therefore most reliable and obedient) classes, has taught me that the physician, even if he knows how to acquire the confidence of his patients, can only rarely enforce abstinence from carbohydrates (bread) for as long time as a month, and that any one by unreasonable demands in this respect only incurs the danger of not being obeyed even in feasible matters.

Experience no less than late advances in physiology and experimental pathology should prevent us from permitting our fears of hyperglycemia with its glycosuria to overshadow other and greater dangers.

There died in Sweden some years ago a man whose case is an illustration of the comparatively insignificant danger of hyperglycemia. The patient was Professor Forsell, well known from his paper on his own case, published in 1883. Forsell was no physician, and his paper bears the stamp of the layman. Some of his conclusions are entirely false. The facts with regard to his diet, his polyuria, and his glycosuria, however, are certainly in the main correct, and correspond with the data of his physician, who died a few years ago. Forsell's diabetes began quite suddenly in 1866; the same year the percentage of sugar reached 7.4, the polyuria 6.5 liters, the specific gravity 1.040, the daily loss of glucose often 425 grams, and on one occasion 850 grams. Professor Forsell never was my patient, and I am not familiar with the details of his case; but although its course proves it to have remained at least for a considerable length of time in the mild stage, there is no doubt that it was, in 1866, already quite an intense diabetes. His physician at first put him on a strict diet; unfortunately, there is no record of its effect on the glycosuria. Forsell, however, soon found that the strict diet, besides being exceedingly unpleasant, always made him feel ill and weak. Having ascertained the evil consequences of this system, he adopted the opposite extreme, consuming a considerable amount of bread and of vegetables, and every day drinking from 6 to 8 pints of Bavarian beer. "By avoiding diet, watering-places, and medicine, I have kept in very fair health since 1873," Forsell writes in 1883. When Forsell died, he had suffered from most pronounced diabetes for about twenty years. Such a prolongation of life in cases of this kind is extremely rare—much rarer than it is for a gouty person with mild diabetes to live for forty years. Is there any reason for believing that Forsell's life would have been longer or happier if he had lived on meat and fat, without carbohydrate or with a scanty supply?

I am particularly anxious not to be accused of approving of Forsell's régime. I am perfectly certain that he might, with advantage, have made some restrictions in carbohydrate—and no one will approve of his enormous consump-

tion of Bavarian beer. The mere fact, however, that a diabetic of this kind can live in fairly good health and do fairly good work for more than twenty years is worthy of consideration, and may afford a foundation for conclusions that, however prudently formulated, are of great practical portent. Professor Forsell's was far from being a good régime, but I feel convinced that if I had to choose for my patients—as a rule, for years—between his régime and an exclusion or a severe restriction of carbohydrates, I should act wisely in choosing the former.

In the mild stage we always have to put a maximum limit upon the daily amounts of carbohydrate. Except in dealing with a certain kind of hypochondriacal patients, we need not trouble ourselves with regard to a minimum limit. In the enormous majority of cases we may feel certain that if the patient does not consume more carbohydrate than we prescribe, he will hardly ever consume less.

In a large number of cases the rational daily allowance of carbohydrate is represented by the maximum that the patient can take without the development of glycosuria. We should never restrict the patient's allowance of carbohydrate below the amount that leaves him free from sugar in his urine, and thus free from any distinct hyperglycemia. Whenever a patient can take the necessary amount of carbohydrates for the maintenance of good digestive action and nutritive equilibrium, without the development of glycosuria, he is permitted to take that amount. According to my experience, the minimum amount sufficient in the long run for a full-grown person is hardly ever less than 60 grams of carbohydrate, and is usually somewhat more. On the other hand, it is rarely necessary to give a diabetic patient in the mild stage more than 100 grams of carbohydrate; neither is he capable of taking more for any great length of time without the development of glycosuria. The rational daily allowance of carbohydrate for protracted periods for a patient in the mild stage thus varies usually from 60 to 100 grams. For reasons mentioned in the preceding chapter, it is well to determine the amount in each case by giving the patient the larger quantity (100 grams) and diminishing it until the glycosuria ceases,* or until the necessary minimum (of about 60 grams) for constant use has been determined.

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* We consider the glycosuria practically to have ceased when Nylander's and Fehling's solutions react only faintly with a sample of the urine collected during twenty-four hours.

If the patient (in the mild stage) continues to exhibit glycosuria when his daily allowance of carbohydrate is restricted to the minimum necessary for maintaining good digestive activity and nutritive equilibrium, it is preferable to risk the moderate disadvantages of the slight corresponding hyperglycemia rather than the more serious dangers of digestive disturbances and inanition. The rational daily allowance of carbohydrate varies not only among individuals, but also from time to time in the same individual. Sometimes loss of appetite or of flesh, exacerbation of neurasthenic symptoms, mental inability to submit to some restrictions, force us to make some concessions. In cases complicated by gout, the hope, always faint, of bringing about recovery from the diabetes by removing the hyperglycemia is lost. The chances that the diabetes will remain mild are almost certain, and we are not inclined to be severe, especially as we have no wish to increase too greatly the proteids, and thus to put a strain on the kidneys, and as we need bread to facilitate the ingestion of the necessary amount of fat. The further advanced in age the patient, the less danger there is of his ever reaching the severe stage of diabetes, and we can afford to be more liberal; in senile cases we never urge severe restrictive measures.

If, on the other hand, there is reason to believe a case of diabetes to be of quite recent origin, we should always estimate at its full value the increased chance, however small, of perfect recovery by removal of the hyperglycemia, and for a long while we restrict the carbohydrate as much as possible. During healing processes of all kinds, or before an operation, it is also desirable to remove as much as possible the hyperglycemia. Finally, a sudden decline in a diabetic patient's power of assimilating carbohydrate makes a rigid restriction necessary.

In those cases in the mild stage in which the patient's power of assimilating carbohydrate is too low to permit of the usual diminution of his daily allowance below his limit of assimilation and of the removal of his hyperglycemia there remain several ways of mitigating the hyperglycemia and its effects.

For this purpose the patient may be advised to take his whole daily allowance of carbohydrate during his first one or two meals of the day; the physician should not forget to insist that he shall

at the same time take as much butter as possible with his bread. By entirely excluding or markedly restricting the carbohydrates of the last meal the hyperglycemia also is excluded or restricted during the larger part of the twenty-four hours. The last meal, thus consisting exclusively of animal food, will then necessarily tend to be a light one. The German system, with an early dinner, is better for this purpose than the custom prevailing in France, England, and the United States, of taking the heaviest meal in the evening.

There is still another way of mitigating the hyperglycemia and its effects in those cases in the mild stage in which even the minimum daily allowance of bread and vegetables necessary for the maintenance of digestive activity and nutritive equilibrium cause glycosuria and hyperglycemia. For this purpose *periods* of exclusion or of such severe restriction of carbohydrates are prescribed that the glycosuria, beyond faint traces in the mixed urine, disappears. Such periods may be prescribed several times a year; they ought to last for at least two weeks, but can scarcely ever be enforced for more than four weeks. If loss of weight, neurasthenic symptoms, and digestive disturbances become too marked, we have to shorten these periods, which rarely pass entirely without some of the troubles mentioned. If one prescribes periods of this kind of as long a duration as four weeks, he may with advantage select the summer for one and the winter for another. In the spring and in the autumn the tendency to mental depression, common among diabetics, is more marked, at least in northern climates.

The absolute or severe diet includes all animal food except milk (and its derivative, cheese), with its nearly five per cent. of lactose, and liver, with its variable, but usually small, amount of glycogen. It thus allows all otherwise wholesome parts of *mammals*, *birds*, *amphibia* (turtles, frogs, etc.), *fishes*, *lobsters*, *crabs*, *crawfish*, *oysters*, etc. It would be unwise and pedantic to exclude from this frugal dietary *eggs* and *butter*, on account of the insignificant proportion of carbohydrates they contain. Eggs are easily taken, easily digested, and, apart from idiosyncrasies, constitute an important item in the severe diet. The butter with its eighty-four per cent. of pure fat usually represents among Teutons and Anglo-Saxons the greater part of the fat in the food, and more than is taken in

bacon, meat of any kind, lard, olive-oil, milk, cheese, eggs, etc., put together. The butter tastes better, is more easily ingested and digested than most other fats, and has, besides, the great merit of not reminding the diabetic, by any rarity of appearance, of his condition. It is therefore somewhat incomprehensible why so many diabetics, except for special indications, are tortured with that unpalatable fat, cod-liver oil. Neither can I understand the superiority of either olive-oil or "lipanin" to butter, which certainly contributes better than anything else to the possibility of ingesting the desirable amount of fat. Unfortunately, few persons are able to take large amounts even of butter without bread.

It is a most important rule to give the patient with the severe diet the advantage of as great a variety of food as possible, and to include different kinds of meat, birds, fish, and eggs in his dietary. When his digestive power is weak, he often derives considerable benefit from the modern condensed forms of proteid food. I have especially often seen good effects from the use of "somatose," which is rich in albumoses.

But whatever is done, the patient will have a trying time during periods when an exclusively animal diet is demanded and it is often possible, even during periods of rigid restriction, considerably to mitigate his dietetic difficulties by introducing into his food small quantities of those vegetables that contain comparatively slight amounts of carbohydrates. The German "*sauerkraut*," the French "*choucroute*," when well fermented, does not contain more than a few tenths of a per cent. of carbohydrate. *String-beans*, picked quite young and before the development of their seeds,* contain much inosite, but only traces of carbohydrate. *Lettuce*, *cucumbers*, and in many cases the leaves of *spinach* may also often be taken in small quantities by patients in an advanced mild stage, without causing the appearance of more than faint traces of glucose in their urine. The mitigation that such an addition to the dietary affords during periods of severe restriction is often underrated by the physician, but never by the patient.

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* When the seeds are developed, string-beans contain several per cent. of starch and sugar, and they no longer constitute an appropriate article of food during periods of rigid dietetic restriction.

During periods of anything like rigid restriction of carbohydrates, the diabetic patient has to choose between two substitutes for bread. The one is the *genuine*, tasteless, expensive, and almost worthless "gluten-bread," of which I have entirely abandoned the use. The other substitute for bread is the "bread" made according to Pavy's and Seegen's prescriptions, of eggs, butter, and almonds deprived of their sugar. The almond bread which, as bought in shops, usually contains starch, ought to be baked at home, according to the original prescription,* and can even then, during periods of severe restriction, be allowed only in small amounts.

The most important question of bread, which must be treated at some length, leads me to the subject of the *more liberal diabetic diet*, in which at least half, often more, of the allowance of carbohydrate is given in the form of bread. All proper bread certainly contains a large percentage of starch, but the human digestive apparatus is too accustomed to this kind of food to be able to get along entirely without it. The bread, besides its other nutritive value, also facilitates the ingestion of fat, which, from its high caloric value and its properties of not increasing either the hyperglycemia or the work of the kidneys is so advantageous to diabetics. In discussing the question of bread with a diabetic patient the physician should never fail to point out its merit as an excellent vehicle for fat, and impose upon him the necessity of always taking butter, or butter and cheese, with his bread.

The impossibility of living without bread and the fear of its starch for diabetics have led to many attempts to produce for these patients something that might possess the advantages of ordinary bread without supplying the much-dreaded starch. I believe this problem to be as impossible of solution as the squaring of the circle or as the problem of perpetual motion. It is the

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* The powder of one-quarter pound dried and finely pulverized almonds is put in a linen bag and cooked a quarter of an hour in water with some drops of vinegar, then well kneaded with three and a half ounces of butter and two whole eggs. Then the yolks of three other eggs and some salt are added to the mass. The whites of the three eggs are well beaten and also added, whereupon the whole is put in a buttered form and baked. When prepared in this legitimate way, without meal or rice, the bread unfortunately often lacks the proper consistency.

starch in the bread that chiefly gives it its good taste and other dietetic merits, and that diabetics, as well as others, need. Every one of the many "*breads for diabetics*" suffers from either of two faults: it contains much starch *or* it does not taste like real bread, and is a substitute for it in almost nothing but name. Further, dishonest speculation has furnished the market with a great number of preparations whose real qualities are concealed beneath false or ambiguous assertions. At this moment there is before me a circular from a baker, accompanied by a sample of his *aleuronat-bread*, —the former couched in such terms as to make the reader believe that the ready-made bread contains only the comparatively few per cent. of starch of the original aleuronat, while in reality it contains, at the very least, four times that amount. Patients easily persuade themselves that they may consume any amount of any bread that is said to be especially prepared for diabetics. This is the case even with the ordinary *Graham bread*, which contains about forty per cent., by weight, of pure starch, or nearly eighty per cent. of what is contained in the same quantity of white bread. The preparations with a small amount of starch or with none at all are tasteless, indigestible, and expensive. Upon the whole I am of the opinion that the "breads for diabetics" have profited the bakers, but injured the diabetics.

I would advise physicians to allow their diabetic patients, except during periods of rigid restriction of diet, daily a fixed amount of the kind of ordinary bread that they prefer. It is only important to limit the daily allowance either by weighing it every morning or by buying it in some customary form containing practically a fixed and definite quantity. If the measurement of the quantity is left to the patient's eye, it will not be long before the urine will show that he has taken far too much of it.

