A clinical treatise on diabetes mellitus / by Marcel Labbé ; translated ... and edited by Charles Greene Cumston.

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EDITOR'S PREFACE

PROFESSOR LABBÉ'S labours of many years in the field of diabetes mellitus are too well known to require comment. The present volume represents the fruit of his vast experience in the symptomatology and treatment of this morbid process, as well as his views on the pathogenesis and pathology of this affection.

Four chapters have been added by the author and three by the editor to this English edition, while the text of the French edition has been thoroughly revised and annotated by the author and editor, thus bringing the present volume completely up to date.

The only excuse for the English edition is that the editor is firmly convinced that from the view-point of actual practice Professor Labbé's book is by far the best exposé of the subject that has as yet been published for the use of the consultant, general practitioner, and advanced student of medicine.

CHARLES GREENE CUMSTON.

GENEVA,
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A CLINICAL TREATISE ON DIABETES MELLITUS

CHAPTER I

THE PATHOLOGICAL PHYSIOLOGY AND SYMPTOMATOLOGY OF DIABETES MELLITUS*

The Definition of Diabetes Mellitus.—Diabetes was formerly regarded as a morbid entity, and an attempt was made to distinguish between diabetic and non-diabetic glycosuria, the first being permanent, abundant, and accompanied by other symptoms of the disease, the second being temporary, moderate, and offering no other morbid manifestations.

This conception can no longer be entertained. If the evolution of a case of diabetes be followed long enough, it will be found that the glycosuria will assume one or the other character according to the phase of the disease. Achard and Weill long since showed the existence of alimentary glycosuria in obese subjects with large appetites which they regarded as latent diabetes. When a diabetic subject recovered, or the symptoms subsided by diet, the glycosuria alone remaining, and at length in turn disappearing, the patient who at first was supposed to be a diabetic was then regarded as merely an obese subject with an alimentary glycosuria.

In reality, glycosuria is always the result of disturbed glycoregulator functions. When this disturbance is mild and temporary the glycosuria is slight and transitory. When, on the contrary, the disturbance is profound and durable, the glycosuria is abundant and permanent, and accompanied by other evidences of hyperglycemia. Hence, there is no difference in the nature, but only of degree, between the various glycosurias.

At present, diabetes is no longer considered a morbid entity, but as *a clinical syndrome governed by a disturbance of the glycoregulation*.

* Clinical lectures delivered at St. Antoine Hospital in 1908.

The Essays at Classification of Diabetes.—According to the way one has envisaged diabetes—clinically, pathologically, or ætiologically—different classifications have been attempted. The most simple clinical data have furnished the division of diabetes into fat and thin. Pathological researches, aided by experimental physiology, showing that in certain cases of diabetes there are lesions of the pancreas, nervous system, liver, or hypophysis, have resulted in the description of pancreatic, nervous, hepatic, and pituitary diabetes; and since certain infections and intoxications have been seen to result in diabetes, forms of the disease have been described based on their special *ætiology*, such as arthritic, syphilitic, and traumatic diabetes.

These groups of diabetes were not made in vain, because they are susceptible of causing the physician to make a logical prognosis and to institute rational treatment, ætiological or opotherapic. But they were premature, and, strictly speaking, do not constitute a classification, because the majority of cases of diabetes cannot be included under any of the aforesaid headings.

True pancreatic or nervous diabetes are rarities; arthritic diabetes is based upon a memorial of principle, because it is enough that a subject be obese and diabetic for physicians and the public as well to dub him with the title of arthritic. Syphilitic diabetes is exceptional, traumatic diabetes is infinitely rare, and the ætiology of the disease completely escapes us in the vast majority of cases.

The Physiopathology of Diabetes.—Leaving aside the pathology and ætiology as being powerless to cast any light on the subject, one is compelled to turn to the study of the physiopathology of diabetes, the only one capable of furnishing any basis of enlightenment for the prognosis, diagnosis, and treatment.

In order to understand the pathogenesis of diabetes, one must be thoroughly familiar with the metabolism of glucose in the body and the functions of the glycoregulator apparatus.

The memorable experiments of Claude Bernard clearly demonstrated that the liver is the principal organ of glycogenesis. It receives the glucose resulting from the digestion of starches and sugar in the food from the portal vein, retains

and accumulates glucose in the form of glycogen, and afterwards transforms into glucose, afterwards to enter the circulation as much as the needs of the body require.

Sugar accumulates in the muscular system, and represents an important reservoir of glycogen as well as a focus of combustion in which is produced the energy utilized in muscular contraction. Combustion of sugar undoubtedly takes place in other tissues as well.

In the normal state glucose does not accumulate in the blood. Thanks to a complex physiological apparatus into which the pancreas, nervous system, and certain vascular glands enter, such as the thyroid and suprarenals, the proportion of glucose in the blood remains constant, varying between 1 and 1·5 per 1,000.

In normal physiological conditions the glycogen of the liver is derived from the CH contained in the food. In certain abnormal conditions—with a diet completely deprived of CH, for example—the liver is susceptible of manufacturing glycogen from the albuminoids or fats contained in the food. Finally, during the act of fasting the hepatic and muscular glycogen becomes exhausted, and the blood will always contain the same amount of glucose resulting from the transformation of albumins and fats of the organism.

Hence there are three processes capable of furnishing the body with glucose—namely, transformation of the CH of the food, transformation of the albumins and fats of the food, and transformation of the albumins and fats of the tissues of the organism. The first of these is a normal process, the second is abnormal, while the third is still more abnormal. When the organism has its choice, it is probable that it only utilizes the first process, and it must be forced by abnormal circumstances to put into effect the second and, above all, the third process.

No matter what may be the details of this metabolism, which we only know incompletely, there exists *a glycemic equilibrium* in the animal organism. No matter what may be the amount of the CH intake or the rapidity with which CH enter the circulation, the liver and muscles retain them in the form of glycogen, and the tissues burn them up completely, so that neither hyperglycemia nor glycosuria develops.

In the pathologic state things are different. As soon as a disturbance arises in the glycoregulator apparatus, the result of a morbid change in one of the organs composing this system, the CH metabolism no longer takes place with regularity, glucose is not carbonized completely by the tissues, and consequently accumulates in the blood and tissues. *The syndrome of hyperglycemia and hyperglycistia* ensues, and diabetes develops.

From the physiopathological view-point, diabetes is characterized by *the absence of combustion of the totality or a portion of the CH introduced into the body with the food or furnished by the organism itself.*

This theory of insufficiency of CH combustion, maintained by Bouchard and the majority of modern writers, can alone explain diabetes. The theory of superproduction of sugar cannot explain it, because the normal organism appears capable of burning an almost indefinite quantity of CH. But a more penetrating physiological analysis must be made in order to exactly understand the functional disturbance characterizing diabetes.

The researches that I undertook with H. Labbé on the nutrition of diabetics led me to distinguish two great categories of diabetes:

1. *Diabetes without denutrition*, which is by far the most frequent. This corresponds to the fat diabetes of the older writers and the arthritic diabetes of the classic writers.

The nitrogenous equilibrium is preserved in these cases, therefore there is no denutrition. The physiological disturbance only involves metabolism of the CH introduced with food; the patient can tolerate a certain amount; the glycosuria originates from the CH in the food.

2. *Diabetes with denutrition* is less common, but the process is more serious. This form corresponds to the thin diabetes of the older writers and to pancreatic diabetes of the classic authors.

In this case the nitrogenous equilibrium is broken, the patient destroys his own tissues, and therefore emaciates. He cannot tolerate even the minutest quantity of CH, and even when these have been cut out of his diet the glycosuria nevertheless continues. It is always abundant and its origin com-

plex; it is derived both from the food and body tissues, and comes from the CH, albumins, and fats.

3. Between these two categories of diabetics, quite different by their physiopathology as well as by their prognosis and treatment, intermediary forms of the process exist whose study is most interesting and the interpretation delicate. These forms I shall not touch upon here, and will only discuss the two principal forms of the disease.

I. Diabetes without Denutrition.

The few case histories that follow are simply given to illustrate this form of diabetes.

Case I.—Female under my care for the past two years and a half; keeping her on a well-regulated régime with a regular weekly analysis of the urine.

When she first came under observation on September 19, 1905, she was 66 years of age, very fatigued and emaciated, and in a state that appeared to me at the time to be serious.

The diabetes had been present for about a year, during which time she suffered from intense thirst, micturated a good deal, lost the appetite, and became emaciated. The teeth fell out; there had been a series of dental abscesses and very painful neuralgia.

In the patient's antecedents only some bleeding from hæmorrhoids occurring after the menopause, an attack of influenza, and a series of respiratory accidents leading one to fear pulmonary tuberculosis, were all that were noted.

When she came under observation the syndrome of hyperglycemia was complete. There was ardent thirst, a polyuria of about 4,000 c.c. *pro die*, a glycosuria of from 250 to 300 grammes, pruritus vulvæ, great lassitude, emaciation (weight = 44 kilogrammes), stomatitis and gingivitis. The liver was hypertrophied; the patellar and Achilles reflexes absent; those of the elbow and wrist were decreased.

At first a mixed diet composed of bread, potatoes, meat, broth, and milk, which furnished 322 grammes of CH, was ordered, and 300 grammes of glucose was excreted in twenty-four hours. The régime was then progressively reduced to 237 grammes, then to 137, 117, 110, 97, and lastly 51 grammes of CH, and the polyuria and glycosuria diminished in direct proportion with the reduction of the CH in the food, so that on November 25, a little more than two months of treatment, the glycosuria had completely subsided, as well as the other symptoms of diabetes. The total twenty-four-hour urine was 1,250 c.c., the patient had increased 4 kilogrammes in weight, and felt stronger.

Given this result, Dr. Ameuille, who continued to follow the patient, progressively increased the CH intake, at first to 95 grammes, then

140, 184, and 225 grammes. Each time that the diet was increased a temporary mild glycosuria was observed, beginning three or four days after each increase, and then subsiding in a few days.

In May, 1906—that is to say, eight months since coming under observation—the patient was more vigorous, had fattened and ate as she pleased, only presenting a mild glycosuria from time to time.

I saw her again on June 10, 1906, and kept her under observation for a few days. I noted that she tolerated 150 grammes of CH without the occurrence of glycosuria, but this did appear after the ingestion of 160 grammes of CH.

Since this date the patient has been working, and has come to see me regularly once a week. The diet has contained 150 grammes of CH per day in the form of milk, potatoes, dried vegetables, bread, and macaroni. Only occasionally was there a temporary glycosuria of not more than 10 grammes.

Upon different occasions the patient has complained of fatigue, digestive disturbances with diarrhœa, congested hæmorrhoids with bleeding, pain in the small joints, and cramps in the legs. She lost 2 kilogrammes, then gained them, and even went beyond her former weight. It never seemed to me that her glycosuria was in any way related to these various morbid incidents.

Briefly, her health has been maintained during the entire year of 1907.

This case report is sufficient to show the close dependence existing between the glycosuria and the CH intake. The syndrome of hyperglycemia disappeared simply by judicious dieting without any medication; after this, upon the condition that the régime was maintained within the proper limits, the hyperglycemia did not recur, so that the diabetes, which at first seemed so serious, has in appearance been cured for the past two years.

This case is also a fine example of the cure of hyperglycemia by reduced diet. In order to cause the syndrome of hyperglycemia to completely disappear, the amount of CH ingested must be greatly reduced, and this for quite a long period. This favours the elimination of the glucose retained in the organism. During the cure of reduced diet the patient eliminated more sugar on certain days than the amount of CH she ingested.

At the end of the cure the patient tolerated 225 grammes of CH without the appearance of glycosuria, but at the beginning 160 grammes caused the glycosuria to reappear intermittently. Therefore the patient had a tolerance of

150 grammes for CH—that is to say, she could burn up 150 grammes of CH derived from the food in twenty-four hours.

The remarkable effect produced by reduction of the diet is the same in all cases of diabetes belonging to this category. It is so constant that when a patient does not respond to it one may be certain that the subject is not following the régime prescribed. The following case is another typical example:

Case II.—Male, with advanced pulmonary tuberculosis, was in a serious condition when admitted to hospital. Diabetes had been diagnosed two years before. Patient very emaciated and weak; intense thirst, polyuria (4,000 c.c.), and abundant glycosuria. Tendon reflexes decreased, vision decreased.

When he first was in hospital the patient was allowed an ordinary diet containing 309 grammes of CH, and on the same day he excreted 277 grammes of glucose. He was then put on a diet containing 60 grammes of CH derived from potatoes, and the glycosuria fell rapidly, with great oscillations, to 4 and 10 grammes *pro die*, in ten days' time.

In three weeks, in spite of a mistake in the diet which caused the glycosuria to increase temporarily, glucose completely disappeared from the urine at the same time that the symptoms of hyperglycemia subsided, and the patient regained strength and weight. The patient was kept under observation for eight months, and with a régime containing 70 grammes of CH the glycosuria did not recur. But if the CH intake was increased above 80 grammes, the glycosuria and all the symptoms of hyperglycemia returned.

The patient therefore had a fixed tolerance of 70 grammes of CH, in spite of the tuberculosis, which continued to progress.

The study of the balance of nutrition in this case showed that the nitrogenous equilibrium was maintained.

The first analysis at the beginning of treatment made by H. Labbé gave the following results:

Diet.—Meat, 300 grammes; potatoes, 300 grammes; 4 eggs; Gruyère cheese, 50 grammes; butter, 50 grammes; wine, 480 c.c.; which corresponds to—

CH	60 grammes.	
Albumin	96 ,,	(N = 15·40 grammes).
Fat	94 ,,	

Urine :

Total amount	1,500 c.c.	
Glucose	16·48 grammes.	
TN	13·54 ,,	
UN	11·31 ,,	
Urea	24·2 ,,	
Azoturic coefficient	0·83	
Phosphoric acid	1·87 ,,	
NaCl	5·1 ,,	

The nitrogenous equilibrium is maintained: 15·40 – 13·54 = 1·86 grammes.

There is an excess of the N ingested over the N excreted in the urine, this being due to the fact that part of the N is excreted in the fæces, and also at the time of the analysis the patient was gaining in weight and probably retained a ittle N.

It should also be remarked that the amount of urea was medium and quite in keeping with the amount of the albumin ingested, that the proportion of phosphoric acid was rather small, and that the azoturic coefficient was normal. Hence there was no azoturia or phosphaturia, which many writers have erroneously mentioned in diabetes, and which I have never observed when denutrition did not exist. This error is due to the fact that these observers analyzed the urinary excretions without taking the diet into consideration.

A second analysis covering full three days gave:

Albumin	118·5	grammes (N = 19 grammes).
CH	96·5	,,
Fats	143·0	,,
Urine :		
TN	18·21	,,
Glucose	4·0	,,
Fæces :		
TN	1·33	,,

Nitrogenous equilibrium maintained. For an intake of 19 grammes of N, the patient excreted 18·21 + 1·33 = 19·54 grammes of N. The slight difference of 0·54 does not exceed the limit of experimental error. For that matter, the patient's weight remained stationary during the three days the analysis was being carried out.

These two case histories give the necessary elements for the study of the pathological physiology of diabetes without denutrition, and show the mechanism by which the syndrome of hyperglycemia develops or subsides.

Clinical Description.

Ætiology.—Diabetes without denutrition usually occurs in adults, while in children and young subjects the disease generally belongs to the category of diabetes with denutrition.

The subject is usually obese from the start and develops diabetes later; I have never observed an inverse evolution. Suralimentation, the ordinary cause of obesity, is therefore the chief factor in the ætiology of diabetes.

In some instances infection or intoxication has been

incriminated, and I have met with some such instances, but they are exceptional. Generally there is no relation between the origin of diabetes and a former infection; and even when an infection is the immediate cause of diabetes, this usually occurs in an obese subject predisposed to this disease.

This is likewise true of intoxications. Alcoholism is very frequently found in the antecedents of diabetics, but it usually is combined with obesity, so that it is difficult to say which of the two factors is the most responsible for the diabetes.

It is usually admitted that diabetes is hereditary. Both Seegen's and Bouchard's statistics have revealed the curious fact that there are families in which diabetes is frequently met with, where fathers and sons suffer from the disease, or several brothers and sisters are affected by it. But obesity will be found with very great frequency in these families, and is mentioned in the hereditary or personal antecedents of diabetics.

These very interesting data establish a relation between diabetes, obesity, and gout, and show that these morbid states are found in the same families, but they do not prove that diabetes is hereditary. Familial affections must not be confounded with hereditary diseases. To show that diabetes is hereditary the child must be removed from the family midst and reared in the same conditions as other children. One could then ascertain whether, brought up in these circumstances, the child of a diabetic offers a greater propensity to become diabetic. In fact, when children are reared in a family they are subjected from the very beginning to the same defective hygienic conditions as their parents, and if they are afflicted by the same diseases it is perhaps not from heredity, but because they are exposed to the same morbid causes, and, in particular, to defective diet and hygiene.

This probably explains the frequency of diabetes among the Jews; the reason is the familial habit of suralimentation and sedentary life, rather than a morbid hereditary constitution.

Conjugal diabetes has a like explanation. Living the same life, partaking of the same food, both husband and wife run the risk of being intoxicated by the same ingredients.

I would propose the same explanation for the relationship of diabetes and arthritism. The majority of French writers

classify diabetes of obese subjects with arthritic affections—gout, obesity, biliary and renal lithiasis, migraine, chronic rheumatism, etc.—and regard them all as manifestations of the same morbid temperament transmissible from father to son; in other words, the slow nutrition of Bouchard or bradytrophic diathesis of Landouzy.

Although accepting the reality of these morbid relations, I am inclined to explain them in another way. The so-called arthritic affections appear to me to be rather the consequence of a defective diet than hereditary transmission. *A person is not born arthritic, but becomes so*, as Maurel has very pertinently remarked. It is prolonged suralimentation, with its different modalities and multiple consequences, which causes obesity, diabetes, and gout. Hence familial arthritism is nothing else than the result of familial suralimentation, and to say that diabetes has an arthritic origin simply means that it is due to overfeeding.

This conception is progressive, since it substitutes the idea of a badly characterized morbid temperament by the notion of a pathological process easy to understand and detect.

These reserves are made in respect to the hereditary theory of diabetes that is generally accepted too readily. I would not, however, be too categorical and deny the predisposition of certain families to diabetes. This is more manifest in the case of diabetes with denutrition. For example, one meets with instances of two brothers successively developing diabetes, or a father who engenders a son who becomes diabetic in early life. These facts are all the more valuable because diabetes with denutrition is more infrequent than that without denutrition, and, unlike the latter, cannot be explained by suralimentation.

The Evolution of Glycosuria.—Diabetes without denutrition does not generally give rise to marked glycosuria. But the amount of glucose varies very greatly. In some cases it may be absent, in others it attains several hundred grammes, and in the same case varies according to phases of the disease. Thus in Case I. it reached 300 grammes at the onset of the affection, and two months later it was completely absent.

It is not the degree of glycosuria that indicates the intensity of the diabetes. There are cases of serious diabetes with

moderate glycosuria and benign diabetes with abundant glycosuria. In Case I. there was a glycosuria of 300 grammes with a curable hyperglycemia, while another patient with a fatal denutrition may not eliminate more than 200 grammes of glucose per day.

In the same patient the glycosuria will vary with the CH intake. If one desires to estimate the gravity of a given case of diabetes, the régime must be known, and then compare the amount of CH ingested with the quantity of glucose excreted. This comparative study of the CH ingested and the sugar excreted, permitting one to calculate the balance of nutrition, is the basis of all physiopathological research work on diabetes.

The glycosuria varies with the CH intake, and by diet it may be made to appear or disappear in large or small amounts at the physician's will.

Thus, in Case I. the glycosuria progressively diminished when the CH intake was decreased, and this was also the result in Case II. In both the glycosuria reappeared when a certain amount of CH was exceeded: 160 grammes in Case I., 60 grammes in Case II.

The best example showing the relationship of glycosuria to alimentation is the following case, that of an obese diabetic whom I followed for more than a year:

Case III.—This patient was at first put on a milk diet (3,000 c.c.); there was no glycosuria. Put on ordinary hospital diet with a supplementary litre of milk in order to satisfy his boulimia—that is to say, a régime containing 480 grammes of CH—glycosuria developed and reached 120 to 130 grammes *pro die*. Symptoms of hyperglycemia—polyuria, thirst, lassitude, and neuralgia—ensued as well.

The quantity of CH was then progressively reduced to 63 grammes *pro die*, and the glycosuria decreased and finally disappeared, while the other symptoms of diabetes subsided.

Then the CH intake was progressively increased to 260 grammes *pro die*, and soon the thirst, then polyuria, and glycosuria returned. The CH intake was then reduced to 160 grammes, and the glycosuria disappeared.

From this time on diet tests were made by varying the quantity and nature of the CH, always giving the same result—namely, that each time the CH intake exceeded 220 grammes, glycosuria appeared.