Graham bread tastes well, but contains about forty per cent. of starch. *Bran-bread, à la* Prout or Camplin, tastes badly, otherwise it contains too little bran and too much starch. Bread may be baked from inulin, a substance found in the roots of certain Compositæ (inula, taraxacum, dahlia, etc.). This bread, producing levulose and not glucose, causes much less glycosuria than starch, but it has a poor taste. *Soya-bread*, from the Japanese *Soya hispida*, demands twenty per cent. of starch to render its taste at all pleasant. *Dika-bread*, made from owala-seeds or the fruits of the African *Pentaclethra macrophylla* (30.5 per cent. proteids and 45.18 per cent. of fat), is still unknown

to me, but does not seem to have made much progress as a food for diabetics. The *meat-bread* of Baron Lühdorf contains much starch. In describing its taste as pleasant, the Baron does so without frenzied protests, only by virtue of the proverb "de gustibus non est disputandum." *Genuine gluten-bread* is perfectly tasteless; what is called gluten-bread generally contains three-fourths as much starch as an equal weight of ordinary white bread. As to "florador," "semolina," and other preparations of like kind, they differ from ordinary bread chiefly in their price.

So far as I know, there are, among the enormous number of "breads for diabetics" at present, only two of those mentioned that really deserve the attention of physicians—viz., Pavy-Seegen's *almond-bread*, and Hundhausen's *aleuronat bread*. I sometimes, as already mentioned, during periods of rigid diet make use of almond-bread, which, prepared in the proper manner, contains only insignificant quantities of carbohydrates. On boiling with the addition of a few drops of acetic acid to the water, the greater part of the nine per cent. of sugar and dextrin is removed, and twenty-four per cent. of emulsin and fifty-four per cent. of fat are left. For the market, however, the bread is often baked with the addition of some flour to give better consistency. It is not easy to digest; it is expensive; and it has a dry, unsatisfactory taste; but it is capable of serving the purpose already mentioned. *Aleuronat* consists chiefly of vegetable proteids. Hundhausen's preparation contains about eighty per cent. of that substance, 8.7 per cent. of water, and eight per cent. of carbohydrate. By mixing it with wheat-flour one may produce a bread that contains less starch than ordinary bread, and that tastes the better the more wheat-flour it contains. If Hundhausen's aleuronat flour is mixed with an equal weight of wheat-flour (the minimum amount of the latter necessary to make a fairly pleasant tasting bread), the whole mixed dry meal contains 45.1 per cent. of proteids, 41.35 per cent. of carbohydrate, and 11.05 per cent. of water. The bread will thus contain nearly as much carbohydrate as it does proteid; it tastes much less well and is much more expensive than ordinary bread. Its merit is that it contains less carbohydrate than ordinary bread—not that it contains vegetable proteid, which tastes less well, and is much less digestible than animal proteid, as it leaves as much as twenty-five per cent. undigested in the feces. Ebstein recommends the unmixed aleuronat flour for sauces and for the grilling of meat; about twice as much of it is taken for these purposes as of wheat-flour.

It is not to be denied that a diabetic patient may derive some advantage from using bread made of as much of aleuronat and as little of wheat-flour as will do for him in the long run, thus obtaining a larger amount of bread, as compared to its quantity of starch, as a vehicle for cheese and butter. Even aleuronat bread, in some respects the best of all "breads for diabetics," has the one merit common to them all—*i. e.*, it is not absolutely necessary. If the physician wishes to prescribe this special bread, he had better have his patient buy Hundhausen's original aleuronat, and bake the bread at home. This is the only easy way of ascertaining its percentage of carbohydrate.

Diabetics, like other persons, know better what they want in the way of food than with regard to anything else. They almost all

want not only bread, but also *potatoes*. Now, there are many things that contain more starch than potatoes; but the cooked potatoes containing at the least fifteen per cent. of starch and little besides but water, we ought to persuade our diabetic patients to do without it, as our ancestors had to do a couple of hundred years ago. When the power of assimilation is active, or when a certain amount of hyperglycemia may be tolerated, we may allow a small quantity of potatoes, always insisting upon the amount being weighed, and upon their being used as a vehicle for butter, in which capacity they fulfil a most useful purpose.

Attempts to find a substitute for potatoes have not been much more successful than those to find a substitute for bread. The tubers of *Helianthus tuberosus* L., the Jerusalem artichokes, by reason of the fact that they contain, when fully developed,* very little starch or glucose, but chiefly inulin and levulose, give rise in diabetes to a comparatively slight glycosuria, and the plants are not rare in kitchen-gardens even as far north as Stockholm, and over the greater part of Europe. Jerusalem artichokes are, to my taste, far inferior to potatoes, but they are certainly of some value to diabetics, and, like potatoes, they constitute a good vehicle for butter. The *tubers of Stachys affinis* are chemically similar to Jerusalem artichokes; but, at least in my country, they are quite small, and offer no advantages over the latter vegetables.

With a more liberal diet one may give those vegetables that contain only a small amount of starch, but which contribute largely to the necessary variety and to the maintenance of the appetite. From the list at the end of this book it will be found that we have chiefly to keep to *lettuce*, *spinach*, *cucumbers*, *young string-beans*, *celery*, *asparagus*, *radishes*, *mushrooms*. *Tomatoes*, the different kinds of *cabbage*, *almonds*, and *nuts*,† and some fruits (*cranberries*, *strawberries*) may often be allowed in small quantities. "*Sauerkraut*" has already been mentioned as almost always admissable when well fermented—unfortunately, many patients, after a short period of warm appreciation, acquire a loathing for it. We almost constantly

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* When younger, the tubers contain a considerable amount of starch and glucose.

† Hazelnuts, walnuts, peanuts, Brazilian nuts, cocoanuts, are permitted, but not chestnuts.

exclude everything containing more than eight per cent. of carbohydrate, except bread and potatoes, which must be weighed. Sometimes, however, we allow a large baked apple at breakfast for the sake of its aperient quality.

Of liquids, *tea* and *coffee* with saccharin or crystallose (see below) or levulose, or without any corrective at all, are permitted during the earlier part of the day except during periods of severe diet. A cup of tea of ordinary size contains about one gram, a cup of coffee about two grams, of carbohydrate. I constantly interdict the use of both of these in the evening on account of their disturbing influence on sleep, which is, at best, not very sound in diabetic patients. A glass of milk, or some alkaline water, or even a weak grog is a better ingredient of the patient's supper or late dinner.

Moderate quantities of red wines, European or American, may be allowed; of white wines those from the Rhine are the best.

Among alcoholic liquors, however, none is better for the diabetic patient than *cognac*, *brandy*, *whisky*, *gin*, and similar drinks. These must be taken diluted, best with some carbonated mineral water, and the amount of alcohol they contain must not in the twenty-four hours exceed one-fourth, at the very utmost one-half, of a gram per kilo of bodily weight.

All sweet wines,—champagne, port, Madeira, sherry, marsala, etc.,—"liqueurs," and punches are forbidden under all circumstances in cases of diabetes.

It is also well to interdict absolutely porter, beer, and ales of all kinds. These contain a good deal of carbohydrates, are generally drunk in considerable quantities, if drunk at all, and are easily dispensed with.

The usefulness of *milk* * for the diabetic patient is more difficult to decide, and to some extent is a matter of individuality. Milk

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* Some physicians forbid milk in all cases of diabetes—a position that may possibly be defended. Dr. Donkin has been unfortunate enough to recommend it *skimmed* as an exclusive food in cases of diabetes. This prescription can not possibly be defended, even if it did not include the skimming, which deprives the diabetic of a large part of the fat and leaves the carbohydrate. I have myself never prescribed the "Donkin cure," but I have several times seen it prescribed by others, with its necessarily signally bad results. An adult person requires about six liters of skimmed milk in order to secure the necessary amount of calories. This gives him nearly three hundred grams of lactose, and does not, in other respects, constitute the best kind of diet.

contains nearly five per cent. of lactose, and can not be allowed at all during periods of rigid restriction of the diet; it ought never to be allowed in large or unlimited quantities in any case of diabetes. In all severe cases, however, and in many mild cases one may allow 200 or 300 cu. cm. of unskimmed milk to be taken at supper. The sour milk, much in use during the summer in the north of Europe, in which the lactose is in large part changed into lactic acid, forms a most pleasant, wholesome, and popular article of food for the diabetic patient. At present there are other methods of removing the greater part of the lactose from the milk; when this can be done, the greatest objection to the use of milk in cases of diabetes (not belonging to the class of persons in whom dyspeptic symptoms arise in consequence) is removed.

Diabetic patients often are very thirsty and consume considerable quantities of drinking water. This is partly a result of the increased amount of sugar and of toxins in the blood, of nature's attempt to eliminate these toxins as far as possible, and of the difficulty in providing the tissues with the necessary supply of water from the strongly sacchariferous blood. There is nothing so absurd that it can not be prescribed, and there are physicians who advise their diabetic patients to restrict themselves in the drinking of water. If this is done at all extravagantly, it tortures the patient, increases the diabetic and other deleterious substances in the blood, changes the working conditions of the heart, increases the dangers from too concentrated secretions (gall-stones, urinary concretions, etc.), acts unfavorably on the nervous system, and in severe cases multiplies the danger of coma. The drawbacks of polydipsia are the distention of the stomach and the increase in the work of the heart. Both of these effects are greatly diminished by the avoidance on the part of the patient of drinking large quantities at *once*. Diabetic patients should be advised to drink as much water as they like during the twenty-four hours, but to take the whole quantity in frequent small portions. Instead of ordinary water they may with advantage sometimes drink carbonated alkaline mineral waters. If the polydipsia is *very* marked, the patient may be spared a couple of hundred calories by heating the drinking water.

Different substances on account of their sweet taste have lately been used as substitutes for sugar in cases of diabetes. The most

common of these is (Fahlberg's) *saccharin* (=anhydro-ortho-sulph-amin-benzoic acid). This substance, taken in amounts of a few centigrams every day, in the form of the small tablets to be had of druggists, sweetens tea and coffee or anything else with which it is used. I am not certain that I have ever observed the dyspeptic effects dwelt upon by Bernstein, v. Jaksch, and others. Small amounts seem harmless in this respect. The use of saccharin, however, causes the appearance of a reducing substance in the urine, and from this fact alone some influence on the kidneys might be suspected. The taste of saccharin is not pleasant, neither is the use of a sweetening substance very important to the patient; most persons become indifferent in this respect. The antizymotic quality of saccharin is too weak to give it any distinct advantage in ordinary small amounts. I usually tell patients of saccharin and advise them to take as few tablets as possible daily; they then generally use it for a time, and then without regret abandon it. *Sucrol* or *dulcin* (=paraphenetol-carbamin) is in large doses a poison (Kossel, Aldehoff). I have not used it, though several writers affirm that they have seen no bad effects from small amounts. I do not know of *crystallose* more than its appearance and its taste, which latter is more pleasant than that of saccharin. *Mannite* causes diarrhea.

Levulose has distinct nutritive value, increases the glycosuria but moderately, and has no other bad effects. It is, however, still too expensive for poor patients, and some persons take a dislike to it.

An enormous and a significant number of "specific" and other remedies have been used in the treatment of diabetes. Upon the whole, too much importance has been attached to any diminution in the hyperglycemia and glycosuria, however transitory, and too little consideration has been given to the first duty of every physician—viz., not to do harm. It seems almost incredible that there are physicians who recommend, *e. g.*, uranium nitrate for the purpose of decreasing the glycosuria, and it seems certain that even minimum quantities of this poison with its violently irritating effects on the alimentary canal and on the kidneys must in the course of an hour do more harm than considerable hyperglycemia

will in the course of a week. The "specific" influence of many drugs may probably be only imaginary, and the diminution of hyperglycemia and glycosuria a result of impaired digestion. Even if this "specific" influence is real, its cost may easily be too great, and I believe it to be good advice to recommend the administration to diabetic patients of only such drugs as can certainly be taken for some time without serious detriment. Even the best "specific" remedies for diabetes are but very uncertain and weak in any "specific" influence, and the longer one has the opportunity of watching the effects of extolled remedies of this kind, the more skeptical does he become of their great value.

Of some real, though not of great, specific value is *opium*, which has been used in the treatment of diabetes at least since the beginning of the nineteenth century. In many cases—but not in all—it distinctly diminishes the glycosuria and, what I consider to be much more important, it improves the patient's general somatic and mental state. I prescribe it when I find a rapid diminution in the power of assimilation and during periods of nervous exacerbations; under the latter condition it is really of decided value. One begins with small doses, increases them to quite considerable ones (from 8 to 10 centigrams—1¼ to 1½ grains—of pure opium per day for an adult), and after some time, perhaps days or weeks, gradually diminishes the dose, and finally withdraws the drug altogether. It is advisable never to use opium for any great length of time.

As to *codein*, and still more as to *morphin*, these are in every respect much less valuable in cases of diabetes than is opium. Considering the great danger to the patient of becoming addicted to them from the prolonged daily use of any of these remedies,—certainly one of the worst of human miseries,—I think it the physician's bounden duty, under all conditions, to reserve them for the mitigation of transitory, severe pains or of perfectly hopeless conditions.

When coma is present or there is imminent danger thereof, the administration of narcotic or hypnotic remedies is avoided as much as possible.