The Origin of Glycosuria.—Such case histories clearly show that glycosuria originates from the CH in the food. It is not

derived from albumins and fats; the ingestion of a supplementary amount of albumin or fat does not increase the glycosuria, while ingestion of a supplementary allowance of CH exercises a direct action on the excretion of glucose.

Thus, in Case III., while a supplementary 100 grammes of glucose determined a glycosuria of 140 grammes, a supplementary ration of 150 grammes of butter with a box of sardines —that is to say, an intake of about 200 grammes of fat, which, according to the hypothetical calculations of chemists, should give rise to 400 grammes of glucose—did not cause glycosuria to appear.

In Case II. a supplementary intake of 300 grammes of meat for four days in succession—that is to say, 54 grammes of albumin, capable of producing 27 grammes of glucose—did not give rise to glycosuria, while a supplementary ration of 26 grammes of glucose produced a glycosuria of 40 grammes several days previously.

This doctrine is contrary to the opinion of many observers. Linossier and Lemoine have maintained that there are cases of mild diabetes in which meat exercised greater influence over the glycosuria than CH. Rathery and Liénard have shown the action of meat on the glycosuria in the majority of their cases, but this influence is not constant, and is in no way comparable to that of the CH. Laufer has also tried to show that a supplementary intake of meat increases the glycosuria. The Germans—Naunyn, Lenne, Kolisch, von Noorden, Falta, Gigon—also admit that in mild diabetes meat influences the glycosuria.

Hence I was led to study this point of physiology with as much precision as possible, and I was able to come to the conclusion that if, above all, the glycosuria of diabetics without denutrition varies with the intake of CH, it is also to a certain degree influenced by the intake of meat.

In a patient kept near the limit of tolerance by a proper régime, with a glycosuria of from 9 to 14 grammes, the suppression of 200 grammes of cooked meat from the diet caused the glycosuria to cease in four days; then with the addition of 300 grammes of meat it reappeared and reached 16 grammes; finally, when the patient was again allowed 200 grammes, the glycosuria dropped to 9 and 13 grammes.

The influence of meat on the glycosuria of diabetes may depend upon three causes: (1) Meat contains from 2 to 4 per

100 of glycogen; (2) the albumins of meat, by their degradation in the organism, liberate a CH nucleus, but it is not known exactly in what proportion albumin is susceptible of furnishing glucose; (3) meat exercises a deleterious action on the glycoregulator mechanism, although it would seem that this does not occur when meat is consumed in moderate amount, but only when it is taken in excess. I agree with Linossier, Lépine, and Maurel in condemning large quantities of meat, especially in the hepatic forms of diabetes, in which it may cause congestion of the liver and aggravation of the disturbance of glycoregulation.

As a conclusion, it may be said that meat influences the glycosuria of diabetes without denutrition, that it is moderate and not constant, that in practice it is not to be compared with that of CH, and that reducing the CH intake remains the chief point in the régime of hyperglycemia.

The CH Tolerance.—Diabetics without denutrition do not lose all capacity for burning CH; they may utilize a certain amount, and, according to von Noorden's expression, they possess a tolerance.

At the first examination one may ascertain if the patient offers a tolerance and the approximate degree of this tolerance. It is enough to know how much CH has been ingested and how much glucose has been excreted in the last twenty-four hours. In order that this datum shall have any value, a special diet must not be ordered, but simply instruct the patient to weigh the food taken during the day without making any change in his customary diet.

The comparison of the amount of CH ingested and that of the glycosuria indicates the apparent tolerance.

In Case I. this was $322 - 300 = 22$ grammes; in Case II. it was $309 - 277 = 32$ grammes; while in Case III. it amounted to $480 - 130 = 350$ grammes.

Unfortunately, the estimate of the tolerance by this procedure is not exact. Further observation of the patient will give the measure of *true tolerance*, and it will soon be perceived that this is almost always different from the apparent tolerance.

To calculate the *true tolerance*, one begins by stopping the glycosuria with a reduced CH diet. Then when the glycosuria is *nil* the CH intake is progressively increased until glucose

is again present in the urine. At this time the CH intake is again reduced in order to stop the glycosuria, and after a series of tests the maximum amount of CH that the organism will tolerate is found.

Thus, in Case I., the glycosuria being 300 grammes per day at the onset with a diet containing 322 grammes of CH, I was able, by slowly reducing the CH intake to 51 grammes, to cause the glycosuria to subside. From this time on the CH intake was progressively increased up to 245 grammes without giving rise to permanent glycosuria; but after several weeks of this diet the glycosuria returned, and it was necessary to decrease the CH to 130 grammes in order to make it disappear. A long period of observation showed that the *true tolerance* varied in this patient between 150 and 160 grammes.

Calculated by the same procedure, the *true tolerance* in Case II. was between 60 and 80 grammes, and in Case III. 220 grammes.

The *tolerance measures the degree of the disturbance of glycoregulation*. Each patient is, in this respect, a law unto himself. It is understood that this tolerance is measured within 10 to 20 grammes approximately. The lower the tolerance, the greater is the disturbance of glycoregulation and the more serious the prognosis, because the patient will have greater difficulty in following a régime which will remain within the limits of tolerance and not give rise to glycosuria.

From the point of view of practice, its estimate offers much importance for the prognosis and treatment. The notion of the tolerance allows one to bring an almost mathematical precision to bear upon the régime. It is known that when glycosuria has been made to subside it will not recur if the patient will not exceed his limit of CH tolerance; on the contrary, it will surely reappear if the patient consumes more CH than his tolerance permits.

Variations of Tolerance.—The true tolerance is remarkably *stable* in the same patient. During the two years that Case I. was under observation it did not vary; in Case II. it remained about constant for eight months; while in Case III. it was about identical during one year and then it appeared to increase, so that from 220 grammes it went up to about 300 grammes.

When diabetes is recovered from, the true tolerance becomes almost unlimited, as in the normal state; on the contrary, when the affection progresses, as in the diabetes of young subjects, the tolerance decreases and at length disappears altogether. Finally, there are cases in which the tolerance decreases for a certain time, and afterwards increases when the diabetes undergoes a temporary outburst in its evolution.

Certain *pathological circumstances* exercise an influence over tolerance. An infection, intoxication, a trauma, overwork, and, perhaps, a violent emotion, may result in a temporary or permanent decrease of the tolerance. Hence it is often after an accident of this kind that a diabetes is discovered for the first time, it having been latent until then.

Nevertheless, too much credence must not be given to the patient's tales. Many of them attribute their illness to emotion, worry, or cerebral overwork, and do not take into consideration their régime, which is the real cause of the diabetes. I do not know of a single authentic case in which emotion directly caused disturbance of glycoregulation.

Digestive disturbances appear to exercise a more marked action on the tolerance. In several of my cases subjected to an unvarying régime I have seen attacks of gastralgia, an outburst of congestion of the liver, or an enterocolitis decrease the tolerance or aggravate the diabetes.

Case II. furnishes a good example of this kind. For some time he tolerated an intake of 80 grammes of CH, when one day the glycosuria was found to be increased and the daily intake of CH was reduced to 40 grammes. Searching for the cause of this drop in the tolerance, we discovered that the patient had hepatic congestion with slight jaundice and fever. Sixteen days later the congestion of the liver had subsided, likewise the fever, and the patient again supported 80 grammes of CH without causing glycosuria. Some weeks later this patient had a sudden attack of fever, the result of an old malarial infection, but on this occasion glucose was absent from the urine. From this I conclude that it is by striking the organs of glycoregulation that infections and intoxications produce a diminution of tolerance in diabetics.

It has been said that certain complications, such as tuber-

culosis or a cachectic state, produce a decrease of glycosuria. Naunyn mentions two instances in proof of this which seem to me to be utterly valueless.

In some cases decrease of appetite and poor intestinal absorption resulting from the disease naturally lead to a reduced diet and consequently a decrease of the glycosuria. This happened in Case III. After a phase of glycosuria induced by an increased régime this rapidly declined, and I discovered that this was due to a smaller food intake resulting from loss of appetite due to an aggravation of the pulmonary tuberculosis.

Usually any change in the general health decreases the tolerance and increases the glycosuria. Thus, in another tuberculous diabetic a diet containing 36 grammes of CH caused the glycosuria to subside. When later on he returned to hospital the same diet did not lower the amount of glucose excreted, which varied between 20 and 30 grammes per day, and on the day before death it even attained 77 grammes.

The tolerance is not identical for *the various kinds of CH*. Certain ones are better tolerated than others. Dongkin used to extol milk diet. Mossé demonstrated the advantages of potato in diabetes. More recently, von Noorden advised oatmeal as a diet in serious cases of diabetes.

In order to verify these various statements, I carried out a series of experiments with the object of determining the comparative tolerance of the organism of diabetics in respect to the various kinds of CH, and I found that they could be classified in the following order: (1) Potatoes; (2) oatmeal; (3) macaroni; (4) chestnuts; (5) rice; (6) beans; (7) lentils; (8) peas; (9) milk; (10) bread; (11) sugars.

This scale is important to consider in order to establish a proper régime, and also clearly shows that, in this question, one must not merely consider the quantity, but also the *quality* of the CH.

The difference of tolerance does not seem to be due to the fact that certain CH are less well absorbed by the intestine, and therefore escape organic metabolism, merely because the starch of potato is more complete than that of bread, as Mossé has shown. Neither do I admit Mossé's explanation that potatoes, on account of their alkaline salts, possess a thera-

peutic value. In point of fact, they have no curative action on diabetes. It is probable that the difference is due to the chemical nature of the various CH, which transform more or less readily into glucose in the organism.

Does medical treatment influence the tolerance for CH ? It does not seem as if medicaments possess any distinct action; the most reputed, such as antipyrine, appears to act more upon the associated disturbances than on the fundamental physiological disturbances of diabetes.

Physical exercise is favourable for some diabetics. However, contrary to the opinion of Külz, During, Finckler, and Albu, it has not appeared to me that exercise increases the coefficient of utilization of the CH; I have even occasionally seen the disturbance of glycoregulation become aggravated following physical exercise, and since the limit of strength is quickly reached in diabetic subjects, exercise is a therapeutical procedure that requires to be handled with great prudence in this disease.

Hyperglycemia and Hyperglycistia.—The action of diet on the evolution of diabetes is explained by retention and accumulation of glucose in the organism. When a diabetic is subjected to a régime containing more CH than he tolerates—a régime that I term *hyperglucosic*—the CH ingested in excess are not immediately or totally excreted by the urine. They accumulate in the tissues and fluids of the body, and it is when the amount retained has actually saturated the organism, when it has produced a state of *hyperglycistia* (υπερ=above; γλυκος=sugar; ιστος=tissue) and *hyperglycemia* (υπερ, γλυκος; αιμα=blood), that glycosuria ensues at the same time as other symptoms of the disease. If the hyperglucosic diet is continued, the glucose not entirely burned is not completely eliminated in the urine; a portion accumulates in the body, so that the hyperglycistia and hyperglycemia increase. Inversely, a diet containing an amount of CH inferior to the patient's intolerance—that is to say, a hypoglucosic régime—provokes elimination partly by combustion, partly by elimination of the glucose retained. If an amount of CH inferior to the quantity that the patient is capable of utilizing is contained in the daily food ration, the subject will burn a part of the retained CH besides the CH of the food, and therefore will

continue to present a glycosuria, so that little by little he will use up his reserve.

Case III. and that of another diabetic permitted me to establish the existence of hyperglycistia in diabetes. On September 28, Case III. was put on hospital diet supplemented by 2 litres of milk, which furnished in all 480 grammes of CH per day. The syndrome of hyperglycemia developed. After thirteen days of this diet the CH intake was progressively reduced to 63 grammes, an amount inferior to the tolerance. The symptoms of hyperglycemia gradually subsided, and the glycosuria disappeared on October 31.

Thus, this patient passed through two successive phases. The first was the hyperglucosic régime, during which he became hyperglycemic; the second, that of a hypoglucosic diet, during which he returned to normal glycemia.

Taking into consideration that the tolerance of Case III. was 220 grammes of CH, calculation gave the amount of glucose retained in the organism during the first phase and eliminated during the second.

During the phase of hyperglucosic diet the glycosuria averaged 128 grammes a day.

The patient ingested $480 \times 13 = 6,240$ grammes of CH, and burned $220 \times 13 = 2,860$ grammes of CH; therefore, he retained $6,240 - 2,680 = 1,716$ grammes of glucose in thirteen days.

During the second phase, which lasted twenty days, the patient ingested 3,682 grammes of CH, and burned $220 \times 20 = 4,400$ grammes, and eliminated $4,400 + 874 - 3,682 = 1,592$ grammes of CH.

If the quantity of sugar accumulated in the organism during the phase of hyperglucosic diet (1,716 grammes) be compared with the amount of sugar destroyed or eliminated during the phase of hypoglucosic diet (1,592 grammes), it will be seen that the two amounts are equivalent.

During the experiment the patient's weight followed that of the retention and elimination of glucose; it at first increased from 78 kilogrammes to 80 kilogrammes, and then went from 80 to 79·2 kilogrammes.

This proves that diabetics make *retention of sugar* when the diet is unsuitable, the result being the clinical syndrome of hyperglycemia, in quite the same way as patients with chronic

nephritis have chloride retention engendering the syndrome of hyperchloruria, when the intake of salt is too considerable.

In some diabetics the retention of glucose reaches considerable proportions. Thus, in Case I. the reserves of glucose eliminated or destroyed during the cure of the hyperglycemia may be estimated at 5,598 grammes. Such an accumulation of glucose in the organism explains why the duration of the treatment is prolonged.

It is impossible to know in what tissues and in what form retention of glucose occurs. The calculation of the amount of glycogen and glucose that the body of a diabetic subject may contain, taking into account the proportions indicated by chemical analyses of the tissues and body fluids, only show a total of 678 grammes for a male weighing 60 kilogrammes. But it is probable that a large proportion of the CH retained in the tissues escapes chemical analysis.

Lépine and Barral have, in fact, shown that, besides the true glucose and glycogen dosable in the tissues and body fluids, one must consider the virtual sugar which cannot be estimated by chemical reagents, and which is capable of furnishing glucose by chemical transformation. These two observers have also shown the existence of glycuronic acid in the blood, a product of incomplete oxidization of glucose, which is found in too large an amount to be explained by the mere transformation of the glucose of the blood.

These very interesting researches show that a portion of the CH products escapes chemical analysis, and that the dosage of glucose and glycogen cannot give the correct measure of the CH contained in the tissues and body fluids. My researches on CH retention in diabetics lead to the same conclusion as those of Lépine on the CH of the blood.

The Syndrome of Hyperglycistia.—Hyperglycemia and hyperglycistia dominate the symptomatic evolution of diabetes mellitus. Under the influence of hyperglucosic diet the retention of glucose progressively increases. The symptoms do not suddenly develop, but slowly unmask themselves when the retention has reached a sufficient degree. Glycosuria is the first to appear, and ensues when the amount of sugar has reached about 1·5 or 2 grammes per 1,000.

Next polydipsia and polyuria develop when the saturation

of the body fluids by sugar requires dilution with water, and makes itself known by the sensation of thirst. The polyuria, therefore, is not a forerunner of polydipsia, as many have maintained. On the contrary, polydipsia precedes and, upon the condition that it becomes satisfied by an abundant intake of fluids, polyuria succeeds it.

Polyphagia is rather more related to the degree of tolerance than to the hyperglycemia. It is due to the fact that the diabetic is obliged to consume a supplement of albumin and fat in order to make up his ration of energy, since the CH ingested are not burned by the organism. It is all the greater the lower the tolerance for CH. Besides, polyphagia is the consequence of food habit of the diabetic, who was, and still remains, a large eater.

The other symptoms—nervous, ocular, buccal, and cutaneous—and the tendency to suppuration are also related to the saturation of the tissues by glucose. They develop along with the hyperglycistia and, inversely, disappear when it subsides from diet.

The profuse glycosurias that ensue during the cure of hyperglycistia in diabetics subjected to a hypoglucosic diet are due to the elimination of glucose pent up in the tissues, and not, as was formerly supposed, to the destruction of tissues.

Therefore, glycosuria is a good symptom, a real defensive reaction. It is to be favoured and not to be prevented. Hence one should be very suspicious of all drugs, such as antipyrine, which decrease the glycosuria at the same time as the urinary secretion, and are consequently more deleterious than favourable. A drug that favours the elimination of retained sugar by temporarily increasing the glycosuria, and will do for the glucose what theobromin does for the chlorides retained in the organism, would, on the contrary, be ideal.

The State of the Nutrition.—*The nutritive equilibrium* is preserved in diabetics belonging to the category under consideration. When the balance of their ingesta and egesta is estimated, it will be found that the balance is equivalent. The nitrogenous principles, as well as the saline principles, which are found in the urine and fæces are in quantity equivalent to those introduced with the food. The organism neither

gains nor loses excepting during phases of fattening or emaciation that occur, just as happens to any individual.

The three cases reported at the beginning of this lecture offer typical examples of *nitrogenous equilibrium*.

Case II. ingested 15·40 grammes of N in his food—corresponding to 96·5 grammes of albumin—and excreted 13·54 grammes of N in the urine, which, admitting a loss of one-tenth in the fæces, shows that there was a slight fixation of N in relation to the increase of the body weight. In the second analysis this patient ingested 19 grammes of N in the food and excreted 18·21 grammes of N in the urine—that is to say, an almost equivalent amount to that ingested. Hence the N metabolism was normal.

The amount of urea eliminated in the urine was perfectly normal if the quantity of albumin ingested capable of giving rise to it be considered. Hence there was no hyperazoturia.

This datum is in contradiction with the classic opinion. It is usually taught that diabetics have azoturia. Bouchard found azoturia present 41 times out of 100 diabetic patients. Some writers have even mentioned formidable quantities of urea. Dickenson and Furbringer noted 70, 80, or even 163 grammes of urea excreted in twenty-four hours. Lecorché and Charrin maintain that all real diabetics have azoturia, and make a distinction between true and simple glycosuria, basing this distinction on the presence or absence of this symptom. This erroneous opinion lies on a false interpretation of the analysis of the urine carried out with defective technique.

In reality, diabetics are usually large eaters, and their régime is apt to result in meat suralimentation. It is consequently natural that they excrete a large amount of urea. If one compares the ureic excretion with a so-called average normal excretion, as is usually done, it is evident that diabetics excrete a much larger amount than normal individuals, but this average has no signification whatsoever, as I have shown with H. Labbé. Ureic excretion depends upon the food intake, and it is with this that it should be compared.

We have also shown that the dosage of urea with sodium hypobromite in Regnard's apparatus gives particularly erroneous results in diabetes, and it is to the use of this defective

method that the extraordinary amounts of urea found in diabetic urine should be attributed.

I conclude, therefore, that hyperazoturia does not occur in diabetes without denutrition, and only exists when there is denutrition.

Besides, the *azoturic coefficient* is normal. In Case II. it was 0·83. Briefly, the transformation of albumins into urea takes place in diabetes exactly as it does in normal individuals; and if the liver is disturbed in its glycogenetic functions, its ureopoietic function is not—an interesting example of pathological dissociation of the hepatic functions.

Uric acid is usually eliminated in trifling amount. One of my patients only excreted 0·33, which was insufficient for a person consuming 300 grammes of meat—an amount capable of furnishing in itself at least 0·45 of purines. In researches undertaken with L. Furet, we showed that the uric excretion is extremely irregular in diabetes; there is a tendency to uric retention, which may explain the rather frequent combination of gout and diabetes.

Phosphaturia has often been mentioned as a symptom of diabetes. Bouchard said that he had met with it 27 times out of 100 cases, and he believed that it was the result of an exaggerated disassimilation of the tissues. I have never met with it in diabetes without denutrition.

The chlorides have seemed to me to be eliminated by diabetics in a normal way; chloride retention does not belong to the syndrome of hyperglycemia. But diabetics who are large eaters have of necessity a large amount of chlorides in the urine.

The acetone compounds are usually absent from the urine.

From what has been said of nitrogenous and saline elimination in diabetes without denutrition, it is evident that the functional disturbance exclusively involves the *metabolism of CH ;* the metabolism of nitrogenous and saline substances is not changed.

Diabetes is therefore essentially characterized, as I have said, by an incapacity of burning CH. The nutrition is not disturbed as a whole, and Bouchard's conception, which regards diabetes as a disease of lessened metabolism, is not justified from the study of the various nutritive functions in diabetic patients.

II. Diabetes with Denutrition.

Diabetes with denutrition is far less frequent than that without denutrition. It corresponds to what the older writers designated by the name of thin diabetes, and to what Lancereaux described by the term of pancreatic diabetes.

It differs from diabetes without denutrition by its ætiology, physiological pathology, and clinical characters.

Unlike diabetes without denutrition, it does not develop in large eaters, and is neither preceded nor accompanied by obesity; it is much more apt to be familial. Its onset is rapid, the syndrome of hyperglycemia becoming constituted in a few days in a subject who had been previously in perfectly good health. By this I do not infer that the onset is marked by major symptoms, or that it is sufficiently sudden so that its exact date can be made out. But it does not have the slow, insidious character belonging to diabetes without denutrition.