Next to opium, *arsenic* may, perhaps, be mentioned as having some specific value in the treatment of diabetes. In some cases it does somewhat, though never to any large extent, cause a diminution in the glycosuria; it may, perhaps, counteract the conversion of glyco-

gen into glucose and favor its transformation into fat in the liver, where, as has been mentioned, it in some way causes a diminution in the glycogen. It is, besides, as is well known, a splendid tonic, and in diabetic patients who are also anemic it may be given with great advantage. In my opinion one had better adhere to small doses, beginning with one and slowly increasing to three or four drops of Fowler's solution thrice daily, after meals, or giving a corresponding amount of arsenic in pills (from gr. $\frac{1}{100}$ to gr. $\frac{1}{30}$). After a couple of weeks the dose is slowly diminished. One may, in cases of diabetes, often with advantage combine arsenic with opium.

The *alkaline salts*, especially *sodium bicarbonate*, have been used in the treatment of diabetes for at least since the time of Willis in the seventeenth century. They are believed to diminish the glycosuria, either by increasing the combustion of sugar in the tissues or by facilitating the storage of glycogen and counteracting the formation of glucose in the liver. The alkaline salts have different merits (see below); but their power of diminishing glycosuria is exceedingly slight, and, unless large doses are given, conscientious investigation often fails to discern any decrease in the amount of sugar excreted in the urine. Mialhe administered twenty grams of sodium bicarbonate a day, with the effect of diminishing the glycosuria somewhat; but such doses give rise to gastrointestinal disorders and weaken the patient. Richardière gives it in doses of from four to ten grams a day for months; but only periodically, and never in cases of pancreatic diabetes or in any case complicated by tuberculosis or by marasmus. Sodium bicarbonate is given chiefly in mineral waters, and then only in doses of a few grams a day, and the enormous doses are used by most physicians only in the presence of coma, or when there is manifest danger of it. The salts of tartaric, citric, phosphoric, lactic, benzoic, salicylic, hippuric, and boric acids are also used, though far less than sodium bicarbonate.

Ammonia, especially as carbonate and citrate, is also used, and has the merit of stimulating and of increasing the perspiration. Bouchardat recommends *potassium carbonate* and *sodium and potassium tartrate* for their powerful effect in eliminating uric acid. *Clemens' solution* contains potassium carbonate, arsenic, and bromids.

Calcium is for the moment and in some places popular in the treatment of diabetes. Grube gives his patients, four times a day, at meals, large doses of a mixture of seven parts of *calcium carbonate* and one part of *calcium phosphate*. These salts do not influence the glycosuria, but they are said to improve the general state and to facilitate the ingestion of fat. Robin uses *calcium phosphate* and *glycerin*. Those who give their diabetic patients large quantities of milk often add calcium carbonate. *Magnesium hydrato-carbonate* and calcined magnesia are also used, especially in cases with hyperacidity of the stomach and constipation. Viau-Grand-Marais recommends *strontium bromid;* Martineau gives *lithium carbonate* (with arsenic).

The alkaline and alkaline-saline spas are visited by large numbers of diabetics. Carlsbad, Vichy, and Neuenahr enjoy at present the greatest reputation for their beneficial influence on diabetes. As a student of diabetes and as a practising physician in Carlsbad I have made it my purpose to acquire as correct an idea as possible of what may be reasonably expected for a diabetic patient from a sojourn of some weeks at one of these health-resorts. I consider it as great an advantage for these resorts as for the medical profession and for the patients that no false pretensions are supported and consequently no disappointments incurred, and that, on the other hand, the knowledge of the good results that undeniably are in many cases to be obtained is spread as far as possible.

As for the glycosuria, Carlsbad and Vichy water, and doubtless, also, Neuenahr water in the moderate and rational amounts recommended at present, which scarcely ever go beyond a liter a day, have no appreciable influence, or one that is extremely slight and uncertain.*

Does this mean that a course of treatment at Carlsbad, Vichy, or Neuenahr has no value at all for diabetic patients? By no means. I feel safe in saying that most diabetic patients, especially in the mild stage, whom I or others have had occasion to observe in Carlsbad, have derived as considerable a

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* I protest, *a priori*, against any denial of this fact not founded on pure experimentation. I pass entirely over the naïve reports on the influence of mineral waters on the glycosuria resulting from a simultaneous restriction of carbohydrates—they are not worth discussing. Neither will it do first to determine the supply of carbohydrate, and the amount of glucose excreted with the patient at home and occupied with his daily work, with its strains and emotions, and then to make the same determinations at the spa with the patient at leisure and subjected to the effect of other therapeutic agents than the mineral water. The experiment requires exact determinations of carbohydrate and glycosuria during two not too short periods, the one with and the other without mineral water, but both otherwise under as nearly similar circumstances as possible. Any one that undertakes the considerable amount of work required in such an experiment will find that the glycosuria,

benefit from their sojourn there as might be expected by any reasonable person. [We know that most laymen, and even some physicians, are not reasonable.] I do not consider the mineral water at Carlsbad, excellent as it is, to be the only or even the first therapeutic resource of the place. Still, the water has a good influence on dyspeptic symptoms, which are common in diabetic patients, as they are in others; it also has a good influence on the constipation, which is equally common. It increases some of the secretions,—diabetic patients are, during its use, often less troubled by dryness of the mouth,—and I believe that this influence on the bile is of benefit in many cases. I am also willing to acknowledge the probability of some beneficial influence on the liver in other respects, and that an enlarged and tender liver becomes sometimes, under the use of the mineral water, smaller and less sensitive to pressure. Finally, I will not deny a favorable influence on gouty symptoms, which are very common in diabetics of the florid type in the mild stage of the dystrophy. The alkaline water must also have some slight neutralizing effect on the acidosis in the severe stage, though, according to my opinion, only a comparatively small number of patients in this stage do well in undertaking a journey of any length. It is, fortunately, not necessary to enter here into details with regard to the influence of the mineral water on the metabolic processes; but if it accomplishes only what I have already acknowledged, it is well worth the drinking.

The patient's absence from home and its cares, his rest from intellectual work and mental worry, the hygienic and dietetic discipline, so much more easily enforced in a health-resort than anywhere else, and the other therapeutic resources available in such a place, are, in my opinion, together of much greater value than any mineral water, and it is these considerations that make up the enormous difference between a "cure" at home and the "cure" at a watering-place. The water, as it bubbles from the springs, or is contained in well-corked and well-preserved bottles, is, as every sensible person can understand, exactly the same.

As I attach less importance to local mineral water than to other therapeutic agents, it is evident that in my choice between different health-resorts I shall be influenced less by the mineral water itself than by other circumstances, some of an individual and some of a local nature.

There is, unfortunately, a single feature common to almost all advice in this respect recorded in the literature—viz., one always finds that the adviser

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cæteris paribus, with or without the use of mineral water, remains the same, or that the variations are no greater than they are without any appreciable external change whatever. Even in cases of simple glycosuria one finds with the use daily of a liter of mineral water that a faint trace of sugar, just large enough to cause a distinct reaction, remains as it showed itself before the use of the mineral water. In the different stages of diabetes one will arrive at the same results, though there may often remain some doubt as to the cause of small variations in the excretion sometimes observed even under apparently perfectly similar circumstances. This will be the case whether the mineral water is drunk immediately at the springs or from bottles; if it were not, who would undertake to explain reasonably any possible difference? Külz's and all other serious investigations on this subject have led to the same results as my own.

recommends, with rare exceptions, the sending of patients to the health-resort in which he is personally interested and is engaged in practice. The late Dr. Schmitz, who practised in Neuenahr, stated that, in order to avoid debilitating the organism, patients had better be sent to Neuenahr rather than to Carlsbad, whose waters, according to Schmitz, contain rather large amounts of sodium sulphate; or to Vichy, where waters were said to contain rather large amounts of sodium bicarbonate. As it is always advantageous not to debilitate the organism, these statements seem to mean that one must never send patients to Carlsbad or Vichy, but always to Neuenahr—and presumably (as long as he lived) to Dr. Schmitz. The French have no great regard either for Neuenahr or for Carlsbad, which latter place they, by the way, often believe to belong to Germany. "Il n'y a lieu d' essayer Carlsbad que dans les cas ou une au deux cures à Vichy n'auraient pas donné de resultats satisfaisants." The physicians of Carlsbad, on the other hand, think Vichy good only for amusement, and smile at mention of the 0.77 gram of bicarbonate which is the essential ingredient in a liter of the "Augustenquelle" in Neuenahr, and affirm that this latter place is dangerous for visitors on account of the risk of death from "the blues," and that their own place, in point of therapeutic resources of all kinds, is the first health-resort that is, or was, or ever will be.

I do not intend to offer like recommendations. I find it a difficult task to decide which of these superstitions is the sillier: the one that ascribes such a debilitating effect to the small quantities of alkaline sulphates, carbonates, and chlorids in Carlsbad,* or the one that attributes such wonderful effects to those salts or to the sodium bicarbonate at Vichy or Neuenahr; and I am willing at once to acknowledge that many diabetic patients can derive benefits from a "cure" at any one of the three places named. I would, however, advise against sending thither patients in constant danger of coma, or suffering from tuberculosis, marasmus, or advanced arteriosclerosis, organic heart disease, or extreme senility. Fully developed mental disease also constitutes a contra-indication.

The seeds of the Indian plant *Syzygium jambulanum* really in many cases diminish glycosuria; in other cases they seem not to have the slightest influence in that direction, whether the fluid extract or the powdered seeds are used. Lewaschew administered from fifteen to thirty grams of the powdered seeds. I generally have given no more than ten grams, and have not observed any dyspeptic or other detrimental results. Fichtner saw the glycosuria increase after the use of the drug. Lépine and Barral believe that it increases both the production and the consumption of glucose.

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* The notion existing among laymen and, in some degree, also among physicians of the debilitating influence of a course of treatment at Carlsbad owes its origin to the absurd system prevailing several decades ago in this Bohemian watering-place of giving patients enormous doses of the mineral water and of starving them half to death.

Weil introduced the leaves of *Vaccinium myrtillus* L. (blueberries) in the therapeutics of diabetes. The twigs, with the young leaves, are collected early in summer, when the bushes are in bloom. An infusion certainly causes diminution in the glycosuria; but at the same time it causes distinct dyspeptic disturbances. I have also heard patients complain of dyspeptic derangement after the use of Jasper's pilulæ myrtilli, and I have of late entirely ceased to use preparations of *Vaccinium myrtillus* L.

Antifebrin, *antipyrin*, *phenacetin*, and *exalgin* have been recommended by French and other writers as "specifics" in cases of diabetes. I should not prescribe any of these substances for any length of time. For the sake of the experiment, however, I gave one of my patients with an unvarying amount of glucose in the urine phenacetin at different times, and always with a distinct increase in the glycosuria. Lépine and Barral believe that antipyrin diminishes both the production and the consumption of sugar. Even though it causes diminution in the glycosuria in cases in which there is increased production of glucose in the liver, I consider the patients better off without antipyrin or related substances.

Quinin was used by Dobson more than a hundred years ago, and it is still recommended as a "specific" by Worms and others. It undoubtedly has a good influence in cases of glycosuria or diabetes due to malaria, of which several reliable instances have been placed on record. In other cases of simple glycosuria and diabetes I have failed to observe any influence on the excretion of sugar.

The *salts of bromin* are excellent and comparatively innocuous remedies, and of great value in the presence of some neurasthenic disorders on account of their sedative action; and they are often used in the treatment of diabetes. I have found it most advantageous to give them only once a day, in the evening, but then in rather large doses—not less than two grams. I prefer sodium bromid to potassium bromid. Neither the one nor the other salt exhibited any influence whatever on the excretion of glucose in a number of cases studied from this point of view.

Among vegetable "nervines," *valerian* is the most recommended and is used especially often in France. It is said chiefly to diminish the polyuria. Bouchard administers ten grams or more of the

extract per day; Lécoché from 0.30 to 0.50 gram; Dreyfus-Brisac from three to four grams with opium.

Canna agra is used in America, but I know nothing of its value.

Potassium iodid is used in the treatment of diabetes, as it is also in that of most other diseases. In some cases of diabetes complicated by syphilis I failed to observe any effect upon the glycosuria, even after the administration of large doses.

Sampson recommends *potassium permanganate* by the mouth, in small doses, especially for anemic or lymphatic diabetics. Some French physicians believe that they have attained "de grands succès curatifs" with this remedy.

Potassium bichlorate and *potassium chlorate* have also been used in the treatment of diabetes, and have shown their uselessness in this respect.

Cantani, earlier in his career, praised *lactic acid* in the treatment of diabetes. It causes dyspeptic symptoms.

Glycerin, introduced in the fifties by Basham, was for a time much used as a nutrient, chiefly on account of Schultzen's theory of diabetes. It is now almost abandoned, less because Külz proved that it somewhat increases the glycosuria than because it causes gastro-intestinal catarrh. So much has been written on the subject that I feel unwilling to add more. If any one should be anxious to give it or to take it, he had better do so according to the following (French) prescription: Fifty grams of glycerin, one liter of water, five grams of citric acid; to be drunk in the course of the day.

Bouchardat tried and gave up inhalations of *oxygen*. Benzi trusted to *ozone*. Richardson produced with oxygen hydrogen dioxid in water and gave of this solution one-half ounce three times a day.

I must not omit to mention the different ferments that have been recommended on various grounds in the treatment of diabetes. *Pepsin* does no harm. *Yeast* (of beer) would appear likely to do so in some degree, but according to Dr. Cassaët its action is perfectly marvelous, and the agent ought to be blessed by every diabetic patient. "Son état général se relève, son appetit renaît, ses forces augment, ses donleurs s'attenuent son poids enfin se modifie," which last means that the bodily weight may increase from three to eight kilograms in a fortnight. I have never used yeast in this way, and I feel certain that I never shall. Lepine saw the glycosuria diminish after subcutaneous injections of *diastatic ferment* (see below).

Robin has devised a system of giving specifics. He begins by administering antipyrin, one gram twice a day, for five days. Even he considers antipyrin contraindicated by anorexia, albuminuria, marasmus, and autophagy, and to be useful chiefly in mild cases ("diabète gras"). Then for a fortnight he gives a mixture of arsenic, codein, and lithium [℞. Sodii arsenitis, gm. 0.002; Lithii carbonatis, gm. 0.12; Codeinæ, gm. 0.02; Pulvis radicis valerianæ, gm. 0.25; Extracti chin. sin., gm. 0.40. One such powder is to be taken at breakfast and one at dinner, daily], with an interval of several days in the middle of this period. The treatment is concluded with opium, belladonna, valerian, quinin, bromids, alkalies, and cod-liver oil. "Quid bonum faustumque sit populo Gallico!"

Theobromin has been used by different clinicians. Lindner's "glycosolvol," put on the market as a specific in the treatment of diabetes, consists of theobromin-trypsin oxypropionate.

Besides the substances mentioned, the greater number of the drugs of vegetable or mineral origin found in the Pharmacopeia have been used in the treatment of diabetes. As I consider all of these as worse than useless, I shall only mention some of them by name: Phosphorus, iodoform, uranium nitrate, alum, thallium sulphate, the salts of copper, the mineral acids, carbolic acid, creosote, thymol, benzosol, salol, naphtalin, balsam of copaiba or of Peru, tannic acid, rhatany, catechu, cubebs, piperazin, camphor, colchicum, santonin, belladonna and atropin, jaborandi leaves and pilocarpin, secale cornutum, and ergotin. The last remedy recommended, so far as I know, is methylene-blue (Pierre-Marie, Le Goff).

Dismissing this long list from mind, we may devote a brief consideration to the proper use of mercury in cases of diabetes associated with syphilis. The diabetic organism is often more sensitive than others to poisons, and medical literature contains warnings against the too free use of mercury for antisyphilitic purposes with diabetic patients. As has already been mentioned, syphilis has in rare cases evidently been the cause of the diabetes by affecting in some way the nervous centers. If any reasons exist in such a case to suspect the presence of an active intracranial syphilitic process, there can be no doubt as to the physician's duty to take almost any other risk than that of an undisturbed continuation of the local syphilitic process. Neither the modern large doses of potassium iodid nor anything else has shown itself as useful an antisyphilitic remedy as mercury, and I would not hesitate to administer it quite energetically in such a case in the manner that continues to be the best, the most efficient, and the least objectionable: viz., the old "inunction-cure," with the usual precautions against mercurial poisoning. I have been governed by the rule to assume any reasonable risk rather than to leave the organism a probable prey to syphilis in any case in which there is a mere accidental complication of syphilis and diabetes, whenever there is overwhelming reason to fear the presence of the first-named disease. Views on the subject of antisyphilitic treatment vary exceedingly even now, when the day of the antimercurial craze has passed. For myself, I treated my syphilitic patients more or less *à la Fournier* before I had ever read his work, and I believe in varying its details in diabetic cases only according to the rules that we follow in general. In my own cases of associated syphilis

and diabetes the latter disease has been in the mild stage, and I have not observed any marked or peculiarly bad effects from the inunctions.

Since thyroidin has yielded such good results in the treatment of myxedema, *organotherapy* (though with much less good results) has been applied to numerous other diseases, and also to diabetes.* Some physicians simply administer portions of pancreas, raw or slightly cooked. Others make an extract of the raw pancreas of sheep or oxen, which is finely cut and macerated for twenty-four hours in its own weight of ("physiologic") solution of sodium chlorid or in glycerin ; this extract is later diluted with water. The filtered extract is afterward used in subcutaneous injection (Comby, Lancereaux, Gley, Thiroloix, Ausset de Cerenville, Battistini, etc.). Lépine macerates a pancreas in one liter of water, with one gram of sulphuric acid and five grams of malt-diastase, for two or three hours, at a temperature of 38° C. (100.4° F.). According to him, *the diastatic ferment is thus changed into glycolytic ferment.* Lépine then neutralizes the solution with sodium bicarbonate, and has the patient drink the whole in the course of twenty-four hours. This remedy is at least harmless. Lépine reports that he has observed from its use a decrease in the glycosuria and azoturia, an improvement in the general state, and an increase in bodily weight. Lépine, like all reliable observers, acknowledges that these results are highly uncertain.

Spermin (Pöhl) is praised by Eulenberg, Hofmeier, Hirsch, and others for its beneficial effects in cases of neurasthenia. Its property of increasing the alkalinity of the blood † ought to add to its therapeutic value in severe cases of diabetes, in which something besides possibly might be expected from it, especially as regards neurasthenic symptoms. Spermin—which is said to exist to some extent in all organotherapeutic remedies—has hitherto, so far as I know, never been used in its pure form in cases of diabetes.

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* Comby was, so far as I know, the first to employ this mode of treatment for diabetes.

† As mentioned by Senator and by Loewy, but considered by Strauss not to be constant.

Blumenthal makes subcutaneous injections of an *extract of the liver* and of the pancreas, and believes this to diminish the glycosuria as much as forty per cent.

Gilbert and Carnot administer an aqueous extract of the *liver* by the mouth or by the rectum,—"*opotherapie hépatique*,"—and believe thereby to diminish the glycosuria.

Thyroidin is sometimes prescribed in cases of diabetes by physicians of a hopeful and of an experimental turn of mind.

Mechanotherapy, long neglected, has at last gained its proper position in many countries, and has also been used in the treatment of diabetes in the forms of both *gymnastics* and *massage*, partly on account of their quality of diminishing glycosuria, partly on account of other effects, in my opinion more important.*

During the warm season I have found it most advantageous to prescribe gymnastics (*i. e.*, systematic exercises) in the form of walks in the open air. When a diabetic patient passes from a sedentary life to one of moderate exercise, this, together with the usual effects on the appetite, circulation, functions of the bowels, and general state of health, also has some effect in diminishing the glycosuria. Fatigue has a contrary effect, and must be avoided, and the amount of exercise must be regulated in proportion to the patient's strength, which in advanced cases often is quite small. I recommend two walks a day, and think it best for the first to be taken early in the morning and the last *several hours* before bedtime. A brisk walk *just* before bedtime, contrary to what is sometimes asserted, has a disturbing influence on sleep. Next in value

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* I have set forth these effects extensively in my "Handbook of Massage," to which reference may be made. I can not enlarge upon the subject here, as this book on diabetes has already grown beyond its intended limits.

Exercise was prescribed in cases of diabetes mellitus in the beginning of the present century by Marsch, and in more recent times it has been recommended by Bouchardat, Brouardel, Zimmer, Külz, and others. I have only recently had time to investigate the effects of general massage in diminishing glycosuria, having used it from time to time since Finkler and Brockhaus (1886) announced their results. While acknowledging the effect of energetic, prolonged general massage in causing diminution in the amount of sugar in the urine, I have not observed by far so good results as Finkler and Brockhaus, and do not consider a diminution from 450 to 120 grams of glucose to be possible as a result of mere massage.

to a moderately brisk walk is horseback-riding. The bicycle, even apart from its liability to accidents, is less beneficial.

In Scandinavian countries Zander's medicomechanical institutes are highly popular in the larger cities during the winter, and they have spread from Sweden to a large part of the civilized world. Their purpose is to give gymnastics and massage (especially the different forms of tapotément) by machinery. Here in the North we consider them in many cases as excellent for giving "mouvement cures" during our harsh winters; they are closed during the summer. Most of the patients suffer from weak heart or from constipation.* Gymnastics is now taught in all large communities, and can easily be arranged in homes without apparatus.

The *massage* should be the "general," with effleurage (stroking) frictions, pétrissage (kneading), and tapotément (striking, vibrations) of the greater part of the body. The different groups of muscles of the limbs and of the trunk should be subjected to this treatment. Frictions of the abdominal wall over the colon, with their excellent influence on the functions of the bowels, should be carefully practised in the way described by me and now known almost everywhere. To exercise any influence at all on the glycosuria, and in order that its well-known beneficial influence may be exerted besides to any great extent, general massage must be practised for a full hour daily, preferably in two *seances*. Under these conditions general massage requires but little technical skill, and it may, after some instruction, be performed by any intelligent and available servant of the same sex as the patient.

Hydrotherapy is of considerable value in cases of diabetes for its effect on the nervous system and on the skin. The diabetic patients, however, are always sensitive and must be protected against excessive temperatures, and, in general, the different forms of baths to be used in these cases vary from 20° C. (68.7° F.) to 36° C. (96.8° F.).

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*I shall entirely omit any description of the details of a "mouvement cure," as carried out in Zander's institutes or elsewhere, but will mention that, since I saw a similar treatment recommended by some Italian physicians and by Charcot, I have sometimes, in cases of neurasthenic sleeplessness, applied vibration to the head by means of Zander's machines, and with surprisingly good results. The vibrations must be given with some force; they are contraindicated by arteriosclerosis.

Different proceedings, constituting a mild *cold-water-cure*, are of considerable value.

A *sheet-bath* is sometimes used and generally given in the morning when the patient leaves his bed. A sheet wrung out of water at a temperature of about 20° C. (68° F.) is for a moment wrapped around the patient, who is then energetically rubbed with a dry sheet.

I prefer to recommend to my diabetic patients another form of bath, often and daily used by healthy persons of the upper classes in many countries and by patients of different kinds. This bath is best taken in an ordinary *sitz-bath*, partly filled with water, which for sensitive persons may be kept at a temperature of about 20° C. (68° F.). The patient, on arising in the morning, sits down in the tub, squeezes the water out of a large sponge three or five times upon his neck, and afterward, while drying the upper part of his body, stands in the tub. The whole bath lasts little more than a minute. At its conclusion the patient either immediately dresses for a brisk walk or returns to bed for a few minutes, until the reaction following the bath is fairly started.

The *half-bath, with gradually lowered temperature*, is an excellent measure which I often prescribe for diabetic and for neurasthenic patients in Carlsbad. The patient sits in a large tub half filled with tepid water (from 30° to 35° C.—from 86° to 95° F.) which, for a little while, is thrown upon his chest and his back. Cold water is then added, and the patient for some few minutes is subjected to energetic rubbing of the greater part of the body. A moderately cold douche or a dip in a moderately cold pond ends the bath.

Douches may also be used alone. They should be begun with tepid water, the temperature being gradually lowered to as low a degree as the patient feels able to endure, and the whole operation lasting not longer than about a minute.

Sea-bathing or lake-bathing is to be recommended only in mild cases of diabetes. It should be indulged in only when the temperature of both the air and the water is comparatively high and with precautions against taking cold. Under these conditions sea-bathing, in my experience, presents no dangers and exerts its usual beneficial influence.

The *tepid bath* at about 35° C. (95° F.) can also be used by diabetics. It should last about a quarter of an hour and ought to be followed by a moderately cold douche. If taken in the evening to promote sleep, the bath may be given for half an hour at a temperature of 36° or 37° C. (96.8° or 98.6° F.), and it should not be followed by any cold-water application.

The *electric bath*, moderately cold or tepid, and the bath in *carbonated water*, are both of some value on account of their stimulating effect.

The *warm bath* (at 38° C.—100.4° F.—or more) should be given diabetic patients only in the presence of incipient coma, and it ought to last about ten minutes.

The addition of different salts, extracts, etc., to the bath is often pleasant to the patient and may be of some benefit to the skin.

Electrotherapy is employed in cases of diabetes in the same way as it is in nervous diseases. It is generally the diabetic patient's neurasthenia or neuritis that necessitates the application of general or local galvanization or faradization. Like almost all forms of treatment, this has also been sometimes considered as diminishing the glycosuria; D'Arsonval lately mentioned such a result from the use of Tesla's apparatus.

Many causes combine to make the tissues of the diabetic patient a poor soil for healing processes. The deleterious effects of hyperglycemia and blood-toxins, of weak heart, of arteriosclerosis, of the diabetic endarteritis in the small vessels, and of defective nervous influences have already been mentioned. The patient's neurotic temperament often adds alcoholism to his other drawbacks. Suppurating and septic processes and hemorrhages are more common among diabetics than among others. The different physiologic phases of the healing process, both in the soft and in the bony tissues, take place with less energy than usual. The surgeon, ready for a needed operation, has often replaced his knife on discovering sugar in his patient's urine, fearing to operate in a case of diabetes, and knowing that he would incur less responsibility by abstaining from than by engaging in an unsuccessful operation. Many a surgeon has thus been saved, and many a diabetic patient who might have

been saved by surgery has been sacrificed. In the sixties, however, antisepsis and asepsis, and the works of Griesinger, Marchal de Calvi, and others on the surgical complications of diabetes began to remove timidity of operating under such conditions. We owe a good deal to the French in this connection, though surgical nihilism in diabetes has had its advocates also in France (Landouzy, Palle, and others). The superstition against operating in cases of diabetes no longer prevails, and statistics prove that even such delicate operations as those on the eyes have almost as favorable an outlook in the presence of diabetes as in its absence.