The ætiology cannot usually be determined. Sometimes diabetes with denutrition is accompanied by a lesion of the pancreas or liver, which is diagnosed by the ordinary symptoms presented. But such is not always the case, and frequently only the syndrome of hyperglycistia will be noted without any other symptom that might indicate a lesion of the organs of glycoregulation.

Some case histories will illustrate the nutritive disturbances, symptoms, and evolution peculiar to this form of diabetes.

Case I.—Male, who stated that he had only been ill for one month. Since then he has had an ardent thirst, obliging him to drink several litres of liquid; he gets up in the night to drink. Total urine in twenty-four hours averages from 8 to 10 litres. He has a large appetite and eats copiously. During the month, in spite of suralimentation, the patient has lost 7 kilogrammes. There is extreme lassitude and violent cramps in the legs. Briefly, the onset was sudden, although the exact date cannot be ascertained.

No cause could explain the development of the diabetes. In the patient's antecedents there was jaundice due to occlusion of the choledochus at the age of 17 which lasted for six weeks, and at the same time psoriasis appeared. At 19 he had gonorrhœa, which was cured in ten weeks. Goitre at the age of 23. No alcoholism, no syphilis. No member of his family has been diabetic. It is to be noted that the patient's father died from a disease of the liver.

The patient is 33 years of age, taller than the average, very thin, and only weighing 53 kilogrammes.

When he entered hospital he presented the complete syndrome of hyperglycemia—polydipsia, polyuria of 8,000 c.c., glycosuria of 421 grammes, with a diet furnishing about 358 grammes of CH. The tongue was dry and red, teeth in bad condition.

There were no apparent gastric disturbances; constipation, but no diarrhœa, no hæmorrhoids. Liver and spleen appeared normal. All the tendon reflexes were sluggish, the patellar and Achilles reflexes were abolished, slight œdema of the lower limbs. Signs of pulmonary tuberculosis in the early phase in the right lung. Anaphrodisia complete.

The patient was ordered a mixed diet, allowing him to eat enough to satisfy his hunger and without reducing the CH intake.

On April 28 an analysis of the urine and fæces was made by H. Labbé, with the following results:

Urine :	
Total amount	10,400 c.c.
Specific gravity	1020
Glucose	639·6 grammes.
Total N	24·5 ,,
Urea (Regnard)	58·9 ,,
Phosphoric acid	0·6 gramme.
NaCl	26·5 grammes.
Uric acid and xanthic compounds ..	0·95 gramme.
Acetone	Trace.
Fæces :	
Weight when dried	87·95 grammes.
Total N	5·6 ,,
Fats	12·16 ,,
Reducing matters	Nil
Diet contained :	
Albumin	161·8 ,,
Fats	124·5 ,,
CH	422·0 ,,

From these figures it is possible to estimate the nutritive balance, and to detect the origin of the glucose eliminated in the urine.

The glycosuria was 639 grammes, the CH ingested amounted to 422 grammes; therefore 422 grammes of glucose could be derived from the CH ingested, while the remainder—that is to say, $639 - 422 = 217$ grammes—must have been derived from albumins and fats.

Now, the excretion of N in the urine was 24·5 grammes, corresponding to the degradation of a certain quantity of albumin. If with von Mering and Minkowski it be admitted that 1 gramme of urinary N corresponds to the production of 2·6 grammes of glucose from albumin, it may be assumed that the albumin metabolized in the organism was susceptible of producing $24{\cdot}5 \times 2{\cdot}26 = 63{\cdot}7$ grammes of glucose. Hence, of the 217 grammes of glucose not produced by the CH in the food,

63·7 grammes could have been derived from the albumins and 217 – 63·7 = 153·3 grammes must have been furnished by the transformation of the fats and albumins of the body tissue.

Now, the 124 grammes of fat ingested by the patient were alone capable of furnishing this amount of glucose, if it be admitted that 1 gramme of fat may, by splitting up, give 2 grammes of glucose.

The amounts of glucose derived from the albumin of the food and body tissue can also be estimated.

The patient ingested 161 grammes of albumin, corresponding to 25·8 grammes of N, but he lost 5·56 grammes in the fæces. Therefore, only 25·8 – 5·6 = 20·2 grammes of N in the food was absorbed, and by degradation this could furnish 52·6 grammes of glucose.

At the same time, there were 24·5 grammes of N in the urine, 20·5 of which were derived from food; 24·5 – 20·2 = 4·3 grammes of N derived from the albumin of the body tissues, and could furnish 11·18 grammes of glucose.

Briefly, in this patient the 639 grammes of glucose in the urine were derived from:

CH in food	422·0
Albumin in food	52·6
Albumin from the body tissues	11·18
Fats from food and body tissues	153·3
	639·08

The case is an example of nitrogenous denutrition and hyperazoturia. The patient ingested 25·8 grammes of N in the food and excreted 24·5 grammes in the urine + 5·56 of N in the fæces = 30·06 grammes. Therefore, the deficit was 30·06 – 25·8 = 4·26 grammes of N.

The elimination of the other principles of the urine was very irregular. Thus 26·52 grammes of NaCl were excreted, which is a large amount; but only 60 centigrammes of phosphoric acid were eliminated, which was a much smaller quantity than was ingested in the food.

Several treatments were essayed—enterokinase, thyroid extract, and Hg—with no result.

At times the patient's weight increased at the same time as the œdema developed, and hydrarthrosis occurred in the knees.

At the end of three months the condition was stationary. The patient had epileptic seizures, with loss of consciousness, recurring every four days. These paroxysms were followed by a polyuria of 16 litres with intense thirst, leaving the patient with headache and vertigo.

The patient was afterwards treated at the Medical Clinic of the University of Geneva. Here the patient became more and more cachectic, the glycosuria varied between 200 and 988 grammes per day, and at times the polyuria reached 18 litres. Two months before death notable amounts of acetone and diacetic acid were found in the urine.

Death took place in coma nine months after the onset of the diabetes. At autopsy the pancreas was found to be small, but was not sclerosed, and presented very highly developed islands of Langerhans.

The following case is an excellent example of diabetes with very marked denutrition:

Case II.—Male, æt. 42 years. Had always been well until he fell ill in January, 1910. At this time he lost strength very rapidly, and glycosuria was found. He was put on a potato diet, and lost 20 kilogrammes in four months.

In August, 1910, he entered hospital. Was very emaciated, weak, and cachéctic. Cavity in right pulmonary apex.

August 28.—Analysis of the urine was as follows:

Total amount	3,000 c.c.
Total N	14·22 grammes.
Urea	26·25 „
NaCl	9·3 „
Glucose	200·0 „

The diet was composed of—

Milk	1,500 c.c.
Raw meat	60 grammes.
Broth	1,250 c.c.
Bread	24 grammes.

and included—

Albumins	68 „
Fats	47 „
CH	69 „

The origin of the glycosuria could be explained in this way: 69 grammes was derived from the CH content in the food, 36·97 grammes was derived from the albumins elaborated in the organism. In point of fact, the patient eliminated 14·22 grammes of N, capable of giving $14{\cdot}22 \times 2{\cdot}6 = 36{\cdot}97$ grammes of glucose.

The remainder, $200 - 69 - 36{\cdot}97 = 94{\cdot}03$, must have been derived from fats. Now, if 1 gramme of fat can furnish 2 grammes of glucose, it is evident that the fats in the food intake alone were not sufficient to explain the glycosuria (because the 47 grammes were not totally absorbed), so that the participation of the fat of the body tissues or a supplementary elimination of the glucose pent up in the organism must have occurred.

Briefly, there was a glycosuria of 200 grammes derived from:

CH in the food	69·0 grammes.
Albumins in the food and tissues ..	36·97 „
Fats in the food and tissues	94·03 „
	200·0 „

The denutrition was characterized by an abundant hyperazoturia. The patient ingested 68 grammes of albumin ($N = 10{\cdot}8$) and excreted 14·22 grammes of N in the urine, without including the N contained in the fæces, which was probably quite large in amount. Hence there was a deficit of at least $14{\cdot}22 - 10{\cdot}8 = 3{\cdot}42$ grammes.

These are very marked denutritions which do not occur in every case. In fact, both cases were cachectic, tuberculous diabetics following irregular régimes.

The most complete example of this form of diabetes is furnished by the following case:

Case III.—Female, æt. 25 years. Was seized in July, 1907, by ardent thirst, and at the same time emaciated and lost strength. In a few days hyperglycemia became constituted, but the diabetes was only diagnosed one month later when she entered hospital. The affection had not been preceded by any illness or obesity, but one month previously there had been a hydrarthrosis of the knee of unknown cause, which disappeared in three weeks.

When the patient entered hospital on January 13, 1908, she then presented the syndrome of hyperglycemia: intense thirst, dry mouth, tongue pasty, considerable polyphagia, polyuria of 5,000 to 6,000 c.c., and a glycosuria of 260 grammes per day; the skin was dry, there was pruritus vulvæ, while the patellar reflexes were almost completely abolished. Patient was extremely fatigued and emaciated, had lost her memory, the menses were suppressed, and the blood-pressure low. But there was no apparent visceral lesion and no diarrhœa.

The patient was put on a diet including milk, 1 litre; potatoes, 400 grammes; meat, 300 grammes; 2 eggs; Gruyère cheese, 30 grammes; butter, 50 grammes. As the patient continued to emaciate, the diet was increased after a time to meat, 600 grammes; 6 eggs; cheese, 80 grammes; and butter, 100 grammes. With this régime, representing 124 grammes of CH, the glycosuria, which at first was 267 grammes, gradually fell to 146 grammes, and the polyuria fell from 5,250 c.c. to 1,500 c.c.

On February 22 the milk and potatoes were omitted and replaced by 400 grammes of green vegetables; the eggs, butter, cheese, and broth were slightly increased. This diet did not furnish more than 20 to 25 grammes of CH, with the result that the total urine was 1,500 c.c. and the glycosuria finally was about 12 grammes per day.

On April 4 the meat was increased to 800 grammes, and the glycosuria progressively went up to 105 grammes.

On April 9 the meat was reduced to 600 grammes, and the glycosuria dropped to 19 grammes.

On April 16 the meat was reduced to 400 grammes, and the glycosuria fell to 6 grammes. The total urine varied between 1,000 c.c. and 1,500 c.c.

On April 27 the meat was decreased to 200 grammes, and the glycosuria ceased in a few days, and the total urine was less than 1,000 c.c.

Thus in this serious case of diabetes diet alone stopped the glycosuria, first reducing the CH intake and then meat. Four months of strict treatment were necessary to obtain this result.

During this time the syndrome of hyperglycemia disappeared, strength came back, so that the patient asked to leave hospital in order to return to her work.

The body weight, which temporarily increased, fell from 46·5 to 43·7 kilogrammes at the time the patient was discharged.

The variations in weight in diabetics have no great signification from the view-point of prognosis; they are largely due to œdema.

The balance of the nutrition, estimated during the patient's stay in hospital, showed that she did not have any nitrogenous waste; she even retained N, while the digestive absorption of albuminoids and fats was perfect. At no time was there any indication of insufficiency of the external pancreatic secretion.

In July, 1908, the patient re-entered hospital, being again very fatigued. However, with a diet comprising 1 litre of milk and 200 grammes of potatoes, she only eliminated from 10 to 30 grammes of glucose.

After October, 1908, she was lost sight of until February 10, 1909, when she returned to hospital in very bad condition. The body weight had fallen to 41·5 kilogrammes and the glycosuria was 100 grammes. The teeth had decayed and fallen out.

There were serious digestive disturbances; the stools were large, pasty, fœtid, whitish in colour, rich in fat and undigested meat. From time to time there was diarrhœa.

However, by proper diet, in which CH were reduced to 20 grammes per day, the glycosuria was only 5 to 6 grammes at the end of a month, the symptoms of hyperglycemia had disappeared, the general health had improved, and the body weight had increased.

On April 16, as the patient felt stronger, she asked to be sent to the convalescent home at Vésinet, but she returned to hospital in a week because no special diet had been given her, and an intense hyperglycemia rapidly ensued with all its train of symptoms, a striking proof of the necessity and efficaciousness of reduced CH diet in diabetes of this type.

During this stay in hospital very complete studies on the nutrition could be carried out. Upon various occasions the nutritive balance was estimated with results that compared well.

February 23, 1909, the régime contained:

Albumin	228 grammes	(N = 36·4)
Fats	175	,,
CH	25	,,

The analysis of urine and fæces by H. Labbé showed that the N equilibrium was respectively:

N ingested	36·4 grammes.
N in urine	15·3 ,,
N in fæces	21·0 ,,
UN + fæcal N	36·3 ,,
Balance	36·4 − 36·3 = + 0·10 centigrammes.

Nitrogenous absorption was very defective; 21: 36·4 = 58 per 100 of the albuminoid substances were excreted in the fæces, while normally this waste is only about 10 per 100.

Absorption of fat was worse; 148:175 = 84·6 per 100 of fats from the food excreted in the fæces, while normal waste is only 5 to 10 per 100.

Later on, microscopical examination of the fæces showed that digestion and absorption of CH substances were likewise defective, because many starch particles were found.

A result such as this, showing a very defective absorption of nitrogenous substances and fats, indicates an insufficiency of the external pancreatic secretion; hence the case was pancreatic in origin.

The nitrogenous equilibrium, which in this analysis was maintained, was found broken in later analyses made by Vitry.

An average of four days of analysis, from March 20 to 29, 1909, gave:

N ingested (albumin 141 grammes) ..	22·5 grammes.
N of urine	15·5 ,,
N of fæces	9·8 ,,
UN + N of fæces	25·35 ,,
Balance .. .. 22·5 – 25·85 = – 3·35	,,

Therefore there was nitrogenous denutrition, moderate and intermittent, but sufficiently characteristic for one to classify the case among diabetes with denutrition.

Afterwards the patient developed an acute bilateral cataract, which was operated on; she died from a rapidly developing caseous tuberculosis. Autopsy revealed pancreatic lithiasis with sclerous atrophy of the gland.

Clinical Description.

With these three cases as illustrations one has the necessary elements for defining diabetes with denutrition.

In the circumstances, the physiological disturbance is not confined to a glycoregulator insufficiency, as in diabetes without denutrition. Not only is the metabolism of CH involved, but that of albuminoids and fats as well. These physiological disturbances give rise to three characteristic syndromes—namely: (1) A glycoregulator disturbance; (2) disturbances of nitrogenous metabolism; and (3) acidosis.

Glycoregulator Disturbance.—It is of the same nature, but much more profound, as in diabetes without denutrition.

The glycosuria is generally profuse. Assuredly, it does not reach the extreme amount of 600 to 1,000 grammes per day unless the patient is allowed to eat as he wishes and obeys his boulimia. If a suitable régime is ordered, one poor in CH, the glycosuria will vary between average limits; it

may even be less considerable than in a diabetic without denutrition who follows a hyperglucosic régime. As in diabetes without denutrition, diet exercises a primordial influence over the glycosuria, therefore over the polyuria, polydipsia, and the entire syndrome of hyperglycemia.

Contrary to what takes place in diabetes without denutrition, it is impossible to cause the glycosuria to cease even by a prolonged reduced régime. *The patient does not have any tolerance for CH*, as his organism is absolutely incapable of burning them.

The glycosuria is not only derived from the CH ingested; it also is due to the CH which are susceptible of forming in the body from albumins and fats taken in the food or resulting from destruction of the body tissues.

While in diabetes without denutrition the quantity of albumins in the food does not exercise any notable influence over the glycosuria if the intake remains within physiological limits, in the form with denutrition the albumins distinctly contribute to the formation of glycosuria.

Mering and Minkowski, Külz, Troje, and von Noorden have mentioned cases showing the deleterious effect of meat on the glycosuria in serious diabetes, as I have shown in the report of Case III. Therefore, when composing a régime, not only the CH intake, but that of albumins must be considered.

It does not appear that all albuminoid substances have an equivalent influence on the glycosuria. Given equal amounts of N and CH, a meat diet gives rise to a greater glycosuria than a milk diet, or a vegetable or oatmeal régime. This may be due to the fact that meat contains a certain dose of glycogen, but this is not the only reason. It would rather seem that the albumins of meat and vegetables have not the same composition, and that the former give rise by their metabolism to a larger amount of CH or to CH less easily utilized by the organism of diabetics.

In diabetes with denutrition a portion of the glycosuria is derived from the fats in the food and those of the body tissues. The balance of the origin of the glycosuria proves this, but as yet I have not had the opportunity of demonstrating it by the test of supplementary ingestion of fat.

These results are not devoid of interest from the view-

point of pathological physiology of diabetes, because the question of the origin of glycosuria is still moot. Although the majority of pathologists freely admit the influence of albumins on the glycosuria of diabetes, all are, however, not of this opinion. Pflüger tried to show that in diabetes following removal of the pancreas in dogs, the very profuse glycosuria that ensues is not derived from albumins or fat, but from the CH reserves of the animal. Luthje has refuted this opinion by showing that if the animals survive long enough, the CH reserves are incapable of explaining the abundance of the glycosuria. My observations in man would confirm this point of view.

Since the glycosuria is not only derived from CH, but also from other foodstuffs, it will always be superior to the amount of CH ingested, and this is a means of recognizing this category of diabetes, although it is relative, not absolute.

Thus, in Case I. there was a glycosuria of 639 grammes with a CH intake of 422 grammes. Case II. had a glycosuria of 200 grammes with a CH intake of 69 grammes. Another patient followed for some weeks had a glycosuria of from 225 to 368 grammes with a CH intake of 160 grammes, while yet another had a glycosuria of from 172 to 188 grammes with a CH intake of 100 grammes. Many more examples could be given, but these are enough.

Briefly, while in diabetes without denutrition the glycosuria is inferior to the CH intake, in diabetes with denutrition the glycosuria is, on the contrary, higher than the CH intake. It is irreducible.

The Disturbance of Nitrogenous Metabolism.—This is the chief characteristic of diabetes with denutrition. It shows itself in two ways—namely, (1) nitrogenous denutrition, and (2) a vitiated nitrogenous metabolism. The nitrogenous equilibrium is broken so that the subject wastes N constantly, which brings the balance of nutrition into evidence, as I have shown. The nitrogenous denutrition explains the emaciation and progressive loss of strength observed in this category of diabetes.

Vitiated nitrogenous metabolism is revealed by the elimination in the urine of abnormal nitrogenous products, such as an excess of ammonia, amino-acids, creatine, colloidal N, etc.

Acidosis.—During the metabolism of albuminoids and fats, products such as β-oxybutyric and diacetic acids arise. Normally these substances are carbonized in the liver, but when not destroyed, or if the alkaline products derived from the combustion of CH are not in sufficient amount to cause saturation of the acids, they accumulate in the blood and tissues, producing a state of acid intoxication known by the name of acidosis. This is what happens in diabetes with denutrition.

The state of acidosis is made known by the presence of non-carbonized acid products—β-oxybutyric and diacetic acid and acetone—and by the elimination of the latter product, which is volatile, by the lungs. Diacetic acid is detected by Gerhardt's reaction, while acetone can be both found and a dosage made with Lieben's reaction. Legal's reaction reveals the presence of both diacetic acid and acetone.

Acidosis is a serious menace to life, and although it may remain moderate for quite a long time, it invariably becomes aggravated, and coma is the final outcome. Hence its prognostic value is great; it should never be overlooked, and at the first examination of a diabetic subject the urine should be tested with the reactions of acidosis.

The Evolution of Diabetes.—While diabetes without denutrition, when well taken care of, may remain almost indefinitely stationary and cause no menace to the patient's life, diabetes with denutrition presents a progressive evolution, becomes aggravated, and is finally complicated by acidosis, which, in spite of all treatment, ends in coma. The patient emaciates, loses strength, and often presents œdema similar to that of chronic nephritis. The patella reflexes are usually abolished. The subject is exposed to three kinds of complications dependent upon hyperglycemia, nitrogenous denutrition, and acidosis.

CHAPTER II

THE CLASSIFICATION OF DIABETES MELLITUS—NITROGENOUS METABOLISM*

In 1907 the study of the balance of nutrition, including not only the metabolism of the carbohydrates, but of nitrogenous substances as well, led both H. Labbé and myself to classify diabetes mellitus in three categories: (1) Diabetes without denutrition, in which the glycosuria is due to the carbohydrate intake; (2) diabetes with nitrogenous denutrition, in which the glycosuria is alimentary and organic in origin, and derived from the carbohydrates, albumins, and fats; (3) intermediary cases, in which denutrition is moderate and can be compensated by alimentation.

Our conception has been accepted by a number of pathologists, among them Lannois, Parmentier, Chabrol, F. Remond, and Rathery. The latter observer calls simple diabetes what we designate as diabetes without denutrition, and consumptive diabetes what we term as diabetes with denutrition. Like ourselves, Rathery admits the importance of nitrogenous denutrition in the second type of diabetes.

The numerous cases that we have collected since 1907 have confirmed the value of the classification proposed. Besides, the research work of the last few years has contributed to bring into relief the defective nitrogenous metabolism in the serious forms of diabetes, and its importance in the pathology of diabetic coma.

I. Diabetes without Denutrition.

This form of the process ordinarily occurs in overfed, obese subjects, and corresponds to the mild forms of the German writers.

The subject eliminates an amount of N equivalent to the

* *Annales de Médecine*, 1914.

quantity ingested; hence there is nitrogenous equilibrium. The glycosuria is often quite moderate, but occasionally it reaches several hundred grammes. It is proportional to the ingestion by carbohydrates, and therefore it can be reduced or increased, or appear or disappear, by diet. The main character is that the glycosuria is always less in amount than the quantity of carbohydrates ingested by the patient, and that he is still capable of destroying a certain quantity of carbohydrates. The diabetic of this category possesses a *tolerance ;* he will only have glycosuria when he consumes an amount of carbohydrates superior to this tolerance; hence it is the degree of the latter which measures the gravity of the disturbance of glycoregulation.

The following case histories are examples of the type of diabetes under consideration:

Case I.—The nitrogenous balance in this case was estimated by two successive analyses at +0·32 and −0·54. In each the gain, like the deficit, of N is too trifling to be taken into account, as the figures do not exceed the limits of experimental error. Hence it may be admitted that nitrogenous equilibrium exists in this patient.

Case II.—Male, æt. 25 years, diabetic for five years, presented a tolerance of about 70 grammes of carbohydrates. No stigmata of acidosis.

The balance was estimated by two days of observation.

Diet :

Carbohydrates	58·0 grammes.
Albumin	115·0 „ (N = 18·4).
Fats	152·8 „

Urine :

Total amount	1,600 c.c.
Specific gravity	1020
Acidity	3·48 grammes.
Total extract	76·16 „
Mineral extract	23·68 „
TN	14·27 „
Urea (Mörner)	26·24 „
Ammonia (salts)	1·0 gramme. (AN = 0·82).
Purines	1·2 grammes.
Organic matter	24·0 „
N percentage	86 per 100
Coefficient $\frac{AN}{TN}$	5 „
Albumin	Trace.
Glucose	Nil.
Acetone	0·19 gramme.

Fæces :

Dry extract	16·5	grammes.
TN	0·78	gramme.
Fats	4·75	grammes.
Carbohydrates	Nil.	

The N balance distinctly indicates fixation of N:

N ingested		18·4	grammes.
N in urine	14·27	15·05	,,
N in fæces	0·78		
Balance		+3·35	,,

Case III.—Female, æt. 66 years, diabetic seven years, with a CH tolerance of about 180 grammes. No stigmata of acidosis. The balance was estimated by three days' observation.

Diet :

Albumin	69 (N = 11·07	grammes).
Carbohydrates	194	grammes.
Fats	67	,,

Urine :

Total amount	1,260	c.c.
Acidity	1·66	grammes.
Urea	19·75	,,
Ammonia	0·68	gramme.
Amino-acids	0·22	,,
Total N	10·67	grammes.
Glucose	8·0	,,
N per cent.	86·0	per 100.
Coefficient $\frac{AN}{TN}$	5·0	,,
Ureogenic imperfection	5·6	,,

Fæces :

Total amount	177·0	grammes.
Dry extract	49·0	,,
TN	1·18	,,

Balance :

N ingested		11·07	grammes.
N in urine	10·67	11·77	,,
N in fæces	1·10		
Deficit		−0·70	,,

The loss of 70 centigrammes of N *pro die* is too small to be regarded as an index of denutrition. When the gain or loss does not reach 1 gramme it may be admitted that nitrogenous equilibrium exists.

The absence of nitrogenous denutrition being characteristic of benign diabetes does not mean that the nitrogenous equilibrium is always respected in these cases, because it is quite possible to meet with temporary nitrogenous denutrition during mild diabetes, caused either by an alimentary insuffi-

ciency or an aggravation of the disease. But in these circumstances the other characters of diabetes with denutrition are wanting.

Not only is nitrogenous equilibrium generally preserved, but the N metabolism takes place in a normal way in this form of diabetes. The N coefficient is normal, and in the three cases given above it was 83·5, 86, and 86 per 100 respectively. The excretion of ammonia did not exceed the norm; thus, in Cases II. and III. the coefficient $\frac{AN}{TN}$ was 5 per 100.

The amino-aciduria did not exceed the norm; in Case III. $\frac{aN}{TN}$ was 1 per 100 only. The researches that I have undertaken on this subject in collaboration with H. Bith have clearly shown that amino-aciduria is not in excess in diabetics belonging to this category.

This is likewise true if one estimates the N metabolism and excretion of ammonia by the coefficient of ureogenic imperfection. Thus, in Cases II. and III. it was 6·2 and 6·8 per 100 respectively, which is normal.

Finally, colloidal N (undialyzable) is usually not in excess in this form of diabetes, as I have proved in my researches carried out with Dauphin.

Correlatively, acidosis is absent. There is no diacetic or β-oxybutyric acid in the urine. Usually the proportion of acetone remains very small and does not exceed the norm, and it only increases in the transitional forms of the disease.

II. Diabetes with Denutrition.

This category of diabetes corresponds to the pancreatic diabetes of the older writers and the serious forms of the Germans.

The patient eliminates a quantity of N superior to the amount ingested. He destroys some of the albumin of his tissues, and is in a state of denutrition. *The nitrogenous equilibrium is broken.* Besides, *the nitrogenous metabolism is abnormal.* The patient eliminates a large quantity of nitro-

genous products incompletely elaborated and an insufficient proportion of urea.

The glycosuria, which is always considerable, is sometimes very great, and may exceed 1,000 grammes. It will vary with the ingestion of carbohydrates and other foods, but it will not cease by privation of carbohydrates. Even in absolute fasting the glycosuria persists, because it not only is derived from the food metabolism, but from tissue destruction as well. Its origin is both *alimentary and from the body tissues*.

In these circumstances the disturbance of glycoregulation has attained its maximum; the organism cannot burn up the CH ingested; it offers *no tolerance*. And what is more, it is even incapable of burning the CH resulting from the transformation of albumins and fats of the food and body tissues.

Diabetes with denutrition sooner or later becomes complicated by acidosis, which, in turn, ends in coma.

The following are illustrative cases:

Case IV.—Female, æt. 19 years, with serious diabetes of one year's duration. Symptoms intense; emaciation and loss of strength made rapid progress; the glycosuria was 270 grammes, but fell to 67 grammes by a reduced diet. Very marked stigmata of acidosis. The balance was estimated after three days' observation.

Diet :

Carbohydrates	46·0 grammes.	
Albumin	131·06 „	(N = 20·96).
Fats	179·46 „	

Urine :

Total amount	2,600 c.c.	
Acidity	3·82 grammes.	
TN	20·8 „	
Urea (Mörner)	33·54 „	
Ammonia (formol)	5·69 „	(AN = 4·6).
Coefficient $\frac{AN}{TN}$	20 per 100	
Azoturic coefficient	75 „	
Albumin	Nil.	
Glucose	67·6 grammes.	
Acetone	4·0 „	
Diacetic acid (Gerhardt) ..	Abundant.	
Urobilin	Trace.	

Fæces :

Dry extract	102·0 grammes.	
Fats	12·67 „	
TN	2·07 „	
CH	Trace.	

N balance :

N ingested			20·96 grammes.
N of urine	20·8	22·87	„
N of fæces	2·07		
Deficit		− 1·91	„

CH balance :

CH ingested	46·0	
Glucose excreted	67·6	
	− 21·6	of glucose derived from metabolism of albuminoids.

Case V.—Female, æt. 14 years, very serious diabetes for several months. Symptoms intense; very considerable loss of strength; the glycosuria, which had been 415 grammes at the onset, had fallen to 88 grammes *pro die* from the influence of diet. Stigmata of acidosis very intense.

The balance of the nutrition was estimated after three days' observation.

Diet :

Carbohydrates	53·0 grammes.	
Albumin	138·99 „	(N = 22·2).
Fats	129·33 „	

Urine :

Total amount	2,666 c.c.
Specific gravity	1023
Acidity (SO_2)	2·85 grammes.
Total extract	190·0 „
Mineral extract	23·5 „
TN	22·16 „
Urea	41·7 „
Ammonia (formol)	3·4 „
Amino-acids	2·6 „
Uric acid (Folin)	0·5 gramme.
Azoturic coefficient	88·0 per 100
Coefficient $\frac{AN}{TN}$	12·0 „
Coefficient $\frac{aN}{TN}$	9·6 „
Organic matters	25·0 grammes.
Albumin	Nil.
Glucose (Fehling)	87·5 grammes.
Acetone	1·7 „
Diacetic acid	Abundant.
Urobilin	Trace.

Fæces :

Dry extract	10·1 grammes.
TN	1·42 „
Fats	6·85 „
CH	Nil.
Stercobilin	Large amount.

N balance :

N ingested		22·2	
N of urine	22·16	23·58	
N of fæces	1·42		
Deficit			– 1·38

CH balance :

CH ingested	53·0	
Glucose excreted	87·4	
	– 34·4	grammes of glucose derived from the albumin in the food and body tissues.

It may happen that denutrition will be wanting in a case of serious diabetes with acidosis at the time the N balance is estimated. However, all the symptoms show that the case is one of diabetes with nitrogenous denutrition, but the excretion of N is not quite regular, and at certain times temporary retention, followed by expulsion, occurs, so that it may happen that the analyses are made just while retention is taking place. In the following case the N balance was estimated several times, and shows the legitimacy of this interpretation:

Case VI.—Female, æt. 10 years, with serious diabetes for one year. Major symptoms of hyperglycemia; glycosuria from 100 to 200 grammes; no pancreatic insufficiency. Emaciation; loss of strength; intense acidosis. Death in coma some days later.

The balance of the nutrition shows:

Diet :

Carbohydrates	84·0 grammes.	
Albumin	116·2 „	(N = 18·6).
Fats	114·1 „	

Urine :

Total amount	2,400 c.c.
Acidity	2·94 grammes.
TN	20·16 „
Ammonia	3·83 „
Amino-acids	2·1 „
Acetone	4·65 „
Diacetic acid (Gerhardt)	Large amount
Glucose (Fehling)	92·2 grammes.
Coefficient $\frac{AN}{TN}$	15·0 per 100.
Coefficient $\frac{aN}{TN}$	8·4 „

Fæces :

TN	1·79 grammes.

N balance :			
N ingested			18·6
N in urine	20·16	21·95	
N fæcal	1·79		
Deficit			− 3·35
CH balance :			
CH ingested..	84		
Glucose excreted	92		
			− 8 grammes of glucose derived from albumins.

The patient was afterwards put on various diets (mixed, milk, cereals, vegetable), very exactly weighed, and the N balance estimated each time gave the following results:

− 1·11	− 0·32	+3·38
+2·99	− 2·85	+0·19
− 4·45	− 4·5	− 1·5
− 9·56	− 0·36	+0·9
− 0·8	− 1·07	

Thus, in a typical case of diabetes with denutrition the estimate of the balance showed a loss eleven times and fixation of N four times out of fifteen. All things considered, the nitrogenous denutrition was considerable, but it may be interrupted by temporary phases of nitrogenous retention. From the view-point of practice these data must be taken into consideration in order not to make a diagnosis of diabetes without denutrition by discovering a positive N balance when all the other symptoms (the origin of the glycosuria and acidosis) show that the case is one of diabetes with denutrition.

If now we estimate the average of the daily loss of N, it will be found it reached 1·30 grammes, which means that during the five months the patient was under observation she lost 204 grammes of N, corresponding to 1,275 grammes of albumin and 6,375 grammes of muscle. Now, at the beginning the patient's weight was 27 kilogrammes; hence she had about 11 kilogrammes of muscle. Therefore she must have lost more than one-half of the weight of muscle. Although this calculation is but approximate, it nevertheless shows the importance and gravity of nitrogenous denutrition in diabetics.

III. The Intermediary Forms of Diabetes and the Evolution of Diabetes.

Diabetes without and diabetes with nitrogenous denutrition do not represent, as might be assumed from the typical examples that have been given, two distinct forms of diabetes having no connection with one another. In reality, they simply represent different degrees of the disease.

What proves this statement is that between the two extremes intermediary forms exist, which if followed from their onset will show a transition from the first to the second form. It is not always possible at the first examination of the patient to at once definitely classify the diabetes presented.

The Intermediary Forms.—The following cases are given to illustrate these forms of diabetes:

Case VII.—Male, æt. 26 years, a son and grandson of diabetics, is himself diabetic without apparent cause. The disease began with thirst, emaciation, polyuria, and a glycosuria of 70 grammes per 1,000 c.c. Liver normal; patellar reflexes normal.

A strict diet, comprising 10 grammes of CH, caused the glycosuria to rapidly disappear, but some stigmata of acidosis appeared.

An analysis of the urine gave the following results:

Diet :

Albumin	119·58 grammes (N = 19·1).
Fats	187·0 „
CH	10·0 „

Urine :

Total amount	2,000 c.c.
Specific gravity	1027
Dry extract	109·2 grammes.
Mineral extract	22·22 „
Acidity	2·62 „
Total N	23·24 „
Urea (Yvon)	44·72 „
UN	20·56 „
Ammonia (formol)	1·22 „
Amino-acids	0·166 gramme.
Azoturic coefficient	88·5 per cent.
Coefficient $\frac{AN}{TN}$	4·5 „
Coefficient $\frac{aN}{TN}$	0·5 „
Ureogenic coefficient	4·1 „
Inorganic matter	14·6 grammes.
Glucose { Fehling	20·2 „
Glucose { Polurimeter	18·08 „
Diacetic acid	Present.
Acetone	0·64 gramme.
Urobilin	Nil.

The N balance according to the above figures is:

N ingested		19·1
N in urine	23·24	25·15
N in fæces	1·91	
Deficit		− 6·05

The body weight began to increase in about five days, and the glycosuria subsided. An analysis of the fæces was then made, which showed:

Fæces :

Total amount	35·5 grammes.
Dry extract	6·97 „
Fats	2·05 „
Total N	0·49 gramme.
CH	Nil.

A second balance N gave:

N ingested		19·1
N in urine	16·92	17·41
N in fæces	0·49	
Gain		+ 1·69

This tissue waste was replaced by a gain in N.

Alkaline treatment caused the stigmata of acidosis to disappear. The patient felt stronger and fattened. He tolerated from 35 to 40 grammes of CH without the appearance of glycosuria.

One year later the condition was the same in spite of an attack of appendicitis during the winter. There was no glycosuria with a diet comprising 60 grammes of CH. The urine contained traces of diacetic acid.

Case VIII.—Male, æt. 54 years, diabetic for ten years. At the onset, although a large eater, especially of sugar, the glycosuria was only 120 grammes, and a proper diet caused it to subside. But little by little the diabetes became worse. The glycosuria reappeared, and in spite of a reduced diet it became permanent. Besides, acetonuria developed, and there was a distinct reaction of acidosis. The results of the analyses of the urine are shown in outline in the table on p. 43.

The N and CH balances with the different diets gave:

Mixed Diet.

N ingested	19·78	CH ingested	33·5
N in fæces and urine	20·54	Glucose excreted	25·0
Deficit	− 0·76	Utilized	+ 8·5

Vegetable Diet.

N ingested	16·43	CH ingested	181·5
N excreted	15·24	Glucose excreted	29·0
Gain	+ 1·19	Utilized	+ 157·5

Cereal Diet.

N ingested	10·65	CH ingested	170·0
N excreted	10·5	Glucose excreted	24·6
Gain	+0·15	Utilized	+145·4

Milk Diet.

N ingested	18·43	CH ingested	88·0
N excreted	19·6	Glucose excreted	75·0
Deficit	−1·17	Utilized	+8·0

Alimentation.	*February 25. Mixed Diet.*	*March 7. Dry Vegetable Diet.*	*March 13. Milk Diet.*	*March 20. Oatmeal Diet.*
Albumin :				
Albumin	123·6 gr.	102·71 gr.	115·2 gr.	66·56gr.
N	19·78 „	16·43 „	18·43 „	10·65 „
Fats	—	117·5 „	139·5 „	164·7 „
CH	35·5 „	181·5 „	83·2 „	170·0 „
Urine :				
Total amount	2,175 c.c.	1,200 c.c.	2,700 c.c.	1,775 c.c.
Acidity	1·77 gr.	0·88 gr.	1·7 gr.	1·2 gr.
Total N (Kjeldahl)	18·57 „	13·6 „	17·76 „	9·44 „
Urea (Yvon)	35·47 „	26·12 „	32·67 „	16·8 „
Ammonia (formol)	0·69 „	0·53 „	0·36 „	0·56 „
Amino-acids	0·65 „	0·24 „	2·28 „	0·3 „
Azoturic coefficient	89·0%	93·0%	84·0%	81·0%
Coefficient $\frac{AN}{TN}$	3·0%	3·0%	1·6%	4·8%
Coefficient $\frac{aN}{TN}$	2·3%	1·0%	1·2%	2·2%
Glucose	2·5 gr.	29·16 gr.	74·97 gr.	24·6 gr.
Acetone	0·43 „	0·12 „	0·27 „	0·17 „
Diacetic acid	Present	Present	Little	Little

As is seen, the N balance at times showed waste, at others a fixation of albumin, but when taken altogether it was practically in equilibrium. The CH balance always showed an excretion of glucose inferior to the CH intake, but the tolerance, especially with a mixed diet, was never much. Practically, this was a case of irreducible glycosuria. The acidosis was moderate, the acetonuria not abundant, while ammonuria and amino-acids were not in excess. The azoturic coefficient was high.

Therefore this was a transitional form of diabetes, resulting from a progressive aggravation of the morbid process. At first there was only a disturbance of glycoregulation, but little by little disturbance of the nitrogenous metabolism developed.

The Evolution of Diabetes.—The following two case histories show the progressive evolution of serious diabetes and the transformation of diabetes without denutrition into diabetes with denutrition:

Case IX.—Male, æt. 33 years. Onset of diabetes in 1908 without apparent cause or hereditary antecedents. The glycosuria, which at first amounted to 85 grammes and afterwards 120 grammes, was reducible by diet during the first years of the disease. In 1911 the diabetes became worse; the glycosuria could not be controlled even by fasting, while the loss of strength continued to increase.

In May, 1911, the balance of the nutrition, calculated after three days' observation, indicated:

N ingested	20·55	
N excreted	21·39	
Deficit	− 0·84	
CH ingested	35·0	
Glucose excreted	57·7	
	− 22·7	grammes of glucose derived from albumins.

At this epoch there was no acetone or diacetic acid in the urine (see table, p. 45).

In May, 1912, the diabetes was still more aggravated. The balance after three days' observation showed:

N ingested	18·1	
N excreted	19·17	
Deficit	− 1·07	
CH ingested	110	
Glucose excreted	150	
	− 40	grammes of glucose derived from albumins.

At this time there was acidosis, a notable diaceturia, and an acetonuria of 53 centigrammes.

Alimentation.	*May* 17, 1911. *Mixed Diet.*	*May* 18, 1912. *Mixed Diet.*	*October* 17, 1912. *Mixed Diet.*	*November* 26, 1912. *Vegetable Diet.*	*February* 28, 1913. *Oatmeal Diet.*	*May* 1, 1913. *Vegetable Diet.*	*July* 21, 1913. *Mixed Diet.*
Albumin ..	128·4	113·0	109·8	70·9	95·0	—	124·64
Fat	180·0	147·0	201·8	110·88	237·7	—	242·3
Carbohydrates	35·4	110·0	35·9	123·5	193·0	107·0	33·0
Urine:							
Total amount ..	1,470 c.c.	2,200 c.c.	3,116 c.c.	3,000 c.c.	4,830 c.c.	6,100 c.c.	11,000 c.c.
Specific gravity	1024	1030	1028	1029	1030	—	1010
Acidity ..	3·15	3·32	3·64	1·74	—	4·75	13·97
Total extract ..	127·6	118·3	223·77	246·0	—	—	220·0
Mineral extract	15·72	14·43	44·8	32·7	—	—	41·8
NaCl	8·0	4·0	15·58	19·3	10·14	—	5·5
P_2O_5	4·0	2·65	4·03	2·14	2·89	—	3·3
So_4H_2	2·56	2·37	2·49	1·86	—	—	1·87
TN	19·4	18·72	12·78	15·06	10·91	17·93	17·49
Urea	28·16	34·69	19·69	22·35	—	35·0	31·46
UN	13·2	16·19	9·19	10·44	7·3	16·1	14·74
Ammonia ..	7·71	1·62	3·39	3·51	—	1·71	3·19
Amino-acids ..	—	0·17	0·5	—	—	0·62	1·1
Purines ..	0·46	0·4	0·84	0·75	1·01	—	0·77
Indican ..	Present	Weak	Very weak	—	—	—	Abundant
Organic matter	22·32	16·28	24·75	36·6	—	—	20·2
Azoturic coefficient	67·0%	86·0%	72·5%	70·0%	—	89·0%	85·0%
Coefficient $\frac{AN}{TN}$	32·0%	—	22·0%	—	—	7·7%	—
Coefficient $\frac{aN}{TN}$	—	0·7%	3·2%	—	—	2·7%	4·7%
Ureogenic coefficient	32·0%	7·5%	23·0%	21·0%	—	8·0%	15·0%
Albumin ..	Trace	—	0·9	0·66	—	Trace	Trace
Glucose (Fehling)	57·7	150·0	95·6	167·7	228·9	254·0	123·4
Glucose (polarimeter)	55·7	134·0	—	—	185·95	146·0	106·7
Acetone ..	Little	0·53	1·23	1·11	4·34	0·75	2·2
Diacetic acid (Gerhardt)	—	Medium	Strong	Intense	Intense	Intense	Intense
β-oxybutyric acid	—	—	33·04	24·78	20·5	25·84	20·68
Bile pigment ..	Trace	—	—	—	—	—	—
Urobilin ..	Trace	Trace	Trace	Present	—	Trace	Trace
Fæces:							
Total amount ..	201·0 gr.	79·0 gr.	—	—	—	—	—
Dry extract ..	31·81 ,,	12·0 ,,	—	—	—	—	—
Total N ..	1·96 ,,	0·45 ,,	—	—	—	—	—
Fats	5·9 ,,	4·0 ,,	—	—	—	—	—
CH	—	—	—	—	—	—	—
Stercobilin ..	Much	Little	—	—	—	—	—

In November, 1912, the aggravation was progressive. With a vegetable diet the balance was:

N ingested	11·3
N excreted	16·49
Deficit	− 4·89
CH ingested	123
Glucose excreted	167
	− 44 grammes of glucose derived from albumins.