Operations on diabetic patients should, if the circumstances permit, be preceded by a course of preparatory treatment. In the mild stage the hyperglycemia should be removed for a couple of weeks previous to the operation, and the carbohydrates be withdrawn from the food until glycosuria disappears, if no urgent reason, as set forth on a preceding page, to the contrary exists. In the severe stage the acidosis is to be feared more than an increase in the constant and inevitable hyperglycemia, and consequently a fair supply of carbohydrates may be allowed. Alcoholic and other bad habits are to be strenuously, but wisely, corrected during this time. The general state is improved by all reconstructive remedies, by iron and arsenic when anemia is present, by nutritious, easily digested food, by general massage, etc., in all cases.

Asepsis is to be preferred to *antisepsis* in operating in cases of diabetes as soon as the preparation of the skin is ended, on account of the irritating influence on the diabetic's sensitive tissues by antiseptics and of the patient's greater susceptibility to the action of poisons.

Another rule among surgeons, in case of diabetes, is to prefer the *thermocautery* to the knife, as soon as there is a choice between the two, the better to avoid hemorrhage (and infection).

Diabetic gangrene, which occurs in about ten per cent. of all cases of diabetes (Griesinger), necessitates operations more often than any other complication, especially upon the lower limbs. In many cases diabetic and senile changes combine to make the general state poor. In other cases, however, diabetic gangrene may exist despite an amazingly good general state of health. It is often possible to bring about healing by the usual local (and general) treat-

ment and to save the limb.* Surgeons recommend *dry* bandages in such cases. If operation becomes necessary for diabetic gangrene in the lower part of the limb, it is usually performed above the knee. Operation at the knee-joint is rarely performed, surgeons demanding a better state of health and better coverings than are generally possessed by diabetics. Godbe recommends operation above the knees in all cases with arteriosclerosis.† In diabetic patients with gangrene in the lower part of the leg thrombosis is quite common at the point of division of the popliteal artery, and operation above the knee is then necessary.

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* Constantin Panel has recently reported a case of diabetic gangrene in the lower part of the leg in which a cure was effected by means of a permanent bath of oxygen, removing the india-rubber apparatus twice a day in order to wash the gangrenous part with a warm solution of chloral (4 : 1000), by giving arsenic and lithium benzoate, and by enforcing strict diet.

† As illustrated in one of my cases, the operation below the knee may sometimes yield good results even in the presence of distinct arteriosclerosis.

ERRATA.

On page 56, seventh line from bottom of page, "other plausible explanations" should read "other plausible explanations than the mere deficiency of oxidation."

On page 153, fourth line from bottom of page, "18 grams of nitrogen" should read "38 grams of nitrogen."

On page 227, after the paragraph on acidosis, the following most important sentence has been omitted: "The alkalescency of the blood may sink to $\frac{1}{10}$ of its normal value, but is never entirely annihilated."

TABLE OF THE COMMONEST KINDS OF FOOD, SHOWING CONSTITUENT PERCENTAGES OF PROTEID, FAT, AND CARBOHYDRATE.*

SIMPLE ANIMAL FOODS.	PROTEID.	FAT.	CARBO-HYDRATE.
Meat, raw (of mammals),	15–22	1.5–34	—
Meat, cooked (roast, boiled, etc.),	34	4.5–12	—
Meat, beef (smoked),	27	15.5	—
Bacon, raw,	10	50	—
Lard,	0.3	99	—
Meat-powder (dried),	75	—	—
Chicken, raw,	20	4	—
Pigeon, raw,	22	1	—
Duck (wild), raw,	22.5	3	—
Fish, fat (salmon, eel), raw,	15–20	7.5–28	—
Fish, lean (cod, pike), raw,	15–20	1	—
Stock fish, dried (cod),	80	1	—
Oysters,	5	0.3	2.6
Eggs,	13	11	—
Eggs, white of,	12	0.5	
Eggs, yolks of,	16	32	
Caviar,	32	14	
Milk,	3.5	3.6	4.8
Milk, skimmed,	3.5	0.6	4.8
Cream,	3.5	20	3.5
Whey,	0.3	0.2	5
Butter,	0.8	83	—
Cheese, rich,	27	30	2.5
Cheese,	35	4	2
Liver,†	x	5–30	—
MIXED ANIMAL AND VEGETABLE FOODS.			
Omelet of eggs, cream, and ham,	15.5	19	1
Omelet of eggs, cream, and flour (pancakes),	12	10	25
Waffles‡ of cream, flour, and water (Swedish style),	10	12	25
Sausages, in general,	17–27	26–40	0.–5
Blood-sausage,	12	11.5	25
Liver-sausage,	16	26.5	6.5
Fish-pudding,	10	12	11

*The figures are chiefly taken from König's well-known work, in part from the publications of Munk and Ewald, Jürgensen, and others. The table has been prepared with a view to conciseness, but it will enable the physician to form an idea as to the caloric value of almost any kind of food.

† Liver, as prepared for the table, contains only a small percentage of glycogen.

‡ Waffles, Swedish style, when made exclusively of cream, flour, and water, usually contain about twenty-five per cent. of carbohydrate; but they are extremely voluminous and light and form a good substratum for butter with a comparatively very small supply of carbohydrate. Except when a rigid diet is to be observed, they can sometimes be used by diabetics instead of bread.

SIMPLE VEGETABLES AND FRUITS (UNCOOKED).	PROTEID.	FAT.	CARBO-HYDRATE.
Jerusalem artichokes (topinambour),	2	0.1	15.2*
Lettuce,	1.4	0.3	2.2
Cucumbers,	1	0.1	2.3
Asparagus,	1.8	0.2	2.6
Spinach,†	3	0.5	3.5
Radishes,	1.2	0.1	3.8
Celery (leaves),	4.6	0.8	10
Onions,	2.7	0.3	6.5
Mushrooms (agaricus),	3.6	0.3	6.8
Cabbage (white),	1.9	0.2	4.9
Cauliflower,	2.5	0.3	4.5
Cabbage (green),	4	0.9	11.6
Cabbage (Brussels sprouts),	4.8	0.5	6.2
Cabbage (red),	1.8	0.2	5.9
Parsley,	3.7	0.7	7.4
Tomatoes,	1.2	0.3	4.1
String-beans,‡	2.7	0.1	6.6
Peanuts (Arachis hypogæa),	28.2	46.4	8
Almonds,	24.2	53.7	7.2
Walnuts,	16.4	69.2	7.9
Hazelnuts,	15.6	66.5	9
Cranberries,	0.1	—	1.5
Raspberries,	0.4	—	5.3
Currants (red and white),	0.5	—	6.3
Blueberries,	0.8	—	5.9
Strawberries,	0.9	—	3–4.4
Gooseberries,	0.5	—	8.4
Plums,	0.4	—	8.2
Cherries,	0.7	—	12
Apples,	0.4	—	12
Pears,	0.4	—	11.8
Oranges (juice),	0.4	—	5.54
Peaches,	0.65	—	11.5
Bananas,	1.9	0.6	23
Grapes,	0.6	—	16.3
Carrots,	1	0.2	9.4
Turnips,	2.1	0.1	11.7
Potatoes,	1.8	0.2	20.6
Sweet potatoes,	1.3	0.3	23
Beans (seeds, dried),	24.3	1.6	49
Peas (seeds, dried),	22.8	1.8	52.4
Apples, dried,	1.3	0.8	59.8
Pears, dried,	2	0.3	58.8
Prunes,	2.2	0.5	62.3
Raisins,	2.4	0.6	62
Figs,	5	—	45.3

* The carbohydrate in the Jerusalem artichokes consists of inulin, levulose, and gum. They are thus especially suitable for the diabetic's table. In many fruits the carbohydrate consists partly of levulose in addition to starch and glucose.

† The figures refer to the green leaves of Spinacia oleracea—not to spinach prepared with flour.

‡ The figures refer to string-beans with full-grown seeds. Before the seeds are developed string-beans contain much inosite, but only an insignificant amount of true carbohydrate, and they are an important item in the diabetic's bill of fare.

SIMPLE VEGETABLES AND FRUITS (UNCOOKED). (*Continued.*)	PROTEID.	FAT.	CARBO-HYDRATE.
Chestnuts,	5.5	1.4	38.3
Coffee (burnt),	12.2	12	13.4
Tea (dried leaves),	21	3.6	17.6
Chocolate, unsweetened,	5	15.2	74.8
Chocolate, sweet,	12.3	52.3	28.3
CEREALS, BREADS, ETC.			
Rice, dried,	9	0.8	88
Sago, dried,	0.8	—	86.1
Indian corn (maize),	11.67	5.5	77.8
Macaroni, dried,	9	0.3	76.7
Flour of the Soya-bean,	3.4	16.4	29.6
Rye-flour,	12.8	2.3	81.3
Wheat-flour,	10.5	1.3	87.1
Oatmeal, dry (coarse),	15	6	64.73
Rye-bread,	6.1	0.4	49.2
Wheat-bread,	6.1	0.4	51
Graham bread,	6	0.3	39–41
English biscuits,	7.2	9.3	75.1

LIQUORS.	ALCOHOL. PERCENTAGE. Vol.	ALCOHOL. PERCENTAGE. Weight.	SUGAR AND EXTRACT.
Cognac, French brandy,	55	47.3	0.6
Whisky, American,	60	52.2	—
" Scotch,	50.3	42.8	—
" Irish,	49.9	42.3	—
Cider,	—	4.2	8
Beers and ales,	—	2.5–4.9	4–7.2
Porters,	—	5.3	8.9
Rhine wines, white,	—	11.4	2.6
Rhine wines, red,	—	10	3.4
Beaune (Burgundy),	9	—	2.7
St. Emilion (Bordeaux),	8.7	—	3
Swiss wine, white,	9.6	—	1.9
Swiss wine, red,	9.4	—	1.6
Austrian wine, red,	9.5	—	2.7
Sherry,	—	17	5
Madeira,	—	15.6	8.6
Marsala,	—	16.4	8
Port wine,	—	16.4	10.2
Malaga,	—	11.5	30.3
Champagne,	—	9	24.8
Curacao,	55	—	57
Arrac-punch (Swedish),	26.3	—	69.8

PERSONAL REGISTER.

A.

Abeles, 26, 38, 65, 177, 178, 186, 252
Abelmann, 105, 167
Achard, 60, 243
v. Ackeren, 129, 135, 209
Acri, 117
Aladoff, 34
Albertoni, 116, 117,133, 223
Albic, 220
Aldehoff, 165, 279
Althaus, 90, 94
Amann, 219
Ambrosiani, 10
Andral, 49, 55, 159
Anger, 98
Anselme, 138
Anstoots, 63
Araki, 13, 51, 56, 57, 58, 68
Argutinsky, 186
Armanni, 110, 113, 116
Arnschink, 171
Arthaud, 33, 48, 49
Arthur, 49
Arthus, 180
Asher, 32
Auché, 94, 97
Auerbach, 94
Ausset de Cerenville, 288

B.

Baisch, 26
Barlow, 36, 62
Barral, 181, 188, 191, 192, 284
Basham, 286
Battistini, 288
Baum, 37
Baumann, 217
Beale, 63
Becker (O.), 119, 120
Begbie, 41
Bence Jones, 11, 13, 26, 159
Benda, 110
Benzi, 286
Bequerel, 35, 36
Beranger-Férand, 15
Berger, 119
Bernard, Claude, 11, 13, 24, 29, 31, 33, 49, 54, 57, 66, 67, 105, 169, 173, 176, 183, 191, 203, 216, 229
Bernstein, 279
Berthier, 87
Bettman, 36, 102
Bial, 170, 180, 182
Bidder, 11
Biedl, 243
Biefel, 56
Bischoff, 11, 171
Bischofswerder, 216
Blair, 18
Blake, 54
Blau, 82
Bleibtreu, 235
Bleile, 170, 181
Blocq, 36
Blot, 65
Blumenthal, 289
Boccardi, 97, 108, 113, 116, 117, 177
Bock, 53, 58, 181, 187
Boecker, 229
Boedeker, 217
Böhm, 34, 38, 68, 176, 181
Bollinger, 50
Bond, 35
Bonome, 113
Borchert, 229, 232
Bordier, 62, 63
Bose, 17
Bouchard, 12, 14, 53, 55, 74, 76, 91, 119, 120, 135, 228, 284
Bouchardat, 12, 13, 203, 216, 267, 281, 286
Bouchut, 62
Bouveret, 121
Brault, 137, 177
Bremer, 101, 244
Breul, 26
Brieger, 133
Brietzke, 186
Bright, 105
Brockhaus, 203, 289
Brogniart, 216

Brouardel, 37, 193, 289
Brown-Séquard, 191
Brücke, 11, 26
Brunelle, 53, 54
Brunner, 135
Buchheim, 171
Budde, 115, 216
Budge, 34, 200
Bull, William T., 105, 135
Bunge, 170, 185, 217
Burdel, 64
Burger, 231
Burghardt, 68
Burns, 94
Bury, 90, 94
Bussenius, 203
Butte, 33, 34, 48, 49, 182, 183, 192
Buzzard, 90, 94

C.