In May, 1913, the condition was still worse; the patient had had an attack of coma. On a diet of milk and dried vegetables the balance was:

N ingested	17·39
N excreted	19·67
Deficit	− 2·28
CH ingested	107
Glucose excreted	254
	− 147 grammes.

This time there was considerable difference between the amount of CH ingested and that of glucose excreted. The metabolism of CH and albumins could not furnish such an amount of glucose; hence it must be supposed that the glycosuria was in part derived from fats, which indicates a profound disturbance of the mechanism of glycoregulation.

At the same time the symptoms of acidosis were considerable; there was also an abundant diaceturia and an excretion of 25·84 grammes of β-oxybutyric acid.

Briefly, when these analyses are examined, it will be seen that in the lapse of two years the diabetes had undergone a progressive and considerable aggravation. The nitrogenous denutrition, which was low in 1911, became very marked in 1913, while acidosis, which had been absent, appeared with great intensity. Finally, the disturbance of glycoregulation had reached its maximum; the glycosuria, which at the onset of the disease was a little higher than the CH ingested and derived from the metabolism of ingested albumins, at length was derived, not only from the CH and albumins of the food, but from the albumins of the body tissues and fats as well.

Case X.—Male, æt. 16 years, had been diabetic for three months. At the onset the glycosuria was 220 grammes, but under the influence of the so-called Bouchardat régime it dropped to 112 grammes. The

patient had emaciated, and presented a complete syndrome of hyperglycemia.

May 15, 1909.—The balance of nutrition estimated after three days' observation with a mixed diet showed:

N ingested	20·64
N excreted	20·19
Gain	+0·49
CH ingested	19
Glucose excreted	0
Utilized	+19 grammes.

The tolerance measured by diet tests was at least 60 grammes.

Diacetic acid	Nil.
Acetone	Large amount.
Ammonia	1·4

November, 1909.—Aggravation; tolerance fell to 20 grammes.

January, 1910.—Progressive aggravation; CH tolerance *nil*; glycosuria irreducible.

May 1, 1910.—Aggravation, emaciation. The balance of nutrition was:

N ingested	20·80
N excreted	22·52
Deficit	−1·72
CH ingested	22·2
Glucose excreted	31·56
	−9·36

The reactions of acidosis began to be manifest:

Diacetic acid	Small quantity.
Acetone	0·35
Ammonia (salts)	1·9

February, 1911.—Increase of disturbed glycoregulation.

December, 1911.—Considerable aggravation of the process; acidosis had become intense and menacing.

April, 1912.—Death in coma.

Briefly, this is the history of a diabetes that began as the type without denutrition or acidosis, with a notable tolerance for CH and a reducible glycosuria, and which later on progressively became worse, assuming the type with nitrogenous denutrition, increase of the disturbance of glycoregulation, disappearance of tolerance, and an evolution of the acidosis to death in coma.

The Disturbances of Nitrogenous Metabolism.

The cases reported place in relief the disturbances of nitrogenous metabolism of diabetes with denutrition.

I. Nitrogenous Denutrition.—Nitrogen waste is one of the most constant symptoms. Contrary to what occurs in the first class of diabetes, it will almost invariably arise when the case is followed for a sufficiently long time. It is interrupted by periods of gain in N, but taken altogether nitrogenous waste predominates.

Nitrogenous denutrition is influenced by the quantity and quality of the diet. A régime rich in albumin will occasionally oppose it, but generally the waste of N can only be controlled to a certain extent without causing it to completely subside. The two following cases testify to this statement.

1. A patient with sclerous pancreatitis and serious diabetes presented the following N balances at three different times:

Albumin Ingested.	*N Excreted.*		*N Balance.*
	Urine.	*Fæces.*	
141 grammes (N = 22·5) ..	16·05	9·8	.. − 5·35
170 „ (N = 27·2) ..	14·19	13·09	.. − 0·08
228 „ (N = 36·4) ..	15·3	21·0	.. +0·10

2. Another patient with diabetes with denutrition presented the following balances:

Albumin Ingested.	*N Excretion.*		*N Balance.*
	Urine.	*Fæces.*	
184 grammes (N = 29·4) ..	28·59	4·68	.. − 3·7
284 „ (N = 45·4) ..	43·72	2·27	.. − 0·9

The nature of the albumin utilized in the régime also has its importance. Thus, the denutrition met with in a meat diet is hindered by a dried vegetable diet, and to a lesser degree by a cereal diet.

This denutrition, the result of ruptured N equilibrium, must not be confounded with azoturia, which many writers have given as a symptom of diabetes. Azoturia, in the sense given it by Lecorché and Bouchard, is merely the result of a high ureic excretion. Now, this usually is the result of an alimentation rich in N; it can be met with when a perfect N equilibrium exists, and by no means does it imply that an

exaggerated destruction of albumin is going on. On the contrary, nitrogenous denutrition may be met with although the ureic excretion is very small; it proves that the subject consumes his muscles and becomes poor in albumin.

The first writers on this question in Germany compared the elimination of urea in diabetics and in healthy subjects submitted to the same régime. Thus, Reich, Rosenstein, Goethgens, and Frerichs found that with equal amounts of albumin ingested diabetics excreted more urea than normal subjects, and therefore came to the conclusion that tissue destruction was accelerated in the former. Others came to the same conclusion. Lusk also admitted that a fasting diabetic subject metabolizes proportionally more albumin than a normal individual. Von Mering and Wegely noted the albumin destruction and N waste in diabetics. Hesse published two cases of serious diabetes followed for a long time in which the N waste was considerable, reaching as high as 16 grammes *pro die*, although the body weight did not decrease, and this in spite of a rich diet comprising 30 to 36 grammes of N per day. Munzer and Strasser have shown that such N waste precedes diabetic coma and leads directly to its development.

But the opinion of these observers is much discussed, and others have not noted any N waste in diabetics.

Weintraud concludes from his researches that diabetics maintain their weight and N equilibrium with food rations that are not superior, and are even often inferior, to those necessary in normal subjects, upon the condition that these rations are properly composed. The N balances that he has established show that the majority of diabetics fix N, no matter to which category they belong. He believes that days of fast, by decreasing the metabolism of albumin, favour the maintenance of the N equilibrium.

Rumpf has met with N retention in serious diabetes in spite of emaciation that may reach 500 grammes *pro die*. He mentions the case of a patient who in one month fixed 210 grammes of N with a diet yielding an average of 20 grammes of N a day. Falta found that even in serious diabetes there was no N waste with a restricted régime containing little N. During fast he was unable to note a greater excretion of N than in normal subjects. Finally, in cases of serious diabetes

he found that there was N waste when an oatmeal diet was taken, but that this was quickly compensated as soon as the patient was put upon a diet rich in albumin; the N retention reached as high as 19·9 grammes a day, and took place without any change in the body weight.

In patients on oatmeal diet and during the days of egg and vegetable feeding, von Noorden often only found low N excretion, less in amount than the quantity of N derived from the food. Luthje met with a case in which in five weeks there was a retention of 395 grammes of N (11·3 grammes of N per day) in spite of an alimentation that was hardly sufficient.

Magnus Levy doubts that N waste occurs, excepting during periods of emaciation due to insufficient alimentation. He believes that subjects with serious diabetes will keep their equilibrium even with a low N intake, and he mentions a patient weighing 65 kilogrammes who maintained his equilibrium for two to three weeks with a diet containing only 60 to 65 grammes of albumin, but rich in fat. He thinks that thin diabetics energetically defend their albumin, that they economize N on a diet which would simply maintain the equilibrium of an ordinary individual, and that they repair their N waste with an energy similar to that of convalescents. In a diabetic observed during and after an attack of diabetic coma, from which recovery took place, Levy did not note any N waste. However, he admits that he has met with a case of diabetes in which there was N waste.

All these cases are rather surprising, and the observers are the first to show astonishment. Falta remarks how difficult it is to understand N retention in diabetics having lost the faculty of burning the CH, which are the principal agents for the storing up of albumin. Levy emits a doubt on the subject of those cases in which inexplicable retentions of 10 to 20 grammes of N take place per day. O. von Furth is astonished at the opinion of those who admit the maintenance of the N balance in diabetics, and refers to La Franca's researches, which show N denutrition in experimental pancreatic diabetes.

In fact, it seems to me very difficult to accept cases such as the one reported by Luthje, in which, with a hardly sufficient diet, the subject stored up 11·3 grammes of N a day; in five weeks the gain of 395 grammes of N corresponded to 2,469

grammes of albumin and to 12 kilogrammes 345 grammes of muscle. That of Falta, in which the patient in twenty-four hours retained 19·9 grammes of N, corresponding to 125 grammes of albumin and to 625 grammes of muscle, without any change in the body weight, is no less incomprehensible. One should be suspicious of extraordinary results that are occasionally obtained in experiments on the nutrition. When a close critique is made of these results, a mistake will often be discovered. In point of fact, all these researches are extremely delicate, not only requiring a very exact chemical technique, but also a strict watch over the patients, as indocile as are most diabetics.

Personally, I have not obtained N balances quite as abnormal, excepting in those cases where I was not sure of the strictness of the observation. All patients that I have been able to follow closely have given differences in + or − of the N balance, but these differences were always very narrow, and I thought it well to exclude in this book those cases which did not fulfil the conditions exacted in scientific work. In those that I have reported, the foods were invariably weighed with exactitude, and the urine and fæces collected with the greatest care. Most of the patients were intelligent, conscious of the importance of their examination, and living in a nursing-home where one was accustomed to régimes, or children closely watched by their parents. In hospital I have rarely been able to obtain exact results on account of the too numerous occupations of the personnel.

Therefore, I believe that, in spite of the contrary opinion of some German observers, the reality of a usual N waste in serious diabetes cannot at present be denied.

Benedict and Joslin have resorted to this study by a different process. They made dosage of the N in the urine of diabetics and normal individuals during fast, and made a comparative estimate of the N excretion per kilogramme of body weight and per hour. Thus in normal subjects they found an average excretion of 685 milligrammes, in mild diabetes 870 milligrammes, and in serious diabetes 960 milligrammes. Hence their researches show that diabetics metabolize proportionately more albumin than healthy subjects, and that this exaggeration of nitrogenous metabolism is all the

more marked the more serious the diabetes. Their conclusion has a similar signification to that of nitrogenous denutrition that I have observed.

II. Vitiated N Metabolism.—Various procedures bring into relief a profound disturbance of nitrogenous metabolism in diabetics with denutrition.

DIABETES WITH DENUTRITION.

Case.	*Ratio* $\frac{UN}{TN}$	*Ammonia.*	*Ratio* $\frac{AN}{TN}$	*Amino-acids.*	*Ratio* $\frac{aN}{TN}$	*Ureogenic Imperfection.*
A. d'A.	75·0% M	5·69	22·0%	—	—	—
Fer.	88·0% M	3·4	12·0%	2·6	—	12·0%
Ant.	94·0% M	4·45	21·0%	1·83	—	18·0%
Men.	—	3·83	15·0%	2·1	8·4%	—
Hut.	62·0% Y	3·85	11·4%	1·27	3·7%	15·0%
Jutt.	72·5% M	3·39	22·0%	0·5	—	23·0%
DIABETES (INTERMEDIARY FORM).						
Br.	88·5% Y	1·22	4·5%	0·16	0·5%	4·0%
Vion.	85·0% Y	0·96	4·0%	0·06	—	5·0%
Grim. ..	89·0% Y	0·69	3·0%	0·65	2·3%	3·2%
Torn 1st ..	87·0% M	1·4	6·0%	—	—	6·3%
Torn 2nd ..	87·0% M	1·9	8·0%	—	—	8·4%
DIABETES WITHOUT DENUTRITION.						
Biss.	83·5% M	—	—	—	—	—
Mal.	86·0% M	1·0	5·0%	—	—	6·2%
Mil.	86·0% Y	0·68	5·0%	0·22	1·0%	6·8%

The Azoturic Coefficient.—The coefficient $\frac{UN^*}{TN}$ is one of the formulæ most employed for studying nitrogenous metabolism. This would be the simplest and one of the surest methods were it not for the fact that all the techniques for the dosage of urea are defective. In only three cases did I find an azoturic coefficient lower than the norm (72·5 and 75 per 100); in all the other cases the coefficient was normal or

* UN = N in the urine; TN = total N.

high. In my opinion this is due to an imperfect dosage of urea. In point of fact, it is not possible that in cases in which the proportion of ammonia is high, the proportion of urea should not be low. The coefficient $\frac{UN}{TN}$ of 94 per 100, with a coefficient $\frac{AN}{TN}$ of 21 per 100, as was estimated in one of my cases, is absurd.

It should be recognized that the Mörner-Sjöqvist method, considered by most chemists, and the Germans in particular, as the most exact for the dosage of urea, gives erroneous results when applied to diabetic urine; it evidently gives the dosage of abnormal nitrogenous substances which are in excess in acidosic diabetics as well as the urea, which results in the erroneous conclusion that there is a large percentage of urea.

Henri Labbé and Vitry have also shown the defects of Mörner's technique when employed for the dosage of urea in diabetic urine. It leaves nitrogenous substances belonging to the group of undialyzable substances in solution in the urine, whose N becomes added to that of the urea. Hence I have discarded this technique, and have returned to the use of Yvon's method. With this procedure I have found the azoturic coefficient lower (62 to 76 per 100) in cases of diabetes with denutrition.

Ammonuria.—The exaggerated elimination of ammonia is appreciated by the total amount of urinary excretion and, better still, by the coefficient of $\frac{AN}{TN}$.* In the normal state the coefficient does not exceed 5 to 6 per 100, but in diabetes with denutrition it may attain considerable proportions. In one case it varied from 11·4 to 22 per 100. In the intermediary forms of diabetes—with and without denutrition—the coefficient varies, being sometimes normal, sometimes a little above the norm, and it progressively increases as the disease becomes aggravated.

Maillard's coefficient of ureogenic imperfection or coefficient of acidosis (Lanzenberg)—$\frac{AN}{AN+UN}$—is another, but less

* AN = the nitrogen of ammonia.

simple, means for estimating ammonuria; hence the disturbance of nitrogenous metabolism as well. It gives results quite the same as the coefficient $\frac{AN}{TN}$, and is invariably higher in diabetes with denutrition. Instead of the normal figures varying from 4·18 to 6·21 per 100, it reached 12 to 23 per 100 in my cases.

Amino-aciduria.—I have shown, in collaboration with Bith, that amino-aciduria increases during the evolution of diabetes with denutrition, and attains a higher degree than in any other morbid process. Instead of the normal amount of 0·05 to 0·35 gramme, the amino-acids varied from 0·50 to 2·6 grammes a day in the cases that I have reported, and I have met with still higher amounts in other instances. The coefficient of $\frac{a\,N^*}{TN}$, instead of remaining below 3·5 per 100 (which is the norm), reached 8·4 per 100 in my cases, while in others I have seen the coefficient attain 12 per 100. These data indicate a considerable disturbance of nitrogenous metabolism.

In order to appreciate the meaning of these figures, one must take alkaline treatment into account, as it notably decreases the excretion of amino-acids.

Similar results have been obtained by other observers. Von Jaksch found an increase of amino-acids; Bergall, Blumenthal, Abderhalden, and Mohr found tyrosin in quite large amounts in the urine of experimental diabetes and diabetic coma. Mohr found glycocoll in the urine of diabetics. Langstein, Rietschell, Masuda, Frey, and Satta obtained contradictory results, due, in my opinion, to the fact that these observers did not make any distinction between the types of diabetes examined.

H. Labbé and Vitry have obtained results similar to mine. In diabetics without acidosis they found the coefficient $\frac{a\,N}{TN}$ = 3·87 per 100 on an average, while in diabetes with acidosis the coefficient was 7·85 per 100.

Amino-acidemia.—Search for the amino-acids in the blood has resulted in similar findings. While in the normal state the amount of N dosed by formol is 0·10 to 0·40 per 1,000 c.c.

* aN = the nitrogen of the amino-acids.

blood-serum, I found, in collaboration with Bith, 0·90 gramme and 1·05 grammes in two cases of diabetes with denutrition and acidosis; in both these cases the coefficient of $\frac{a\,N}{TN}$ was 8·1 and 7·9 per 100, while in normal subjects it did not exceed 4 per 100.

The Residual N of the Blood-Serum.—At the same time, an increase of the residual N (TN – UN) and a drop in the azoturic coefficient (UN divided by TN) will be found in the blood-serum. In both of my cases the residual N reached 0·32 and 0·51 respectively, instead of the normal amount, which never exceeds 0·12, and the azoturic coefficient of the blood-serum was down to 36 and 24 per 100.

Hence analysis of the blood leads to the same conclusion as that of the urine. I would add that Maguin, in a case of diabetes with acidosis, found 0·27 gramme residual N and an azoturic coefficient of 20 per 100. On the other hand, J. Courmont found the azoturic coefficient normal in the blood-serum in cases of diabetes without denutrition.

Colloidal N.—By a new procedure, the dosage of colloidal N, the imperfection of nitrogenous metabolism can be demonstrated.

H. Labbé and Vitry have shown that there is an increase of undialyzable N in the urine of diabetics with denutrition and acidosis with threatening coma.

In collaboration with Dauphin, employing Salkowsky's chemical procedure, I also noted an increase of colloidal N in the urine of diabetics with denutrition; it reached the proportion of 3·29 to 7 per 100, while normally it does not exceed 1·5 per 100.

Several writers have incidentally found an increase of the colloidal N in diabetic urine, but they did not take into consideration the type of diabetes. Now, the interest is to note, as I have done, that colloidal N increases during diabetes with denutrition, while it does not in other types of diabetes, or at least very little.

The Signification of Disturbances of the Nitrogenous Metabolism.—All procedures for estimating nitrogenous metabolism show that it is profoundly disturbed in serious diabetes, while in benign diabetes it is normal.

Up to the present time most writers have attributed little importance to these disturbances. Von Noorden and M. Levy doubt that they exist. They regard the ammonuria as the consequence of splitting up of the non-carbonized fatty acids, and as a defensive action against acid intoxication. Assuredly the necessity of saturating free acids is a cause of ammonuria, but it does not appear to me to be the only one, because ammonuria may occur in hepatic lesions in cases where there is no exaggerated excretion of either diacetic or β-oxybutyric acid. Finally, in diabetics exaggerated excretion of the cetonic fatty acids that have not been carbonized, and whose principal origin is protein matter, is revealed by ammonuria, and from this very fact indicates a defective metabolism of proteins.

Magnus Levy attributes no signification to amino-aciduria occurring in diabetes, but Krauss and Umber have admitted the hypothesis of a degeneration of the tissue albumin in diabetics in which the amino-acids which usually constitute the albuminoid molecule are replaced by different amino-acids richer in N and less so in carbon. This conception may, according to these observers, explain the genesis of a greater quantity of glucose derived from metabolized albumins.

It is, in fact, possible that partial chemical changes occur in the albumins of the tissues of diabetics; these changes can account for the progressive weakness and depression of the patients. Magnus Levy objects that they are incompatible with the functions of the cellular protoplasm; but this is just what explains why, in the evolution of diabetes, when too large a proportion of protoplasmic albumin has undergone degeneration, the vital functions are no longer carried out, and hence death ensues. When one follows the evolution of a case of diabetes with denutrition, one has the impression that the patient destroys a little each day, that death is steadily approaching, and, although the subject overcomes the menace of acid intoxication with the aid of diet and other treatment, a day will come when a fatal attack of coma will occur which nothing can prevent.