Calmette, 18, 64
Camplin, 274
Cantani, 12, 14, 41, 77, 267
Cantlie, 18
Caparelli, 165
Carnot, 289
Caroe, 16
Carrion, 138
Cartier, 53, 54
Casal, 57
de Cassaët, 286
Cavazzani, A., 35, 183
Cavazzani, E., 35, 183
Celsus, 10
Charcot, 24, 63, 90, 94, 97, 216, 257
Charrin, 129
Chauffard, 137
Chauveau, 12, 32, 33, 49, 165, 166, 181, 185, 186, 189, 194–198, 229
Chittenden, 54, 182
Chvostek, 36
Coignard, 52, 216
Colasanti, 218
Colenbrander, 192
Colrat, 49
Comby, 288
Coolen, 60, 61
Coranda, 133
Cornevin, 62
Couturier, 49
Cowley, 135
Cramer, 66
Cremer, 60, 174, 175, 185
Crichton-Browne, 87
Cruikshank, 10
Cunningham, 36
Curée, 54
Cyon, 34
Czapek, 208

D.

Dalton, 180
D'Arsonval, 292
Dastre, 49, 56, 179, 192
Davis, N. S., 81
Davy, 101
Decker, 63
De Dominicis, 165
Deichmüller, 133
De Jong, 35, 200
Delamare, 60
Demant, 57, 176
Demme, 35
Derignac, 219
Deutschmann, 119, 120
Devie, 113, 219
Dickinson, 96
Dieulafoy, 128
Dittrich, 108
Dobson, 10, 77, 284
Doch, 57, 174
Donkin, 277
Dreyfus-Brisac, 286
Dufour, 183
Dufresne, 58
Dujardin-Beaumetz, 127
Dumontpellier, 36
Duponc, 34
Duponchet, 64
v. Dusch, 76, 131

E.

Ebstein, 12, 14, 37, 86, 116, 117, 175, 216
Eckhard, 32, 33, 55, 57, 58
Edel, 187
Edwards, Mlle. Blaine, 35
Ehrlich, 117, 177, 178
Eichhorst, 63, 66, 94, 97, 98
Eliotson, 105
v. Engel, 215
Engelmann, 231
Erlenmeyer, 91
Ernst, 115
Eulenburg, 35, 55, 288
Ewald, 51, 58, 178, 181, 187, 295
Exner, 49

F.

Fahlberg, 279
Falkenberg, 38
Feilchenfeld, 54

Féré, 36, 133
Ferraro, 97, 100, 108, 113, 116
Fichtner, 116
Fick, 186
Finkelstein, 229, 232
Finkler, 37, 135, 203, 289
Finlayson, 86
Finn, 174
Fischer, 37, 62
Fitz, 110
Fleiner, 134
Fleischer, 57
Fles, 105
Fleury, 98
Flint, 186
Fodor, 129
Foerster, 119
Forsell, 268
Foster, 203
Fræntzel, 175
Frank, Peter, 64, 78
Franque, 158
Frazer, 34
Frerichs, 11, 12, 34, 35, 36, 52, 54, 55, 56, 62, 63, 69, 93, 96, 98, 105, 108, 117, 131, 132, 172, 176, 177, 188
Freund, 58, 190
Fürbringer, 77, 103, 218, 229
Futterer, 96

G.

Gabritschewski, 178
Gaglio, 57, 165
Gallard, 137
Gans, 37, 104, 180
Gara, 63
Garofalo, 57
Garrod, 76
Gascuel, 83
Gäthgens, 229, 231
Gaudard, 118
Gelmo, 62
Geppert, 52
Gerhardt, 11, 133
Gerhardt, D., 102, 212, 227
Geyer, 237
Gianturco, 113
Gib, Paul, 37
v. Gieson, 117
Gilbert, 289
Gilles de la Tourette, 257
Girard, 182
Giron, 81
Glénard, 111
Gley, 60, 62, 165, 229, 288
Gmelin, 10, 54
Godlee, 294
Goerlitz, 120
Golowin, 49
Golz, 52
Goodhart, 96
Goolden, 36, 63, 158
Gorup-Besanez, 208
Græfe, 119
Graf, 54
Graham, 17, 61
Gräser, 62
Griesinger, 12, 25, 36, 102, 293
Grohe, 178
Grube, 19, 76, 114, 282
Gruber, 207
Gubler, 63
Guckelberg, 215, 230
Guéneau, 63
Gueudeville, 10
Guiard, 115
Guignard, 129
Guinon, 93, 94
Gull, 107
Gumpertz, 88
Gürtler, 57

H.

Habershon, 69
Hale White, 207
Haller, 135
Hallervorden, 133
Hammarsten, 170, 215
Hammerschlag, 101
Hanot, 113, 137, 138
Hansemann, 110
Harden, 127
Harley, 49, 55
Hartge, 116
Hartsen, 105, 106
Hartz, 216
Hasse, 56
Haughton, 229
Haycraft, 207
Hedon, 32, 120, 165, 166, 193
Heidenhain, 81
Heine, 159
Heinemann, 109
Heintz, 63
Heller, 170
Henrat, 98
Henriot, 235
Hensay, 97
Hensen, 181
Hergenhahn, 49, 173, 174, 176
Hernandez, Gonsalez, 137
Heyneman, Newton, 185

Heyse, 207
Higgins, 32, 74
Hirsch, 288
Hirschberg, 119, 122, 226
Hirschfeld, 105, 170, 213
Hodgkin, 81
Hoesslin, 14
v. Hoesslin, 94
Hoffmann, 55, 220, 252
Hoffmann, G. A., 12, 34, 38, 53, 58, 176, 181, 187, 214
Hofmeier, 288
Hofmeister, 24, 30, 65, 67, 171, 200, 203
Holmgren (E.) 219, 237
Holsti, 65
Honigmann, 104
Hoppe, 173
Hoppe-Seyler, 52, 177, 190
Horner, 121
Huber, 50
Hubner, 180
Hübner, 15
Huchard, 35
Hugonenq, 52, 219
Hundhausen, 275
Hunt, W., 81
Huppert, 14, 63, 177
Husband, 29, 66

I.

Ingerslev, 159
Irisawa, 56
Isenflamm, 159
Israel, 100

J.

Jaccoud, 14
Jacobson, 119
Jacobson, Otto, 64
Jacoby (New York), 86
Jacoby (Strassburg), 58, 69
v. Jaksch, 53, 57, 101, 133, 215, 217, 226
James, A., 101, 131
Jasper, 285
Joffroy, 97
Johannowski, 65
Johnson (St.), 217

K.

Kahler, 30, 31, 35, 56
Kaiser, 210
Kalm, 219
Kalmus, 97
Kaltenbach, 65
Kaposi, 81, 127
Kassel, 215
Kassowitz, 129
Kaufmann, 12, 32, 33, 49, 165, 166, 167, 181, 185, 189, 194–198, 229
Kausch, 69, 165, 174, 175, 179
Kemmerich, 214
Kessler, 53
Kinnicutt, 158
Kirchner, 124
Kirmisson, 83
Kirsten, 65
Kisch, 66
Klebs, 34
Klemperer, 58, 60, 67, 69, 115, 207
Knies, 119, 120
Köbner, 170
König, 121, 295
Koninck, 59
Körner, 124
Kossel, 279
Kowalewski, 54
Kratschmer, 24, 177, 229
Kraus, 36, 192, 243
Kraus, I., 79
Kravkow, 215
Kuhn, 124
Kühne, 26, 31, 177
Külz, E., 17, 30, 33, 34, 38, 52, 53, 132, 133, 157, 159, 170, 175, 176, 181 203, 205–209, 213, 224, 229, 230
Kumagawa, 185
Kunkler, 36
Kuntzel, 53
Kupper, 172
Kussmaul, 54, 131, 133

L.

Laache, 36
Laborde, 158
Lallier, 35, 36
Lamanski, 34
Lambert, 54, 182
Lancereaux, 36, 108, 135, 288
Landouzy, 293
Landwehr, 219
Lang, 66, 179
Langendorff, 57, 165
Lapique, 138
Laseque, 107
Laub, 53
Laulanié, 235
Laves, 176, 235
Lavoisier, 11

Leber, 119, 122, 123
Leblanc, 15
Lecanu, 102, 212
Leconte, 54
Lecorché, 14, 94, 98, 100, 286
Le Goff, 287
Legroux, 39
Lehmann, 11, 67, 181, 214, 217
Leichtentritt, 97
Lemaire, 65, 219
Le Nobel, 105, 134, 135, 209
Leo, 209, 220, 235
Lépine, 12, 33, 58, 69, 95, 165, 181, 190, 191, 193, 220, 284, 288
Leroux, 157, 159
Letulle, 137, 203
Leube, 178, 219, 229
Leudet, 35
Leval-Piquechef, 94
Levene, 61
Lewaschew, 284
Lewin, 54
Levin, 171
Leyden, 90, 94, 97
Lichtheim, 134, 221
Liebig, 11, 174
Lindemann, 175
Lionville, 57
Livierato, 232
Loewy, 245, 288
Lohnstein, 247
Loye, 192
Lubinoff, 98
Luchsinger, 58, 172, 174
Ludwig, 36, 187
Lühdorf, 275
Lusk, 60, 61, 170, 171, 181, 224
Lussanna, 182
Lustig, 34

M.

McDonnel, 38, 173, 182
McGregor, 10
Magendie, 11
Magnus-Levy, 51, 115, 235
Maitland, 10
Manchot, 51
Mannkopf, 35, 67
Maquenne, 207
Marcet, 14
Marcus, 66
Marcuse, 165
Marechal de Calvi, 81, 293
Marie, 94
Marinesco, 36
Marinian, 91
Marklen, 103
Marsh, 289
Marthen, 116
Martin-Damourette, 52
Martineau, 282
Masoin, 53
Matrai, 190
Mauthner, 122, 209
May, 175
Mayer, 52
Meissner, 182
v. Mering, 12, 51, 52, 53, 55, 59, 60, 61, 105, 135, 136, 164, 170, 174, 177, 181, 185, 187, 188, 203, 229
Mermod, 14
Metroz, 192
Meyer, Jacques, 35, 36, 100
Mialhe, 281
Michael, 35, 96
Minkowski, 12, 38, 52, 105, 106, 133, 135, 136, 164–168, 177, 193, 202, 207, 223, 229
Minnich, 134
Minor, 97
Miura, 185, 199, 200, 213, 224
Montuori, 182
Morat, 33, 34, 183
Moriggia, 66
Moritz, 26, 59, 60, 185, 200
Morrison, 69
Moscatelli, 217
Mosler, 229
Mosse, 182
Mosso, U., 14
Müller, Fr., 106, 115, 171
Munck, 34
Munk, 171, 184, 295
Münzer, 50, 53, 132, 133, 229
Musculus, 170

N.

Nasse, 101, 210, 231
Naunyn, 14, 29, 32, 35, 36, 37, 38, 50, 52, 66, 69, 71, 94, 102, 103, 107, 111, 115, 116, 118, 134, 174, 203, 216, 268
Nebelthau, 174, 175, 176
Neisser, 177
v. Nencki, 13, 174, 234
Nesbi, 116
Nettelbladt, 158
Neubauer, 220
Neumann, 28, 58, 98
Neumeister, 182
Neusser, 49, 102

Ney, 65
Nicolas, 10
Niedergesäss, 157
Niedieck, 33
Nommès, 191
Nonne, 91
v. Noorden, 12, 58, 185, 224
Nordenson, 121, 123, 149, 162
Nylander, 26

O.

Obici, 116
Ogden, 32, 74
Ollivier, 35, 56
van Oordt, 35
Oppenheim, 35, 93, 186
Oppler, 247
Orth, 135
Otto, 171, 172, 181, 187, 188

P.

Palle, 293
Palma, 207
Panas, 36
Panel, 294
Papanikolau, 119
Paracelsus, 10
Parkes, 186
Parmentier, 138
Parrot, 158
Paschutin, 177
Paton, Noël, 182
Pautz, 170, 232
Pavy, 12, 13, 19, 20, 32, 34, 36, 38, 52, 61, 69, 159, 174, 178–183, 186, 190, 215, 275
Peiper, 34
Penzoldt, 57
Percy, 98
Pettenkofer, 11, 214, 229, 232
Petters, 133
Peyrot, 81
Pflüger, 174, 186
Philipeaux, 63
Pichon, 58
Pick, 77
Pickhardt, 187
Pierre-Marie, 36, 137, 287
Pincus, 34
Pisenti, 116, 117
Pitres, 82
Poli, 62, 63
Pollak, 56, 66
Pollatschek, 52
Popper, 13
Praussnitz, 59, 60, 171, 177, 185
Prevost, 63
Price, 94, 97
Prout, 63, 75, 218, 267, 274
Purdy, 17, 19, 20

Q.

Quinquaud, 53, 189

R.

Rabuteau, 54
Rangé, 64
Raynor, 87
Reale, 38
Rebitzer, 68
v. Rechenberg, 232
v. Recklingshausen, 35
Redard, 63
Redon, 62, 157, 160
Reich, 229
Reichhardt, 219
Reignault, 11, 186, 234
Reiset, 11, 186, 234
Reynoso, 28, 53, 63
Richardière, 35, 37, 281
Richardson, 35, 56, 120
Riegel, 107, 108
Rienzi, 38
Riess, 216
Ringer, 36
Ritter, 55, 60, 182, 185
Roberts, 159, 247
Robin, 282, 286
Roger, 59, 62
Röhmann, 170, 208
Rolf, 52
Rollo, 10, 264
Roos, 26
Roque, 113, 219
Rosenbach, 53
Rosenbaum, 176
Rosenblath, 82, 101
Rosenfeld, 61, 226
Rosenheim, 171
Rosenstein, 57, 91, 94, 104, 108, 229
Ross, 26, 90, 94
Rossa, 66
Rovere, 84
Rubner, 11, 171, 172, 200, 232
Rumpf, 133, 218, 227
Rupstein, 230
Ryndsjun, 34

S.