The disturbances of nitrogenous metabolism are never so considerable in other morbid processes as they are in diabetes with denutrition. They in the end consist of an exaggerated

destruction of the albumins of the food and tissues of the body, as well as an abnormal elaboration of these albumins. The destruction of albumins recalls what occurs in infectious diseases, in the major intoxications, and in subjects treated with large doses of thyroid extract. The abnormal metabolism can be compared with that met with in serious lesions of the liver, but with greater intensity.

These disturbances are undoubtedly the consequence of an intoxication from some unknown substance, perhaps elaborated in the liver, which is the essential organ for the metabolism of albuminoids. But great obscurity still reigns over the mechanism of this intoxication. In many cases the liver appears to be histologically intact; hence one is compelled to admit that, in spite of the apparent anatomical integrity, the physiology may be profoundly disturbed. Thus, the liver and vascular glands, which play a part in the nutrition, no longer secrete the necessary ferments, so that both nitrogenous and carbohydrate metabolism are not carried out, or are only imperfectly executed. In place of the physiological acts necessary for maintaining life, which result in non-toxic and easily eliminated waste products, pathological acts take place which are insufficient to maintain the vital functions, and give rise to substances eminently deleterious for the cells. Therefore we are still obliged to retain this physiological conception of diabetes mellitus, although it is imperfect.

Conclusions.

The physiological interest in the disturbances of nitrogenous metabolism in cases of serious diabetes becomes more evident as times goes on. It is not merely *nitrogenous waste* that is in play, as I, with H. Labbé, showed in 1907, but there is also an *abnormal metabolism of nitrogenous substances*.

Modern researches have produced data which confirm this. I have mentioned numerous arguments that clearly show the existence of this disturbed nitrogenous metabolism. I could also base this opinion on the origin of the acetone compounds —the factors of acidosis—whose derivation from fats is known, and which also, and above all, are derived from an abnormal elaboration of protein matter. Diabetic coma itself appears to

me to be the inevitable consequence of this disturbed nitrogenous metabolism. No matter what theory one may accept to explain it, be it that of acid intoxication (Stadelmann) or intoxication from the polypeptids (Hugounenq and Morel), it is invariably an accumulation of abnormal substances derived from a vitiated metabolism of the albuminoids that is responsible for its development.

The work of the American school also tends to attribute an important signification to disturbances of nitrogenous metabolism. Macleod admits that there is an imperfect metabolism of the fats in the most serious forms of diabetes, an insufficiency of the protein metabolism in the less serious forms, and a simple insufficiency of the carbohydrate metabolism in mild diabetes.

The cases I have reported clearly demonstrate the two types of diabetes that I have endeavoured to distinguish.

1. Diabetes without denutrition, characterized by a disturbance of the carbohydrate metabolism only, without defective nitrogenous metabolism or acidosis.

2. Diabetes with denutrition, in which the disturbance of glycoregulation is combined with a vitiated nitrogenous metabolism, characterized by nitrogenous denutrition and an imperfect elaboration of nitrogenous substances, and finally acidosis.

Although I have taken nitrogenous denutrition as characteristic of the serious forms of diabetes, I am not prepared to say that the presence of hyperazoturia is sufficient for classifying a case of diabetes among the serious forms of the disease, because there are cases in which a temporary nitrogenous waste may occur that has no such signification. In order that denutrition shall possess this signification, it must not only be the result of rupture of the nitrogenous equilibrium, but other disturbances of nitrogenous metabolism must exist, as well as marked defects in the process of glycoregulation.

In reality, the existence of nitrogenous waste is not easy to place in evidence. A very close observation of the case is essential, combined with very exact dosages of the food intake and analyses of the urine. In practice one will meet with only a few patients who will lend themselves to examinations necessary for establishing a reliable nitrogenous balance. The

notion of nitrogenous denutrition, which is capital from the view-point of physiology, has not, therefore, the same importance from the view-point of everyday practice. Clinically, one must first make the diagnosis of diabetes with denutrition before the nitrogenous balance has been estimated by taking into consideration all the characters which belong to this form of diabetes.

There are cases of diabetes—and they are the most numerous—which remain confined to a disturbance of glycoregulation, while others develop nitrogenous denutrition very early in the process. One must not regard these two types as distinct morbid entities, but rather as different degrees of the same pathologic process. What proves this is the existence of intermediary forms of the disease, and the evolution of the diabetes from the first to the second type.

The prognosis is not the same in the two types. In the first, the danger only results from the accumulation of glucose in the body, ending in hyperglycemia, with its train of symptoms and possible complications. In the second, what is to be feared besides hyperglycemia is the progressive weakening resulting from nitrogenous denutrition, and especially acidosis, which sooner or later results in coma.

Treatment also is different in each type. In the form without denutrition the hyperglycemia is especially to be dealt with, the principle being the reduction of the CH intake or even of the total alimentation. In diabetes with denutrition nitrogenous waste must be compensated by a sufficient alimentation, and, on the other hand, to keep acidosis under control by feeding the patient as far as possible on vegetable albumins, which are less deleterious than animal albumins. The danger of acidosis being more redoubtable than hyperglycemia, it follows that this is the most important element in the process to combat.

CHAPTER III

GLYCEMIA IN DIABETICS*

For a long time the complicated and imperfect methods of dosage of glucose in the blood were the means of preventing the study of glycemia and its clinical aspects in relation to diabetes. Since Claude Bernard few papers on this question were published, other than those by Lépine and Baudouin. Then I. Bang introduced his method of dosage of glucose in the blood, while the discovery of a series of other procedures by Lewis and Benedict, Folin and Wie, Cammidge, and others, has favoured the development of biochemical researches, and has introduced glycemia into the domain of clinical investigation.

Since 1914 many papers on glycemia have been published, testifying to the general interest in the subject.

Before commencing our researches with our collaborators, an essay with the various methods was first carried out. Henri Labbé and F. Nepveux selected Bang's method, which they found to be the most practical and at the same time the most exact; with some changes that they have made in it, it has now become a technical procedure, unquestionably delicate, but devoid of certain causes of mistake presented by the procedures of colorimetric dosage or those requiring a large amount of blood.

In normal subjects we have noted, as others have, that glycemia examined during fasting varies between 0·80 and 1·10 per 1,000 grammes of blood. It increases after a meal, and in direct ratio with the amount of carbohydrates ingested. The increase can be produced by the ingestion of glucose. We have carried out the alimentary hyperglycemia test by giving the subject during fast 100 grammes of commercial glucose, which is equivalent to 45 grammes of pure anhydrous glucose. The glycemia at once increases, attaining its maximum in about thirty minutes; it then decreases, reaching its

* Written for the English edition.

initial percentage in from two hours and a half to three hours (see Fig. 1). From its minimum to maximum, the rise in the glycemia varies from 0·25 to 0·50 gramme, according to the case, while in some the rise is hardly appreciable. Similar results have generally been obtained by other workers, the increase of the percentage of the glycemia being in direct ratio with the amount of glucose ingested (Baudouin, Liebmann and Stern, Franck, Wacker, Mendelssohn, Jacobsen, Hopkins, Hamman and Hirschmann, Williams, Cammidge).

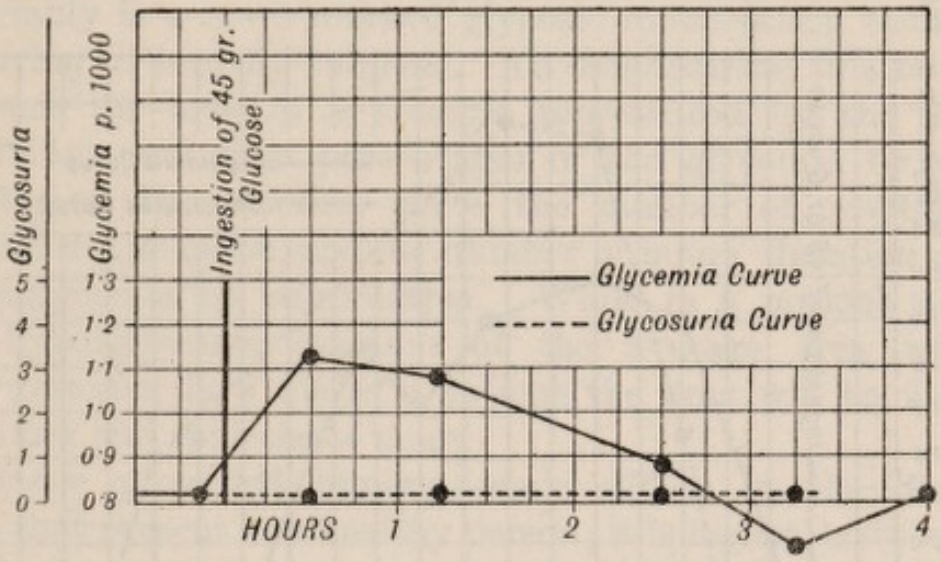

FIG. 1.—ALIMENTARY HYPERGLYCEMIA TEST IN A NORMAL SUBJECT.

————Glycemia curve.

- - - - - - - - -Glycosuria curve.

Denis, Aul, and Graham are the only writers who did not observe hyperglycemia following the ingestion of 100 grammes of glucose in healthy subjects.

In diabetics the glycemia measured during fast varies in very considerable proportions. Its percentage in general is higher than the normal; it may be as high as 1·5, 2, or even 3 grammes. Hence there is hyperglycemia.

The percentage of glycemia during fast is essentially dependent upon the gravity of the case of diabetes and the diet followed by the patient. In an untreated subject a very high percentage may be found, while in the same subject, after having followed a diet tending to reduce the carbohydrates or a fasting cure, the percentage will fall to normal.

Thus Lag after having presented a glycemia of 2·25

grammes at fast, this fell to 0·92 gramme at the end of a fasting cure of three days, while it was 0·85 gramme at the end of a second cure. The percentage of the glycemia during fasting is not enough to characterize the diabetes any more than is the search for glucose in the urine; there are diabetics with a normal glycemia at fast, just as there are diabetics who have no glycosuria.

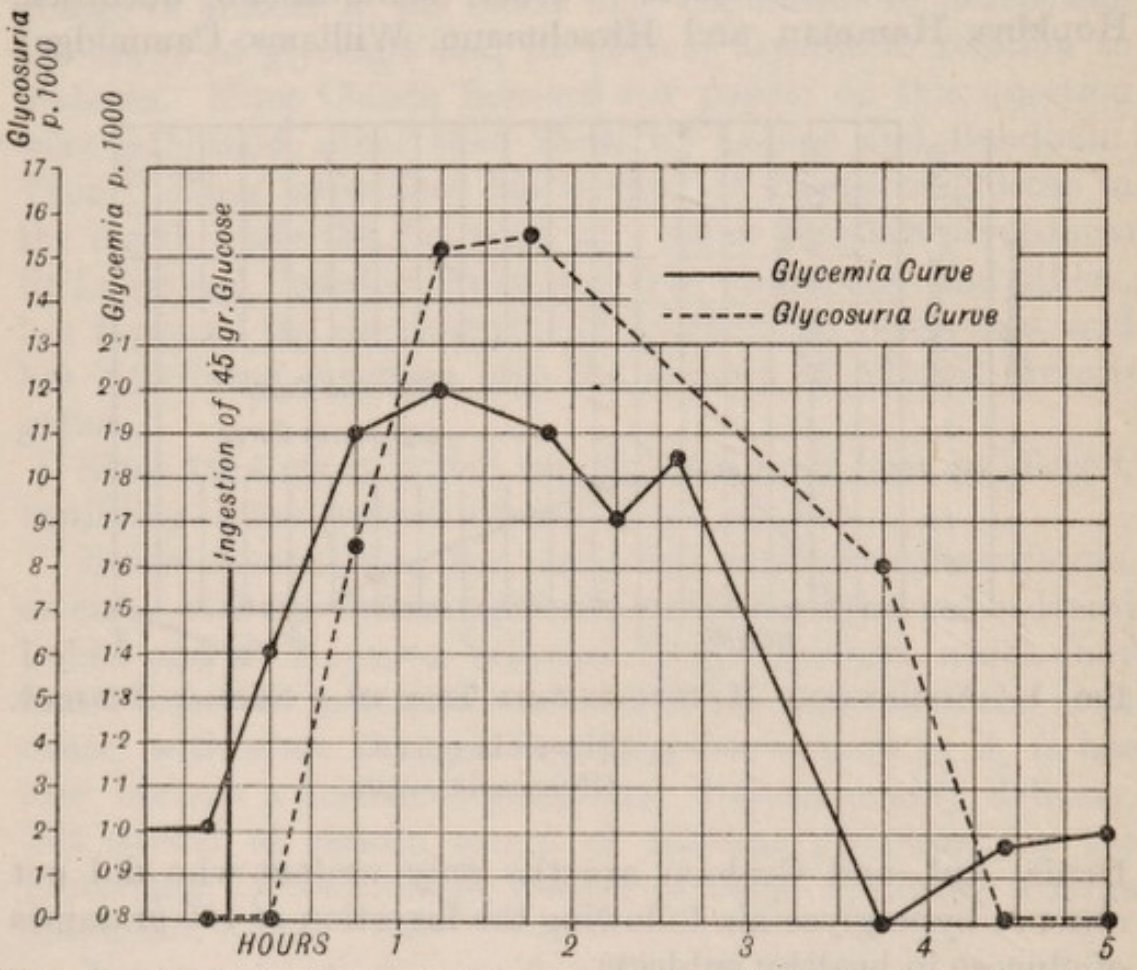

FIG. 2.—ALIMENTARY HYPERGLYCEMIA TEST IN A DIABETIC SUBJECT.

——————Glycemia curve.
- - - - - - - - - - Glycosuria curve.

After a meal, the glycemia is higher in a diabetic than in a normal subject. If the alimentary hyperglycemia test with glucose be made, following the procedure indicated above, the resulting curve will present the same shape as in a normal subject, but it will differ from the latter in its height and protraction (see Fig. 2). The glycemia reaches its maximum in a lapse of time varying from forty-five minutes to three and a half hours; it reaches the initial percentage in from two

to four hours. The total duration of the induced hyperglycemia is from five to seven hours. The height of the glycemia above the initial percentage offers an average of 1 to 1·5 grammes, but varies from 0·50 to 2 grammes. Occasionally the maximum is rather high; we have seen it measure from 2·28 to 4·20 grammes.

The Reaction following the Ingestion of Glucose.—Sometimes there is, above all, a marked hyperglycemia; at others the hyperglycemia is moderate, but the reaction is protracted and the return to the initial glycemia percentage is slow; there invariably is a more marked glycosic mobilization than that occurring in healthy subjects. To demonstrate this fact, we measure the area of a triangle represented by the initial, maximum, and final percentages of the glycemia by representing on the reaction curve the number of grammes of glucose in the blood, and the number of hours' duration of the hyperglycemia by centimetres. While in a normal subject the hyperglycemic reaction of the average area will be 0·45 gramme, in a diabetic patient the area will be 3 cubic grammes and sometimes more.

Hence provoked hyperglycemia differs in the diabetic from that present in a healthy person; it is higher, lasts longer, and is slower to reach its maximum, while its area is far more considerable. In this respect our observations agree with those of Baudouin, Bang, Jacobsen, Hamman and Hirschmann, Williams and Cammidge.

The induced hyperglycemia test in diabetic patients presents quite characteristic features, so that it can be utilized for the diagnosis of diabetes. Gilbert and Baudouin regarded it as a hæmatological sign of a diabetic process. It can serve to detect a concealed or latent diabetes, or one that is obscured by diet and in which the glycosuria has disappeared.

Some American physicians have resorted to its use for detecting disturbances of glycoregulation in diseases following lesions of the endocrinic glands. In the future this test may be employed for the detection of disturbances of glycoregulation in numerous pathologic conditions in which they may arise, as in affections of the liver, nervous system, pancreas, and vascular glands (the thyroid, hypophysis, and suprarenals especially), and, lastly, in infectious diseases.

The first question that occurs to one's mind is to ascertain if a relationship exists between the percentage of glycemia and glycosuria. We are working with the idea that the intensity of the glycosuria is in direct ratio with that of the glycemia present; severe glycosurias have been met with in diabetics with severe glycemia, while mild glycosurias have been encountered in patients with a low degree of glycemia. All this is quite true when facts are considered collectively, and we could mention a series of figures which could demonstrate this; but when the details of the cases are gone into this concordance becomes less clear. Thus, of three patients having the same degree of glycemia (1·77 grammes), one had a glycosuria of 2·51 grammes per 1,000; the second, 18·90 per 1,000; while in the third it was 30·16 per 1,000. One patient with a glycemia of 1·56 grammes, and later with 1·55 grammes per 1,000, presented a glycosuria of 4·41 grammes, and later 2·11 grammes, per 1,000. Another with a glycemia of 4·54 grammes per 1,000 at first presented a glycosuria of 94 grammes per 1,000, while at a later date with a glycemia of 2·95 he presented a glycosuria of 171 per 1,000. It is enough to mention these figures to show that no mathematical relationship can be established between the concentration of glucose in the blood and that in the urine. No formula will permit one to estimate a glycosuria corresponding to a given glycemia.

The same incertitude occurs when an attempt is made to determine the glucose concentration in the blood which will give rise to the appearance of the glycosuria—that is to say, what is generally termed the *glucose limit*.

Claude Bernard formerly admitted that glucose began to enter the urine when its percentage reached about 3 per 1,000 in the blood. During the past few years it has been shown that this estimate was too high. Jacobsen gave 100 grammes of glucose to healthy subjects, and noted that glycosuria appeared with a glycemia varying from 1·60 to 1·70 per 1,000. Hamman and Hirschmann put the glucose limit for the appearance and disappearance of the glycosuria between 1·70 and 1·80 grammes per 1,000. Knud Faber, who has determined the time at which the glycosuria ceases in diabetics undergoing a fast cure, estimates the average glucose limit at 1·40 to 1·70

per 1,000 grammes. He believes that the limit is constant in the same subject examined at intervals of several months.

On the contrary, Bailey believes that the glucose limit varies according to the subject, and gives figures which range from 1·25 grammes in cases of mild diabetes to 3 grammes in diabetes complicated with nephritis. Williams puts it between 1·5 and 2·5 grammes per 1,000, and believes that it increases with the gravity of the diabetes. Goto and Kuno, and Cammidge do not admit the constancy of the glucose limit.

Rathery and Gruat have attempted to determine the glucose limit in diabetes by resorting to Ambard's formula, and have come to the conclusion that it varies from one subject to another, and that it varies at different times in the same subject; neither did they find any relationship between an excess of the glycemia and the intensity of the glycosuria. Unfortunately the use of a theoretical formula whose physiological value has never been demonstrated renders these results difficult of interpretation.

What makes the glucose limit very difficult to appreciate is the existence of minimum glycosurias, in which the percentage of sugar is so small that a dosage cannot be made, and still appear to correspond with the first passage of sugar into the urine, and upon which one is at first tempted to base one's results. Working along these lines, we found that the glucose limit varied from 0·90 to 2·10 grammes, while the same patient offered the percentages of 0·90, 1·13, and 1·81 grammes. There are subjects who eliminate, with very varied glycemia percentages, an excess of reduction substances for a long time without presenting a glycosuria of sufficient amount to be estimated. We believe that these minimum glycosurias need not be taken into account, as they are only exaggerations of normal glycosuria, and thus a pathological glycosuria exists only when the percentage of sugar in the urine can be estimated by the usual well-known procedures.

In a certain number of patients we have estimated the percentage of glycemia corresponding to the apparition and disappearance of the glycosuria during the alimentary hyperglycemia test, and found that the appearance of the glycosuria in the phase of ascending hyperglycemia corresponds to a glycemic rate varying between 1·33 and 2·67 grammes per 1,000;

while in the phase of descending hyperglycemia, the disappearance of the glycosuria corresponds to the rate of 1·22 to 2·01 grammes per 1,000. Hence, nothing is less fixed than the glucose limit. Not only does it vary from one individual to another within the lapse of a few days, but the difference is notable. In one of our diabetics the first time the limit of the appearance and disappearance of the glycosuria was respectively 1·67 and 1·33 grammes, while four days later it was 1·33 and 1·20 grammes. The only constant finding was the difference between the limit of appearance and disappearance of the glycosuria, the limit of appearance always being higher than that of disappearance. Hamman and Hirschmann already observed this fact, although they could offer no explanation of it. Perhaps there may be a kind impulse imparted to the kidney for glucose filtration. This would explain why, in a cure of reduced carbohydrate intake in diabetics, one frequently notes that the glycosuria after a rapid drop persists for a very long time at a very low percentage before completely disappearing.

Liebmann and Stern and others have admitted that the limit generally increases the older the diabetes; a certain number of writers accept this opinion. Williams maintains that the increase of the glucose limit is bad from the viewpoint of prognosis, that it indicates a severe diabetes or one that has become complicated, especially by arterial hypertension. Bailey also believes that this limit is particularly high in diabetes complicated by nephritis. On the contrary, other observers hold that the glucose limit does not increase with the duration of the disease. In fact, it is probable that it is not the age of the diabetes that causes the increase of the limit, but rather renal impermeability to glucose resulting from a nephritis complicating the diabetes. Now, since it is usually instances of moderate diabetes with a slow evolution that become complicated with Bright's disease, while severe cases with a rapid evolution are not associated with a nephritis, it can readily be conceived that at an advanced phase in cases of long-standing diabetes the glucose limit should be high.

Nevertheless, this uncertainty surrounding the glucose limit should teach us that this notion need not be taken into

consideration for establishing the prognosis of diabetes, as some writers would have us believe.

The study of glycemia has resulted in a certain number of interesting notions in respect to both the physiology and treatment of diabetes.

To control the results of a given diet, it is at present not enough to merely watch the glycosuria. The glycemia must likewise be measured, as it gives more perfect data of the results obtained. When, following a cure by reduction of carbohydrates, the glycosuria has ceased to exist, it is not at all certain that the desired result of this treatment has been completely obtained, and if a dosage of the glycemia is made it will, in fact, be quite possible that it will be found above the normal. This indicates that the treatment must be pushed still further, and if a fasting cure be carried out the glycemia will drop to the normal standard. Likewise, when the patient is being fed after a fasting cure, it is the rise in the glycemia that should be a warning before the glycosuria appears, showing that the carbohydrate tolerance has been exceeded.

Neither the percentage of glycemia nor glycosuria taken by itself is enough to indicate the gravity of a case of diabetes; it varies with the phases of the disease and the diet followed. One may meet with cases of mild diabetes with severe glycemia or serious diabetes with a mild glycemia. What is of interest to us is the fall in the glycemia under the influence of a reduced diet; in the mild cases the glycemia easily returns to the normal, while in the serious cases the glycemia is with difficulty reduced, and even in cures of fasting its drop only will be temporary. The ease with which a drop in the glycemia takes place, as well as the ready disappearance of the glycosuria, are favourable signs.

The induced hyperglycemia test, which renders great help in the detection of a latent diabetes or revealing disturbances of glycoregulation in various pathological states, only gives mediocre indications as to the gravity of a given case of diabetes. Undoubtedly, the area of the hyperglycemia curve usually increases with the intensity of the glycoregulating disturbance, but there does not seem to exist an exact relationship between the degree of the reaction and the intensity of the diabetes.

On the other hand, a search for the glucose limit is of utmost importance, as it will reveal a renal diabetes, thus separating it from a true diabetes dependent upon a glycoregulator disturbance whose consequences are sometimes serious, although, taken by itself, this physiological disturbance offers no gravity whatsoever.

Search for the glucose limit will show that, besides kidneys fairly permeable to glucose, there are kidneys which are permeable to exaggeration, as well as insufficiently permeable kidneys. The first allow the glucose of the blood to pass even when the glycemia is low or when it has dropped below the normal percentage from a fasting cure. This permanent glycosuria with a normal glycemia has been improperly called "renal diabetes." In the second condition the kidneys do not allow the glucose of the blood to pass even when the glycemia is high. These are kidneys with lesions of chronic nephritis, and hence can be explained why the glycosuria of certain diabetics simultaneously the subjects of Bright's disease remains low or intermittent, regardless of a syndrome of manifest hyperglycemia.

CHAPTER IV

THE DIAGNOSIS AND PROGNOSIS OF DIABETES MELLITUS

Diabetes is such a common affection, and so fertile in complications of all kinds, that the clinician should always be upon the look-out for it in order that it may not escape detection.

When diabetes reveals itself by its *cardinal symptoms*, the diagnosis is generally easy to make. The patient will consult the physician for frequent desire to micturate, which is annoying, especially in women. The pollakiuria corresponds to a polyuria which will be discovered by measuring the twenty-four-hour urine. An intense thirst torments the diabetic, obliging him to drink incessantly, but he usually will refer less to the polydipsia than to the polyuria. Often a diabetes will at the onset be detected by a rapid loss of strength, an unusual lassitude, a feeling of stiffness of the back and limbs, or rapid emaciation. These symptoms are principally marked in serious diabetes with denutrition; on the contrary, in mild diabetes without denutrition the onset may be accompanied by fattening.

In some exceptional cases the patient will call attention to certain *unusual signs*, such as heavy white spots soiling the clothes or linen, or in summer the patient may notice that flies collect around the vessel containing the urine. But one must not rely on these data for making the diagnosis of diabetes.

In reality each of the elements composing the syndrome of hyperglycistia is to be interpreted and discussed; if taken singly, they have nothing characteristic. They should, above all, raise the suspicion of a possible diabetes, and incite the physician to search for the one great symptom—glycosuria.

At its onset diabetes will frequently be overlooked, and is only discovered when some *complication* arises. Some specialist —ophthalmologist, dentist, dermatologist—will stumble on to the diagnosis.

It often happens that the first indication of diabetes is a whitlow or a wound which is slow to heal, recurring furunculosis, a carbuncle, a senile gangrene which develops into the moist variety, or a perforating ulcer of the foot. Hence there is the rule from which there is no exception—namely, that in all cases of suppurating processes the urine should be systematically examined, from furunculosis to gangrene.

Often also the diagnosis of diabetes is made upon the occasion of a neuritis or neuralgia rebellious to treatment. There are cases of intercostal, facial, or sciatic neuralgia which resist every sort of treatment, but rapidly subside when a glycosuria has been found and a suitable diet ordered, especially a reduced carbohydrate régime.

Oculists often have opportunities to discover diabetes; a rapidly developing cataract in a young subject, a retinitis not due to Bright's disease, an unaccounted-for ocular paralysis, or progressive amblyopia without lesion of the fundus oculi, sometimes due to disturbances of accommodation, lead to the diagnosis of diabetes.

The dentist discovers diabetes when he finds an expulsive gingivitis, or receding gums, resulting in the loss of perfectly sound teeth.

Certain persistent intertrigos, eczemas, or vulvar pruritus result in the recognition of their true cause—diabetes.

Sometimes the patient consults the physician on account of sexual impotency or for a persistent balanitis.

These examples are enough to show why every physician should invariably have diabetes in mind and be ready to detect it.

In children, although rare, the diagnosis is not so easy. Diabetes is not so apt to be thought of, and in many cases the diagnosis is delayed for weeks. Hence, when a child loses strength and rapidly emaciates, although the appetite may be excellent, diabetes should be suspected if there are no lesions in the various viscera that may account for the progressive cachexia. It is to be especially suspected when the child is exceptionally thirsty with a polyuria, or when, in spite of the advanced age of the young subject, he has incontinence of urine.

Finally, it is far from exceptional for diabetes to be dis-

covered when an apparently healthy subject applies for life assurance.

The conclusion derived from these data is that a patient should invariably be examined from top to toe, and should never be allowed to leave the consulting-room until a specimen of his urine has been obtained, and examined for albumin, glucose, and bile pigment. A systematic analysis of the urine is a guarantee against mistakes in diagnosis.

Sometimes it may not be a question of the diagnosis of diabetes, but rather to resist making this diagnosis in *cases of simulation*. Usually all that the individual will do is to put some ordinary sugar in the urine, and since saccharosis does not reduce Fehling's reagent, diabetes is easy to exclude. When a more artful person has added glucose to his urine, there is only one means of detecting the fraud, and that is to have the urine voided by the subject in the presence of the physician and then immediately examine it.

Glycosuria having been found, it remains to decide whether or not it is *a diabetic glycosuria*. The distinction depends upon the definition of diabetes, which is the clinical expression of *a persistent disturbance of glycoregulation*. Glycosuria in itself is merely a contingent symptom of diabetes; even if the glycoregulator disturbance remains constant, it may, according to the diet, appear or disappear. Hence one can take as a basis for the diagnosis of diabetes the persistence of disturbed glycoregulation, and not the persistency of the glycosuria. Now, the former has this property of causing glycosuria to recur every time that the same conditions obtain.

Take, for example, a glycosuria developing after a severe mental strain: it lasts for twenty-four hours, and then disappears. The disturbance of glycoregulation was temporary and the glycosuria was not diabetic. On the other hand, take a glycosuria appearing after an excess at table in an obese subject and large eater: it lasts for a day and then subsides, but it will again recur in a few days if the excess in eating is repeated. Here, then, there is a persistent disturbance of glycoregulation, and although intermittent, the glycosuria is certainly diabetic in nature.

However, one should also take into consideration the degree of the disturbance of glycoregulation. If it is so trifling that,

practically speaking, no glycosuria develops, it will be impossible to say whether this is or is not diabetic, because never, even with a diet rich in carbohydrates, will one be able to set up hyperglycistia and its symptoms. This is the case of certain glycosurias related to hepatic cirrhosis, in which the disturbance of glycoregulation is so slight that in order to detect it the special test of alimentary glycosuria must be resorted to. In these circumstances the condition cannot be regarded as diabetes.

Consequently, the physician must not mince matters with the patient. It often happens that after an examination of a diabetic the family will ask to hide the true nature of his affection from him in order that he may not be frightened, and to tell him he has glycosuria, but not diabetes. I do not think that this is a good system. For diabetics, as for tuberculous patients, it is better, when the process is curable, to warn the patient and make it understood that his salvation depends upon his goodwill. This is the only means we possess to make a diabetic submit to suitable diet.

The prognosis of a diabetes depends upon a certain number of conditions. The most important is the *degree of the disturbance of glycoregulation*. The gravity of the case is in direct relation to this disturbance.

To estimate it, it is not enough to ascertain the percentage of glucose per 1,000 c.c. of urine, as is often supposed; it is even not enough to ascertain the total elimination of glucose in twenty-four hours, because in all types of diabetes the amount eliminated depends upon the diet followed by the patient. Patients with serious diabetes submitted to a strict diet may eliminate less than 100 grammes of glucose in twenty-four hours, while subjects with a moderate diabetes who indulge excessively in carbohydrates may present a glycosuria of 400 to 500 grammes.

The degree of the disturbance of glycoregulation is estimated by comparing the diet and the glycosuria. It is estimated by the figures expressed by the tolerance of the patient for carbohydrates. The apparent tolerance can be measured by comparing the amount of carbohydrates ingested and the amount of the glycosuria. Thus, a diabetic on a diet containing 200 grammes of carbohydrates who eliminates

60 grammes of glucose has an apparent tolerance of 140 grammes. Another individual who, with the same carbohydrate intake, eliminates 250 grammes of glucose has no tolerance, and appears to manufacture his glycosuria not only from the carbohydrates in the food, but at the expense of the albumins and fats contained in the food and body tissues as well.

Unfortunately, the figures thus obtained, although giving useful data, do not express the real tolerance of the patient; these are only exact when the subject has been following a constant diet for quite a time. Let us suppose that a diabetic who has followed a diet containing 500 grammes of carbohydrates for some time presents a glycosuria of 300 grammes in twenty-four hours. Put him on a diet containing 200 grammes of carbohydrates: the glycosuria will drop to 250 or 300 grammes on the first day, and afterwards will progressively diminish. But at the beginning of the new régime he will eliminate more glucose than the total amount of carbohydrates ingested, thus leading one to suppose that there is diabetes with denutrition.

In order to estimate the true tolerance, the régime must be progressively reduced until the glycosuria has ceased, and then is to be slowly increased until the glycosuria reappears. After a series of clinical tentatives one will at length be able to exactly measure the amount of carbohydrates that the organism will be able to consume. This calculation is very necessary, in order to appreciate the gravity of the diabetes and to direct the suitable régime.

In order to decide upon the *nature of the diabetes*, it is essential to calculate the nitrogen balance. This is done by calculating the quantity of albumin—that is to say, the N ingested—and then comparing it with the amount of N eliminated in the urine and fæces. One can thus ascertain whether the nitrogenous equilibrium is respected or destroyed —that is to say, whether there is or is not denutrition. The latter is benign with a long survival, the former invariably serious.

Search for *acidosis* is very important, because its existence, when marked, is a menace of diabetic coma and danger of death, hence necessitating dietetic precautions and special

treatment. Acid intoxication is revealed by dosage of the acetonuria with Gerhardt's reaction and the dosage of ammonia, whose proportion in the urine is in direct ratio with the amount of β-oxybutyric acid eliminated.

The degree of the disturbance of glycoregulation is not the only point to be considered. The *cause of the diabetes* is highly important for the prognosis. Thus it is known that traumatic diabetes, when not accompanied by irreparable lesions of the nervous system, is often curable. Among the diabetes due to a lesion of the pancreas there is one which, although causing a very trifling disturbance of glycoregulation and a mild glycosuria, is very serious on account of the cause—namely, cancer.

Age is useful for the prognosis. While diabetes of adults may offer very variable degrees of gravity, although the majority of cases are happily benign, a diabetes occurring in a child or young adult is invariably very serious.

Certain complications considerably aggravate diabetes. Such is pulmonary tuberculosis, which from the day of its onset usually means death in the near future. Suppurative processes are always serious in diabetic subjects.

The social position of diabetics plays a part in the prognosis. Poor people who cannot take care of themselves and are obliged to come to hospital frequently die of tuberculosis. On the contrary, the well-to-do can greatly prolong their lease of life if they will strictly follow a suitable régime. Thus, of a total of 141 cases of diabetes in poor people, Naunyn found that only 22 lived over five years. These statistics are particularly unfavourable, but this is not always the case. Croner of Vienna, out of a total of 119 cases met with in hospital practice, found that 36 per cent. lived over five years, 12 per cent. lived more than ten years, and 3 per cent. lived over twenty years. Even in hospital practice, when suitable advice is given to diabetic patients, and when they are made to understand the necessity of diet, very good results are obtained, and their lives are prolonged many years.

Is diabetes *curable?* Some writers say yes, but the majority of observers who have made a special study of the subject are of contrary opinion. Assuredly, the great majority of diabetics offered as cured, are not; the diet has caused the

syndrome of hyperglycistia to disappear, but the disturbance of glycoregulation nevertheless persists, and the subject is only well upon the condition that he does not consider himself cured and continues to follow diet. Nevertheless, there are some cases of acute diabetes following trauma or an infection which unquestionably recover, and I have published some instances.

The duration of life of a diabetic is difficult to foresee, because it depends upon numerous contingencies. However, by taking into consideration the patient's age and the nature of the diabetes, a prognosis can be made. Certain very serious cases of traumatic diabetes, or diabetes complicated by acidosis or tuberculosis, do not survive more than a few weeks or months. Cases of serious diabetes, such as those met with in children, last on an average for two to three years. Mild diabetes—and this represents the majority of cases—may permit a survival of twenty years or more. Some cases of diabetes are more an infirmity than a real disease.

These data pertaining to the prognosis of diabetes are utilized by assurance companies, who formerly refused to assure subjects with glycosuria. The subject is rejected when under 35 years of age, and all diabetics with denutrition, no matter what may be their age. On the other hand, nervous or post-traumatic diabetes can be accepted if after an adjournment of six months recovery can be proved. Obese diabetics over 35 years of age, and whose viscera appear to be normal, can be accepted, but with an increased premium.

Patients and physicians must not forget the fact that in diabetes the prognosis much depends upon the *care* taken. When treatment is not suitable the patient will die, while with proper diet and well-directed treatment the survival amounts to many years. Treatment is almost entirely dietetic; drugs have little use.

CHAPTER V

POLYPHAGIA AND PHAGOMANIA IN DIABETES

POLYPHAGIA, which is an almost constant symptom in diabetes, assumes very different proportions. Most commonly it is a mere exaggeration of the appetite, but it may assume a real passion, a pathologic mania.

Four types exist, which I shall endeavour to delineate by examples and to demonstrate their signification:

1. *Compensation polyphagia*, a physiological phenomenon.
2. *Polyphagia from prejudice*, resulting from the patient's misunderstanding of the situation.
3. *Habitual polyphagia*, not exceeding the physiological limits, but which, from excess, may become pathogenic.
4. *Phagomania*, a pathological phenomenon, entering into the class of mental disturbances.

(*a*) **Compensation Polyphagia.**—The mechanism of this type is easy to understand.

Take, for example, an individual who maintains his organic equilibrium with a mixed diet equivalent to 2,400 calories. This individual becomes diabetic and incapable of utilizing the lightest trace of carbohydrates; from this time on his régime, which ordinarily contained carbohydrates furnishing one-half of energy, becomes insufficient, as in his case it only represents 1,200 calories. This insufficiency is made evident by the need of consuming a greater quantity of food, and by compensation this diabetic becomes polyphagous.

For that matter, the polyphagia is often insufficient for compensating the defective utilization resulting from the glyco-regulator disturbance, and this is why diabetics often emaciate at the onset of their disease. When the patient is taught how to select his aliments among those that a diabetic is capable of utilizing, the emaciation usually ceases, so that polyphagia becomes useless.

(*b*) **Polyphagia from Prejudice.**—There is still a belief in the public mind, and even among physicians, that the alimentary needs of diabetic patients are greater than in other individuals, and that there is danger to allow them to emaciate.

This prejudice, that with Linossier, Lemoine, and Maurel I have endeavoured to disperse, is one of the causes of suralimentation of diabetics, and which is often ordered by the physician. What has already been said of the alimentary needs of diabetics reveals the origin of this prejudice, and shows that with a well-combined diet polyphagia becomes unnecessary.

(*c*) **Habitual Polyphagia.**—Diabetes without denutrition often develops in obese subjects who have for a long time been large eaters. And be it understood the diabetes does not decrease their appetite; they remain polyphagous both before and after the development of their affection. In this case the polyphagia preceded the diabetes, hence it is not the consequence, and one may very well question if it may not even be the origin of the morbid process, because it would seem as if habitual suralimentation may, like obesity, be one of the causes of diabetes.

(*d*) **Phagomania.**—There are cases in which polyphagia far exceeds the habitual suralimentation of large eaters, and which from its clinical physiognomy presents a pathologic character which allies it to impulses observed in the major neuropathies. To show its analogy with dipsomania and morphinomania, I have designated it by the name of *phagomania* or *oreximania*. A few case histories will suffice to illustrate its characters.

Case I.—Female, æt. 53 years, a nurse by profession. Has always been a large eater, becoming obese early in life, and attained the weight of 110 kilogrammes. Finally, for several years she has had diabetes without denutrition, made evident by intense thirst and a glycosuria of 100 grammes *pro die*, continual lassitude, and a gingivitis with loss of teeth.

In spite of these miseries, and although being perfectly aware of their cause, she is incapable of following a régime. She will not give up bread, and consumes numerous pieces of sugar. During the night while on duty she sucks sugar and drinks highly sugared coffee.

This irresistible passion for ternary foodstuffs—a true amylomania and saccharomania—is accompanied by a very accentuated neuro-

pathic state. She relates how she has had the most extraordinary disease, and upon several occasions she has developed nervous paroxysms beginning with a violent pain in the head like the driving-in of a nail and accompanied by an impossibility to speak, although she retains the notion of what is taking place about her. All her stories are stamped with evident exaggeration.

Her family antecedents are very loaded from the neuropathic standpoint. She says that her mother was neurotic, and that five brothers and sisters are also neuropathic. Finally, her son is very nervous and had convulsions in childhood.

Case II.—A very intelligent woman, although mentally somewhat unbalanced, imaginative, and mythicist, and afflicted with obesity and diabetes, incessantly requested me to prescribe a régime, which she said she would follow with the utmost strictness. The patient had put scales in her room and inscribed in a little book the weight of the foods consumed. In spite of the reduction of the carbohydrates, I was surprised that the glycosuria did not decrease, when in great secret the cook told me that the weights inscribed by the patient with such care in her notebook were all false ! Evidently the poor woman had devised this régime comedy in order to retain her physician's attention.

Tricksters of this kind, who recall things observed in morphinomania, are not rare. I met with a similar case in an obese patient whose illogicality revealed the pathologic character.

Case III.—A young woman was admitted to hospital to undergo treatment for obesity. During the first few days she rapidly emaciated, and then her weight remained stationary, although she pretended that she ate nothing but the reduced diet ordered her. She even affirmed that she vomited part of her meals. She was then watched, and it was found that she passed much time in the w.c. in order to eat food on the sly that she had purchased outside the hospital. These hurried repasts, being undigested, were the cause of the vomiting.

The following is a case with a more accentuated pathological character:

Case IV.—Female, æt. 35 years, with diabetes without denutrition. Glycosuria of more than 600 grammes *pro die*. This large amount was due to the fact that the patient consumed an enormous quantity of soup and bread. She refused to follow a diet, complained constantly of hunger and thirst, drank 8 to 10 litres of fluid a day, and gorged herself with all sorts of food that she pilfered by persuasion or by force from other patients in the ward.

In order to observe her carefully, she was put in a room by herself, and then, since she could only consume the food ordered, the glycosuria immediately fell to an average of 133 grammes a day. It was then noted that she developed the habit of rumination, and when meal-

time came—which she impatiently awaited—she would throw herself with voracity on the meat, tearing it into long bands of more than 5 centimetres, and swallowing them without masticating. In the intervals between meals the meat came back into the mouth by the phenomenon of mericism, and it was then that she slowly chewed them and finally swallowed them.