Saikowski, 53, 57
Salkowski, 175, 214
Salomon, 172
Samoje, 63
Sampacchia, 113
Sandmeyer, 97, 105, 165, 174, 177
Sauer, 56, 57
Saundby, 17, 96, 110, 113
Savage, 87
Scharlau, 36
Schenk, 186, 188
Schermetjewski, 13
Schierbeck, 14
Schiff, 13, 31, 32, 33, 36, 38, 56, 57, 182
Schilder, 26
Schindelka, 15
Schindler, 77
Schirmer, 119
Schmidt-Rimpler, 119, 122
Schmidt, G., 11, 181
Schmitz, 20, 25, 49, 76, 115, 284
Schultze, 14
Schultzen, 13
Schütz, 35
Schwarz, 168
Schwiening, 180
Scolozoboff, 54
Sée, Germain, 60
Seegen, 11, 12, 29, 35, 38, 58, 71, 118, 171–178, 183, 186, 187, 188, 194, 200, 208, 275
Segalas, 10
Seitz, 105, 110
Semmola, 63
Senator, 39, 55, 67, 84, 115, 159, 217, 288
Senff, 56, 57
Senn, N., 105, 135
Settenbom, 82
Seyfert, 62
Sieber, 13, 234
Siebert, 36
Siebold, 55
Silver, 105
Simons, 10
Sinety, 65
Smith, 35, 93
Sobeiran, 10
Socin, 174, 175
Soldani, 35
Sotniskewski, 177
Souques, 93
Spiegelberg, 65
Spitzer, 192
Spitzka, 35
Stadelmann, 52, 110, 133, 220, 227
Startz, 216
Steinhaus, 113
Stern, 63, 157
Stokvis, 173
Strasser, 132, 133, 229
Strassmann, 213
Straub, Walther, 57
Straus, 35, 37, 53, 58, 116, 234
Straynowski, 118
v. Strümpell, 37, 90
Subbotin, 214
Susruta, 10, 127
Sydenham, 64

T.

Tangl, 49
Taylor, 96
Tcherinoff, 173, 174
Tebb, 170
Telz, 55
Tenbaum, 231
v. Terray, 63
Teschemacher, 58
Tessier, 25
Thiel, 60
Thierfelder, 229, 237
Thiermesse, 15
Thiroloix, 165, 166, 229, 288
Tholozan, 18
Thomas, 90
Thompson, 11
Tiedeman, 10
Tiegl, 180
Toepfer, 58, 140
Toll, 148
Tollens, 133
Topinard, 35
Toralbi, 88, 202
Trambusti, 116
Traube, 11, 220
Triboulet, 138
Troye, 221, 228
Truc, 120
Tscherinow, 49, 173

U.

Uhle, 229
Ulrich, 219

V

Vahl, 207
Vamossy, 57
Vas, 63
Vauquelin, 10

Velisch, 38, 165
Vergely, 94
Verron, 95
Vespa, 77
Vetlesen, 240
Viaud-Grand-Marais, 282
Vogel, 219, 220
Vogler, 36
Voisin, 57
Voit, 12, 170, 174, 210, 214, 229, 232
Voit, E., 214
Voit, Fr., 171, 174, 206, 207, 232, 243
Voit, Hans, 34
Vulpian, 63

W.

Wagner, 63
Walkow, 217
Walter, 52, 133
Watson, 159
Wedenski, 26, 209, 219
Weichselbaum, 35
Weil, 243
Weintraud, 12, 104, 165, 179, 211, 221, 234
Weir-Mitchell, 84, 119
Weiss, 174, 185
Werther, 177
West, 159
Whitehouse, 54
Wickham-Legg, 177
Wiersma, 177
Wiesinger, 119
v. Wildt, 124
Williams, 66
Williamson, 97, 101, 245
Willis, 10, 281
Winogradoff, 57, 217
Wislicenus, 186
v. Wittisch, 49
Wolf, 208
Wolfberg, 174
Wollaston, 10
Wood, Horatio, 91, 127
Worm-Müller, 26, 30, 46, 199, 200, 204
Worms, 14, 284
Woroschiloff, 173
Woroschilski, 54

Z.

Zander, 257, 290
Zenker, 103
Ziemssen, 90, 94
Zillesen, 56
Zimmer, 13, 54, 68, 69, 191, 203, 208
Zinn, 62
Zuntz, 57, 62, 184, 186

INDEX.

A.

Acetone, 61, 84, 133, 168, 214, 215, 221
Acetonuria, 168, 169
Achroodextrin, 170
Acid, acetic, 217
  butyric, 217
  carbonic, 56, 234
  dextronic, 52
  diacetic, 52, 53, 61, 133, 168, 214, 221, 228
  formic, 215
  glycosuric, 217
  glycuronic, 51, 52, 179, 218, 239
  hippuric, 217
  homogentisinic, 217
  hydrochloric, 52
  lactic, 51, 52, 55, 57, 168, 179, 218
  levulinic, 215
  mucous, 52
  orthro-nitro-phenyl-propionic, 52
  oxalic, 52, 218
  β-oxybutyric, 52, 61, 133, 168, 214, 221
  phloretic, 59
  propionic, 217
  prussic, 52
  salicylic, 52
  sugar, 52
  sulphuric, 52
    coupled (etherous, aromatic), 53, 59, 172, 219
    in sulphates, 53, 172, 219
Acidity of gastric juice, 104, 108
  of urine, 219, 227
Acidosis, 72, 168, 227, 263
Acids, fatty, 52, 217
Aciduria, 227
Acne, 127
Addison's disease, 68
Adiposity, 140
Age, 19, 158
Akromegaly, 36
Albuminuria, 51, 52, 59, 76, 114, 228, 248
Alcohol, 54, 203, 212, 232
Alcoholism, 137
Alkalies, 51–53, 259, 281
Alkapton, 217, 239
Altitude, 20
Amaurosis, 123
Amblyopia, 95, 123
Ammonia, 55, 61, 224, 227
Amyl nitrite, 51, 55
Analgesia, 91
Anatomy of blood, 101
  of brain, 95, 96
  of gastro-intestinal tube, 108
  of heart, 100
  of kidneys, 116
  of liver, 110
  of lungs, 103
  of muscles, 128
  of nerves, 97, 98
  of ovaries, 118
  of pancreas, 108
  of skin, 126
  of spinal marrow, 96, 97
  of spleen, 113
  of testicles, 118
  of uterus, 118
  of vessels, 101
Anesthesia, 91
Aneurysms, 35
Angina pectoris, 99
Anhidrosis, 79, 91, 126
Annulus Vieusseni, 34
Anorexia, 80, 107
Anthrax, 63
Aromatic substances, 172
Arsenic, 53, 203, 280
Arterial blood, sugar of, 182, 188
Arteriosclerosis, 99
Artery, ligation of femoral, 38
  of gastroepiploic, 49
  of splenic, 49
Asphyxia, 38, 55, 158
Assimilation, 200, 203, 241
Asteatosis, 79, 126

Asthenopia, 124
Atrophy, acute yellow, of the liver, 49
Autophagia, 81, 168
Azoturia, 228

B.

Balanitis, 118
Balanoposthitis, 118, 160
Basophilia, perinuclear, 102
Bile, 49
Blood, acids in, 133, 224
corpuscles, 101
glycogen in, 177
hemoglobin of, 138
specific gravity of, 101
sugar of, 187
tests of, 244
Bones, 128
Brain, 32, 35, 36, 86, 95
Bread, 274
Breath, 84
Bulimia, 79
Butter, 271
Butyric acid. See *Acid, Butyric.*

C.

Cachexia, 68
Calculi in gall-ducts, 37, 49, 79
in kidneys and urinary ducts, 115
in pancreas, 109
Calories, 232
Cane-sugar. See *Saccharose.*
Carbohydrate, 24, 57, 105, 170, 184, 232
Carbon dioxid. See *Acid, Carbonic.*
monoxid, 56
Carbuncle, 83
Casts, renal, 248
Cataract, 119–121, 160
Chalazion, 124
Chloral, 51, 55
Chloralamid, 51, 55
Chloroform, 55
Cholera, 63, 64
Chorea, 35
Circulation, 98
Cirrhosis of kidneys, 115
of liver, 50, 137
of pancreas, 109, 137
Classes, social, 22
Climate, 20
Cold, 20, 68
Coma, 85, 131–133, 161, 258
Constipation, 106, 258
Cramp, 89
Crises gastriques, 106
Croup, 63, 158
Crura cerebelli, 31, 32
cerebri, 32
Crystallose, 279
Curare, 57
Cysticercus racemosus, 35
Cystitis, 115

D.

Decubitus, 83
Deiter's nucleus, 31
Delphinin (=methyl delphinin), 57
Dextrin, 170, 219
Diabetes alternans, 44, 216
bronze-colored, 137, 138
constitutional, 136
decipiens, 78
fat, 136
gastro-intestinal, 137
gouty, 136
hepatogenic, 137
herpetic, 136
in animals, 15
infantilis, 157–164
insipidus, 28, 39, 67
mild, 10, 129, 202, 220
muscular, 137
neurogenic, 134
pancreatic, 134, 164–169
periodic, 44
renal, 137
severe, 10, 130, 202, 220
Diacetic acid. See *Acid, Diacetic.*
Diamins, 220
Diet, 203, 227, 261
Digestion, 104, 170
Digestive organs, 104–114
Dilatation of stomach, 104
Diphtheria, 62, 158
Diplopia, 95
Disaccharids, 170
Distribution of diabetes, 16–18
Diuretin, 58
Dysentery, 62

E.

Ears, 124
Eczema, 41, 91, 124, 127
Electrotherapy, 292
Emotions, 22, 37, 38, 159, 203
Encephalomalacia, 36
Endarteritis, 97, 101, 138
Energy. See *Vital Force.*
Enuresis, 158
Epilepsy, 36, 86
Episcleritis, 124
Erysipelas, 63, 84
Erythema, 127
nodosum, 63

Ether, 55
Etiology of diabetes mellitus, 16–25. (Race—mode of life—sex—age—climate—heredity—profession—excesses—emotions—sedentary life—diet—exposure—trauma—sunstroke—adiposity—gout.)
Excesses, 22, 23, 203
Exophthalmic goiter, 36, 86
Exposure, 24
Exudates, 203
Eyes, 118–124

F.

Fat, 60, 105, 170, 171, 184, 209, 212, 232
Fatigue, 68, 203
Feces, 58, 105, 135
Fermentation, 000
Ferments in blood, 180, 191
in liver, 179
in urine, 220
Fesselungsglycosurie, 38
Fever, 166, 203
Fibrin, 57
Food, 170, 189
Frequency of diabetes mellitus, 15–18
Furunculosis, 41, 83

G.

Galactose, 207, 240
Gall-stones, 37, 49, 79, 112
Ganglion, celiac, 34, 35
inferior cervical, 34
superior cervical, 34
thoracic, 34
Gangrene, 81, 91, 103, 293
Gastric juice, 108
Gingivitis, 85
Glands, gastric, 108
peptic, 108
salivary, 38
thyroid, 38
Glucose, 167, 170, 184, 206, 232, 239
Glycemia, 29, 188
Glycogen, 52, 97, 168, 170, 172, 173–180
Glycolysin, 191
Glycolysis, 191–193
Glycosuria, alimentary, 29, 48, 173, 199
cachectic, 68
cardiac, 28, 58
concomitant, 28
experimental, 31
fatigue, 68
fetal, 66
from cold, 68
Glycosuria, gouty, 67
hepatogenous, 48
in animals, 37
marasmic, 68
nervous, functional, 37–48
organic, 30–37
pancreatic, 165, 166
puerperal, 65
renal, 69
senile, 68
simple, 9, 42–48, 242
starvation, 67
toxic, 50–62. (From acids—metals and salts of alkalies, phosphorus, arsenic, mercury, lead, uranium—alcohol, ether, chloroform, chloral, chloralamid, amyl nitrite, ammonia—carbonic acid, carbon monoxid—curare, strychnin, delphinin, morphin, veratrin, ergotin, caffein—diuretics thyroidin, tuberculin, pancreatin, fecal extract—phloridzin and phloretin.)
Glycosurias, 26, 204
Glycosuric acid. See *Acid, Glycosuric.*
Glycuronic acid. See *Acid, Glycuronic.*
Gout, 25, 39, 67
Graves' disease. See *Exophthalmic Goiter.*
Gum, animal, 219, 240
Gummata, 63
Gums, 85

H.

Hair, 127
Heart, 98, 100
Hemianopsia, 95
Hemoglobin, 138
Hemorrhage, 94, 100, 124
Hemosiderosis, 101, 138
Heredity, 21, 159
Herpes, 91, 124, 127
History, 10–15
Homogentisinic acid. See *Acid, Homogentisinic.*
Hordeolum, 124
Hunger, 79
Hydrotherapy, 290
Hygiene, 255
Hyperesthesia, 90, 124, 125

Hyperglycemia, 29, 48, 49, 56, 57, 71, 165, 190
Hyperidrosis, 91
Hypermetropia, 121
Hypochondriasis, 87
Hypoglycemia, 29, 33, 49, 56, 61
Hysteria, 88

I.

Ichthyosis, 127
Icterus, 53
Impetigo, 127
Impotence, 117
Incontinence. See *Enuresis.*
Infection, 25
Infectious diseases, 62, 159
Influenza, 62, 64
Inosit, 207
Insomnia, 41, 256
Inulin, 207
Invertin, 170
Iridocyclitis, 123
Iritis, 123
Irritability, 41
Isomaltose, 219

K.

Keratitis, 123
Kidneys, 69, 114–117
Knee-jerk. See *Reflexes.*
Kreatin, 217
Kreatinin, 217, 239

L.

Lactaciduria, 53, 57
Lactose, 62, 66, 167, 171, 206, 208, 232, 239
Lactosuria, 65, 199
Laios, 208
Lassitude, 128
Lead, 53
Leucin, 219
Leukemia, 68
Leukocytes, 177, 178
Leukocytosis, 101
Levulose, 167, 171, 206, 208, 239, 279
Levulosuria, 167, 199
Lichen, 127
Life-insurance, 243
Lipaciduria, 218
Lipemia, 102, 212
Lipuria, 212, 218
Liver, 48, 50, 57, 59, 110, 137, 173, 214
Lobus diabeticus, 31, 32
hydruricus, 31, 32
opticus, 32
Lungs, 103
Luxuries, 23
Lymphangitis, 84
Lyssa, 63

M.

Malaria, 62, 64, 137
Mal perforant, 83, 91
Maltose, 167, 170, 209, 219, 239
Maltosuria, 135, 199, 209
Mannite, 207
Marasmus, 68, 102, 161, 204
Marriage, 254
Massage, 203, 290
Mastication, 104
Masturbation, 158
Measles, 62
Mechanotherapy, 289
Melancholia, 87
Meningitis, 35
Meningomyelitis, 36
Mental treatment, 255
Mercury, 53
Metabolism, 168
Metallic salts, 53
Migraine, 89
Milk, 276
Milk-sugar. See *Lactose.*
Monosaccharids, 170
Morbus gravesi. See *Exophthalmic Goiter.*
Morphin, 57, 61
Mouth, 79, 84
Mucin, 214, 215
Muscles, 128, 203
Mydriasis, 121
Myelitis, 36
Myocardium, 99
Myopia, 121

N.

Nails, 91, 128
Nephritis, 60
Nephrolithiasis, 115
Nerve, abducent, 95
crural, 91
depressor of the pneumogastric, 33
dorsal, 34
facial, 95
oculomotor, 95
optic, 122
pneumogastric, 31, 33
sciatic, 33
splanchnic, 34
supraorbital, 89
sympathetic, 34, 98, 183
tibial, 97
Nervous symptoms, 86–95
Neuralgia, 37, 88, 158

Neurasthenia, 39, 70, 88, 106
Neuritis, 90, 97, 102
Neuroses, 36, 37, 87, 106
Neurotabes, 94
Nitrobenzol, 51
Nitrogen, 166, 170, 233
Nitrotoluol, 51
Nuclein, 214, 215
Nutritive needs, 168, 232, 260

O.

Obesity, 25, 39, 66
Oidium albicans, 160
Operations, 292
Ophthalmic goiter, 86
Opium, 203, 280
Orchitis, 118
Organotherapy, 288
Osteomalacia, 231
Osteoporosis, 85, 129
Otalgia, 125
Otitis, 124, 125
Ovaries, 118
Oxalic acid. See *Acid, Oxalic.*
Oxaluria, 41, 45, 218
β-Oxybutyric acid. See *Acid, β-oxybutyric.*
Oxygen, 234

P.

Pancreas, 108, 164–169
Pancreatic juice, 105, 168
Pancreatin, 58
Paralysis, 91
  agitans, 35
  general, progressive, 35
Paraplasma, 57, 172
Paraplegia, 91
Paresthesia, 88
Paronychia, 128
Pedunculi cerebelli, 32
  cerebri, 32
Pemphigus, 127
Pentoses, 175, 215, 219, 240
Peptonuria, 53
Pericementitis, 85
Periostitis, 85
Perspiration, 231
Pertussis, 63, 158
Petechiæ, 127
Phenacetin, 203
Phimosis, 118, 160
Phlegmon, 84
Phloretin, 59
Phloridzin, 59, 166
Phloroglucin, 59
Phlorose, 59
Phosphaturia, 230
Phosphorus, 49
Phthisis (pulmonary tuberculosis), 102
Pigment, 138
Piqûre, Bernard's, 31
Pityriasis, 127
Pneumaturia, 115
Pneumonia, 63, 103, 161
Pollakiuria, 41, 78
Polydipsia, 76
Polyneuritis, 90
Polyuria, 31, 58, 76, 207
Potatoes, 276
Potency, sexual, 89
Pregnancy, 66, 118, 254
Presbyopia, 121
Professions, 21
Prognosis, 63, 138–141, 160
Prophylaxis, 253
Propionic acid. See *Acid, Propionic.*
Proteids, 57, 105, 170, 171, 184, 201, 212, 232
Pruritus, 126
Pseudo angina pectoris, 99
Pseudotabes, 93
Psoriasis, 127
Psychoneuroses, 21, 87
Ptomains, 220
Ptosis, 95
Pulse, 77, 98, 131
Pupil, Argyll Robertson, 92
Purpura, 127
Pylethrombosis, 49
Pyorrhea, alveolar, 85
Pyrocatechin, 5, 217

Q.

Quotient of respiration, 185, 235

R.

Race, 17
Raynaud's disease, 83, 91
Recovery, 65, 160
Reflexes, 92
Remedies, 280
Respiration, 131, 234
Respiratory organs, 102
Retinitis, 122
Rupia, 127

S.

Saccharids, 170, 174
Saccharin, 279
Saccharomyces apiculatus, 239

Saccharose, 167, 170, 206, 232
Saccharosuria, 46, 47, 199, 201
Salicylic acid. See *Acid, Salicylic.*
Saliva, 104, 202
Sanatoriums, 256
Scarlet fever, 62, 158
Sciatica, 36, 88
Scleritis, 124
Sclerosis, multiple, 35
Secretions, 79, 104
Sedentariness, 23
Senility, 68
Sensibility, 91
Sex, 19, 159
Simulation, 252
Sleep, 32, 256
Spinal cord, 32, 36, 57, 91, 96, 97
Spleen, 113
Spondylitis, 37
Sputa, 203
Stages of diabetic dystrophy, 9, 10, 42–47, 129
Starch, 52, 170, 206, 232
Starvation, 24, 67, 159, 167, 183, 203
Sterility, 118
Stools, 105, 134
Strains, emotional and intellectual, 22
Strychnin, 51, 57
Sugar in blood, 10, 187
in liver, 11, 180
in urine, 9, 11, 73. See *Galactose, Glucose, Lactose, Levulose, Maltose, Saccharose.*
Sulphates, 172
Sulphonal, 56
Sulphuric acid. See *Acid, Sulphuric.*
Sunstroke, 25
Sweat, 202
Sweets, 24, 158
Symptoms of diabetes, 70–138
Syphilis, 35, 63, 287
Syzygium jambulanum, 62, 168, 284

T.

Tabes dorsalis, 35
Tears, 202
Teeth, 42, 85
Temperature, 85, 160
Test, Barfoed's (glucose), 239
Bernard-Seegen's (glucose), 238
Biebrich's (blood, color), 245
Bremer's (blood, color), 244
Ehrlich-Biondi's (blood, color), 245
Esbach's (albumin), 248
Fischer's (glucose), 237
Test, Gerhardt's (diacetic acid), 11, 71, 240, 247
Heller's (albumin), 248
Kjeldahl's (nitrogen), 248
Nylander's (glucose), 237, 239
Robert's (glucose), 247
Troemmer's (glucose), 237
Williamson's (blood, color), 245
Worm-Müller's (glucose), 237
Testicles, 118
Theories, 12–14, 179, 194–198
Thirst, 42, 76
Thyroidin, 58
Tongue, 84
Toxins, 71, 220, 221
Transmutation, 86
Trauma, 32, 140, 159
Tuberculin, 58
Tuberculosis, 68, 102, 137, 161
Tumors (new growths), 35
Typhoid, 62, 64
Tyrosin, 219

U.

Urea, 216
Uric acid, 216, 239
Urinary organs, 114–117
Urine, 73–76, 160
color, 75
density, 75
quantity, 77, 246
specific gravity, 75, 246
substances in. See under the different headings: *Acetone, Albumin, Alkapton, Ammonia, Butyric Acid, Casts (renal), Dextrin, Diacetic Acid, Diamins, Fatty Acids, Ferment, Glycogen, Glucose, Glycosuric Acid, Glycuronic Acid, Gum, Hippuric Acid, Homogentisinic Acid, Indoxyl, Inosite, Isomaltose, Lactic Acid, Lactose, Laios, Levulose, Leucin, Maltose, Oxalic Acid, β-Oxybutyric Acid, Pentoses, Ptomains, Pyrocatechin, Reducing Substances, Saccharose, Skatoxyl, Sulphuric Acid (in sulphates and coupled), Toxins, Urea, Uric Acid, Urobilin, Urochloralic Acid, Uroleucin.*
toxicity, 220
Urobilin, 219
Urochloralic acid, 239

Uroleucin, 219
Urticaria, 91
Uterus, 118

V.

Vaccinia, 63
Variola, 63
Vein, portal, 181, 189
Veins, hepatic, 181, 182, 188
in general, 181, 188
Ventricle, fourth, of the brain, 31, 95
(stomach), 104
Veratrin, 51, 58
Vermis, 32
Vessels, arterial, 181, 188
Virility, 41
Vital force, 184–187
Vulnerability, 81
Vulvitis, 118, 160

W.

Water, 231, 278
Weighing, 249
Weight of body, 80

X.

Xanthoma tuberosum diabeticum, 127

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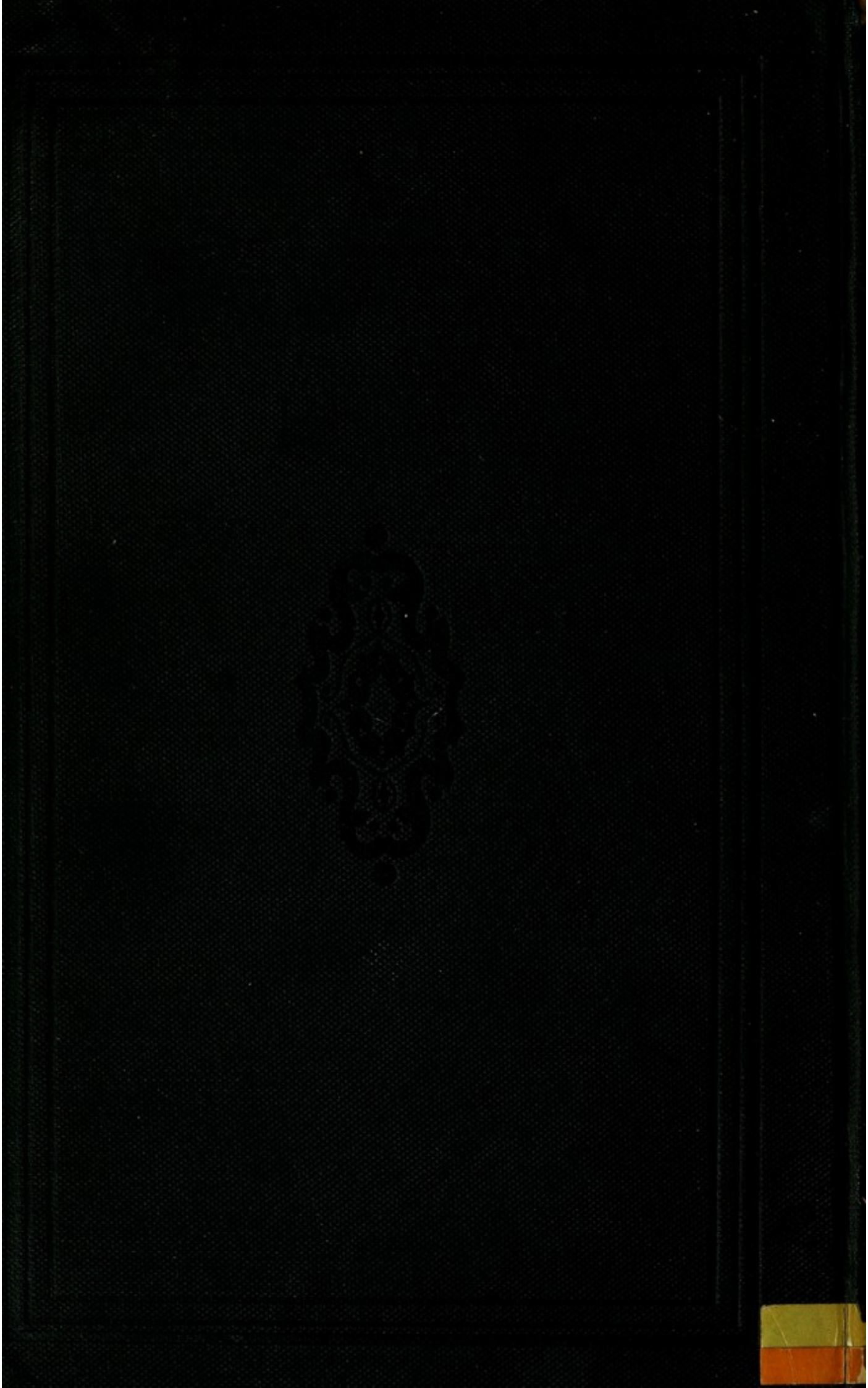
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