At a hospital at Orleans where she had been previously treated the same phenomena had been noted; indocile to all treatment, she pilfered the food of the other patients, and even went to the garbage pails in search for more.

This phagomania was accompanied by a manifestly pathologic mental state. The intelligence was only slightly developed, although the patient could read and write. She never presented any attacks of hysteria, although she had violent paroxysms of crying. She also showed a great propension to exaggerate and to mythomania.

Case V.—Male, æt. 42 years, with diabetes without denutrition, who nevertheless had a glycosuria of about 1,000 grammes per day, due to the large amount of food ingested.

He never was satisfied, and although allowed an abundant diet, the patient pilfered the food of the other patients and finished what remained on their plates after meals. At about meal-time he would rush out of the ward to steal bread, meat, and vegetables on the food-trays. He even went to the kitchen to obtain food, and his fear that he might be wanting in provender was so great that he hid it in various places. Thus 3 pounds of bread were discovered underneath a trap-door in the ward.

He could not be reasoned with, and no menace would stop him. The patient's intelligence was mediocre; he was crafty, and when questioned would only reply that he was unable to stop eating.

No treatment whatsoever—bromides, valerian, antipyrine, or douches—had any effect on the phagomania. The patient soon died in an attack of acidosis.

Such cases demonstrate the neuropathic nature of phagomania. Not only is the polyphagia extraordinarily excessive and in no way in proportion with the physiological requirements of the patient, but it has the character of an irresistible impulse that nothing can control. Only forcible measures can stop it.

It is a true fixed idea implanted in the brain of an individual, and annihilates all others; the thought of these patients is entirely dominated by the desire for food, which they attempt to procure at any cost, and their life is oriented around this one desire. From the repetition of these psychical impressions a *mental pseudo-hunger* (Déjerine) ensues.

The will is powerless to overcome this passion. The obese

or diabetic subject may recognize the necessity of undergoing a diet, and may *desire* to submit to one, but they are *unable* to do so, and this explains the inconsequence of their actions. The patient with phagomania is in respect to food the same as a dipsomaniac or a morphinomaniac in respect to alcohol or morphine; his passion is stronger than his will, and he can only be cured by isolation and a diet imposed by force.

Phagomania is occasionally accompanied by perversion of the taste. Certain patients will even eat garbage in order to satisfy their morbid hunger. In other cases phagomania is accompanied by abnormal habits, such as mericism.

These patients almost always reveal nervous or mental disturbances or stigmata of degeneration, hence they are to be looked upon as true mental cases. Some have nervous paroxysms or complete or incomplete hysterical crises. Others are liars, crafty, and inventors of false stories, like mythomaniacs. The intelligence is frequently obtuse, and there is often a marked neuropathic heredity.

All these characters should cause phagomania of diabetics to be included in the same class as dipsomania, erotomania, and the like.

Phagomania does not belong only to diabetics; it is met with in obese subjects and in certain cases of polyuria which are related especially to dipsomania. It occasionally happens that excessive polyphagia will reveal a very slight glycoregulator disturbance, and the polyuria of these subjects is accompanied by a mild glycosuria. Phagomania also occurs in many confirmed mental diseases, although no diabetes is present. It has been studied by Mathieu and Soupault, who classify it among the psychoneuroses. They refer to the case of a man who died of indigestion, who consumed an 8-pound loaf of bread after having partaken of a copious meal.

Briefly, phagomania of diabetes is not a consequence of this disease; it is an independent concomitant nervous disturbance. However, it may be questioned whether or not the polyphagia and diabetes may not occasionally have a common origin in an organic or functional disturbance of the central nervous system. At any rate, phagomania reacts on the diabetes by aggravating it and increasing the difficulties of the treatment.

CHAPTER VI

PALMOPLANTAR XANTHOCHROMIA IN DIABETES*

One is often struck by a very pronounced yellow colour of the palmar and plantar surfaces of the hands and feet in diabetic subjects.

This colouring can be aptly compared with that of goose feet. It is bright yellow with a slightly rosy tint, almost exactly the colour of Indian yellow. There may be a little red tinge added to it when the integuments are sufficiently vascular. In order to see it well, the hand must be put upon the stretch, so that the integument becomes tense and a slight anæmia results. Then the rosy tint given by the blood decreases and the yellow colour becomes more manifest. To this condition we have given the name of palmoplantar xanthochromia.

This xanthodermia, which we supposed we were the first to describe, has also been referred to in 1914 by von Noorden and Umber. These writers have described under the name of diabetic xanthosis "a canary yellow colour of the skin, seated in the nasolabial fold and on the feet and hands, and susceptible to disappear."

Xanthochromia has also been described by Besnier and Carry as a special yellow tinge of the skin occurring in subjects whose urine does not give the reaction of biliverdin.

Palmoplantar xanthochromia is similar to the colour of the hands observed in cholemia, and only differs by its greater intensity. Hence we at first supposed that this phenomenon was due to a cholemic state related to hepatic superfunction, but both clinical and blood examination of the patient refutes this interpretation. The mucosæ are not involved; the conjunctivæ especially remain perfectly normal in colour, or may even present the bluish hue met with in anæmia. Usually the skin of the face does not offer any yellow tinge, but, on the

* Société médicale des Hôpitaux, July 19, 1914, in collaboration with Dr. Meaux Saint-Marc.

contrary, is rather pale; only occasionally do the ears offer a yellow tinge, but the integuments of the trunk and limbs are never yellow.

Examination of the urine shows absence of bile pigment; the urine is clear, as is usual in diabetics, and Gmelin's reaction is negative. There is absence of bile salts, and even urobilin was wanting in the cases we have observed. The blood-serum is clear, and does not give a blue ring when nitric acid is added, while no test reveals the presence of bilirubin. Finally, in our cases the liver was not hypertrophied, and there was no clinical evidence indicating a reaction of this gland.

The first patient in whom we noted palmoplantar xanthochromia was a woman æt. 45 years, who had had diabetes without denutrition for ten years and a low carbohydrate tolerance; the glycosuria, which at first could be reduced by diet, was now practically constant. The patient had always been thin, but had not lost much weight since the onset of the diabetes. The liver was not hypertrophied, and there never had been any jaundice.

The second case was a male, æt. 35 years, with diabetes with denutrition and acidosis. He had always been thin, and never had had jaundice. Following an attack of coma cured by sodium bicarbonate in large doses, at the time of convalescence we were struck by the yellow colour of the palms of the hands and plantar aspect of the feet. In this patient the yellow tinge extended to the face, especially over the malar region and chin. After a few days the yellow colour slightly diminished, but did not disappear.

The third case was a male, æt. 36 years, with diabetes with denutrition of serious nature and attacks of curable acidosis; there were at the same time polydipsia, polyphagia, and a neuropathic state. The patient absolutely refused to follow any diet. The glycosuria was 350 grammes and the polyuria 10 litres. The liver was not hypertrophied. The yellow colour of the palmar aspect of the hands was extraordinarily intense, and the skin of the body contrasted by its whiteness.

The fourth case was a male, æt. 34 years, with diabetes and moderate denutrition (intermediary form). The diabetes had un six months previously, and had undergone a notable

aggravation. The liver was not hypertrophied; the glycosuria averaged 20 grammes with a mixed diet containing 40 grammes of carbohydrates. There was a mild acetonuria, but no diaceturia. As in the preceding cases, there were no bile pigments or urobilin in either the urine or the blood.

Therefore, xanthochromia is especially prone to occur in the serious forms of diabetes. We have never as yet met with it in cases of hepatic diabetes, and it does not appear to have any relationship to disturbances of biliary secretion or cholemia.

As might be supposed, it is not cholemia arising independently of the liver by destruction of the blood and direct transformation of hæmoglobin into bile pigment in the circulation.

We do not believe that it is a cholesterinæmia, because our patients did not present xanthelasma, while the yellow tinge of the skin did not recall the chamois yellow of deposits of cholesterin, and the palmoplantar surfaces have never been mentioned as ordinary sites for the deposit of cholesterin.

Hence we can offer no pathogenesis of this xanthodermia, our object merely being to call attention to this phenomenon on account of its interest and the mistake in its differential diagnosis with cholemia to which it might give rise.

CHAPTER VII

THE PAINFUL SYNDROMES IN DIABETES*

Among the accidents which bring the diabetic patient to the physician the painful syndromes occupy a large place; they may be regarded as revealing signs of diabetes in the same way as furunculosis, carbuncle, disturbances of sight, and polyuria. I have invariably made it a rule to systematically examine the urine of every individual who comes complaining of neuralgic, muscular, or articular pain, and upon more than one occasion the result has been the discovery of an unsuspected diabetes.

The nature of the painful accidents in diabetes is not always easy to precisely estimate. However, by an attentive study of the phenomena, four categories of syndromes can be made:

1. Neuralgias and neuritides.
2. Algias due to arterial lesions.
3. Myalgias.
4. Arthralgias.

Neuralgias and Neuritides.

These are among the most common complications of diabetes mellitus.

Neuralgias.—The following is a typical example of neuralgia in a diabetic:

Female, æt. 33 years, entered hospital on September 25, 1907, for a left-sided intercostal neuralgia which began in the middle of 1906, and which had become much worse of late. The pain was seated along the course of the fifth left intercostal nerve, and presented the three classic spots of election. Medical treatment had been without avail. The patient was corpulent, although she had lost some weight during

* A clinical lecture delivered at St. Antoine Hospital, and published in the *Tribune Médicale*, March 14, 1908.

the last two years, and had diabetes with a glycosuria of 100 grammes per day.

A reduced carbohydrate diet was ordered, after which the glycosuria and other symptoms of hyperglycemia as well as the neuralgia subsided in a few days. When seen two months later the neuralgia had not recurred.

Diabetic neuralgias may affect all the nerves of the body: the great sciatic, crural, lumbar, genital, intercostal, facial, dental, brachial plexus, and even the pneumogastric (Peter), etc. According to Vergely, they are often limited to the terminal portion of a nerve—in the sole of the foot, for example —as in a case reported by Magnin. Such a condition obtained in the following case:

Female, had suffered for eighteen months with pain in the oles of the feet, making walking a difficult matter, to such an extent that the patient was compelled to lean upon the furniture in order to get about. When she came to hospital a year ago an abundant glycosuria was found.

Diet caused the glycosuria to disappear, and at the same time the pain diminished, pain that had previously resisted all treatment. At present she walks about easily, but the plantar pain still exists, and is worse at night from the heat of the bed. Methyl salicylate and aspirin give relief.

Worms, in 1880, was the first to give a good exposé of the peculiar characters of the neuralgias of diabetics. According to him, they are symmetrical, more painful than other forms of neuralgia, and do not yield to medication; they become worse or better parallelly with the glycemia, but are improved by diet. Peter confirmed these conclusions, but Hardy denied that symmetry belonged to this form of neuralgia.

It is certain that bilaterality and symmetry are not constant characters, because von Noorden's statistics show that the neuralgias of diabetes are symmetrical in only about one-fifth of the cases.

The action of treatment has also been much discussed. Several writers have recorded cases stubborn to both diet and medication. Raymond says that "because a neuralgia has developed from diabetes it must not be supposed that it will be recovered from by an antidiabetic régime." Assuredly, while neuralgia will yield completely and easily to diet, a neuritis is improved but not cured by it, and this is what distinguishes neuralgia-neuritis.

Plicque maintains that diabetic neuralgias offer the paradox of being uninfluenced by antidiabetic treatment. This is perfectly true, but this is simply because the multiple treatments that have been employed until now do not appear to have any effect on the diabetes; alone, diet produces therapeutical results.

Berger's, Roser's, and Drasche's cases show without question that diabetic neuralgia, even of long standing, yields to appropriate diet. In Drasche's case the patient had suffered from intercostal neuralgia for ten years; after the diabetes had been recognized and a diet ordered, the neuralgia subsided in five days. It was the same in my case, in which the neuralgia had been present for a year, and ceased in a few days from diet, although there was no need of causing the hyperglycistia to completely disappear.

The curative effect of diet may therefore be manifest even in neuralgia of long standing. But such fortunate results are not always forthcoming; the more recent the case, the greater are the chances for a rapid and complete cure.

The Neuritides.—Many neuralgias of diabetics are dependent upon a true neuritis. The clinical distinction between simple neuralgia and neuralgia-neuritis is occasionally very difficult to make. It is based upon the following characters: The only symptom of neuralgia is spontaneous or awakened pain caused by pressure on the nerve. Besides pain, neuritis is made evident by objective disturbances of the sensibility (anesthesia, paresthesia, delay of sensibility), by motor disturbances (paralysis or paresis), trophic disturbances (smooth skin, gangrene, changes of the nails and hair, perforating ulcer of the foot), and disturbances of the tendon reflexes (decrease or abolition).

Here are some cases of diabetic neuritis that have been under my observation:

Case I.—Male, æt. 44 years, large eater and drinker, obese, diabetes without denutrition. Entered hospital because for some time his strength has decreased and the legs give way while walking. The upper limbs are also weak.

Patient complains of severe osteocopic pain over the tibiæ and cramps in the upper and lower limbs. The disturbances of the sensibility are very developed; there is a notable decrease of the feeling to a pin-prick over the foot and posterior and internal aspects of the leg,

especially on the left, and a slight diminution over the external aspect of the leg and thigh. In the upper limbs there is anesthesia of the hand and wrist, hypoesthesia of the forearm and arm. The sensibility becomes normal at the roots of the limbs.

The muscular masses are atrophied.

The patellar reflexes are greatly decreased, those of the Achilles abolished; the radial, olecranon, corneal, and pharyngeal reflexes are absent.

Three months later these disturbances persist, but their localization is somewhat changed; there seems to be an area of complete left-sided hemianesthesia extending to the upper half of the thorax. Delay of the sensibility to cold and heat is especially marked.

Now, hemianesthesia is often due to hysteria. Perhaps alcoholism and hyperglycemia may have acted like saturnism and hydrargyrism in this patient by creating a kind of toxic hysteria similar to the cases described by Debove.

But, however that may be, when the patient was seen a year later the disturbances of the sensibility were still present.

Case II.—Male, æt. 50 years, was suddenly seized on December 15, 1904, with lumbar pain and intercostal neuralgia. At the same time there was pain in the elbow-joint, wrists, and knees, with tingling sensation in lower limbs. Legs weak, walking impossible. Patient was obliged to remain in bed for ten days, during which time he lost about 10 kilogrammes in weight.

A physician consulted had the urine examined, and glucose was found. Hence the neuralgia was the revealing symptom of diabetes. The patient had probably had the diabetes for two or three years, because white spots of sugar from the urine were found on his trousers, and to which he had attributed no importance. The patient also recalled that his mouth had been dry with a continual thirst, and that he urinated frequently.

When he entered hospital a mean glycosuria was found, with neuritis of the lower limbs, cramps, tingling, and muscular pain, hyperesthesia rather than anesthesia, paresis, absence of Achilles reflex, and decrease of the patellar reflexes. He presented quite marked digestive disturbance and a history of previous alcoholism.

Case III.—Male, æt. 45 years, blacksmith, large eater, alcoholic, obese, diabetic with a mild glycosuria, complained especially of pain in the spine and girdle pain. The pain was intermittent and occasionally was intense, especially at night when in bed.

Patellar reflexes weak, Achilles much decreased, the left being hardly perceptible. Olecranon and radial reflexes preserved. The thenar pre-eminence on the right somewhat atrophied; sensibility

slightly diminished in the domain of the ulnar on the outer border of the hand. Two years ago patient had had a slight paresis in this region.

CASE IV. (*from notes kindly given me by Dr. Joltrain*).—Female, æt. 29 years, had diabetes complicated by pulmonary tuberculosis. The diabetes appears to have developed a few months ago. Glycosuria from 200 to 400 grammes in twenty-four hours.

Shortly after the onset of the diabetes nervous disturbances developed—namely, pain and weakness in the legs.

When the patient entered hospital she complained of continual tingling in the lower limbs with occasional sharp pain. There was a distinct paresis of the extensor muscles, but walking was about normal, although to stand the patient is obliged to hold on to the bed, as she feels that the legs give way.

For five weeks there has been a paresis, with pain, of the left arm. The limb can be moved, but cannot hold any object without letting it drop. When she raises a glass to the lips there is no tremor, but the arm rapidly gives way and has to be supported by the other hand. Sensibility to pain and heat is diminished in all the limbs. The stereognostic sense appears to be decreased in the left hand, because the patient cannot recognize a watch placed in the left hand, while she recognizes it perfectly in the right hand.

Patellar reflexes absent, Babinski's sign absent.

From these four cases one may conclude that the neuritides of diabetes are more frequently polyneuritides, that they preferably affect the lower limbs, assuming especially a mixed sensitivo-motor form, and that diet and treatment improves but does not cure them. Polyneuritides are more common, mononeuritis less so.

According to Vergely, the muscular atrophy in diabetic neuritis is characterized by its limitation and absence of any tendency to generalization.

Bruns points out the predilection of neuritis for the crural and obturator nerves, but it may involve any nerve of the body—the ulnar, circumflex, brachial plexus, facial, motor nerves of the eye, etc.

The polyneuritides may also affect all the nerves of the body, but their predilection is for those of the lower limbs. There are three principal forms—viz.: (1) Sensitive polyneuritis, characterized especially by pain and objective disturbances of the sensibility; (2) motor and amyotrophic polyneuritis; and (3) peripheral neurotabes. This is characterized by fulgurant pain in the lower limbs, inco-ordination of movement with

preservation of muscular strength, absence of the tendon reflexes, vesical disturbances, and Argyll-Robertson's sign, as well as of deep visceral sensory disturbances and absence of cerebrospinal lymphocytosis, which differentiates the process from peripheral neuritis of true tabes dorsalis.

A differential diagnosis is sometimes very difficult to make, because glycosuria may arise in locomotor ataxia when the lesions involve the bulb. On the other hand, some diabetics are also syphilitic, and therefore may develop locomotor ataxia.

The lesions of the nervous system of diabetics afflicted with neuralgia or neuritis are not yet well known. Auché has observed lesions of peripheral neuritis of various degrees, from segmentary periaxial neuritis to parenchymatous neuritis with degeneration of the axis cylinders. Williamson, Souques, and Marinesco have found lesions of the posterior columns in diabetics whose patellar reflexes were absent. Marinesco has met with lesions of neuritis with muscular atrophy and changes in the cells of the medullary grey matter in a paraplegic diabetic patient.

The pathogenesis of the neuritides of diabetics is not the same in each and every case. It must not be forgotten that very often diabetics are also alcoholic, tuberculous, or syphilitic. These are three factors capable of creating lesions of the nervous system; alcohol often causes neuritis, tuberculosis sometimes, while syphilis is the most ordinary factor of lesions of the nervous centres.

There is therefore reason to distinguish neuritides *in diabetic subjects*, which may have an alcoholic, tuberculous, or syphilitic origin, from *true diabetic neuritis* caused by hyperglycemia.

Sicard is inclined to attribute an important part to syphilis in the production of medullary symptoms and lesions in diabetes. In two cases of diabetes with perforating ulcer of the foot reported respectively by Sicard and Mosny and Beaufumé, the cerebrospinal fluid offered a lymphocytosis. At the autopsy of Sicard's case classic lesions of tabes were found, and this observer supposes that the patient had an unsuspected syphilis. The hypothesis of syphilis in the pathogenesis of the nervous complications of diabetes was put forward some

years ago by Dufour, who found a cerebrospinal lymphocytosis in a diabetic presenting Argyll-Robertson's sign, but who had preserved the patellar reflexes.

The relative importance played by alcohol and diabetic intoxication in the neuritides of diabetes is not always easy to decide. In certain cases the neuritis is unquestionably dependent upon alcoholic intoxication, as in the following case:

CASE V.—An inveterate male alcoholic had a moderate diabetes and pulmonary tuberculosis. He complained of pain in the arms and legs, but did not present any objective symptoms of the sensibility; the patellar and radial reflexes were exaggerated. There was tremor of the tongue, professional dreams, and hypertrophy of the liver.

The exaggeration of the reflexes which belongs to the syndrome of alcoholic neuritis at the onset, in opposition to the absence of reflexes in diabetes, the intensity of the symptoms of alcoholism, and the mildness of the glycosuria in this case must lead one to attribute the nervous lesions to alcohol, and not to the diabetes.

In the majority of cases the patient will be both diabetic and alcoholic, and three of my cases enter this category (Cases I., II., III.). It is certain that neuritis is principally met with in diabetics tainted with alcoholism, and that most usually it appears in diabetes without denutrition with moderate hyperglycistia, rather than in the serious forms of diabetes with denutrition. Consequently, one is inclined to question whether alcohol does not play a part in its production. But it would be erroneous to attribute all neuritides met with in diabetes to alcohol.

The existence of true diabetic neuritis is unquestionable, because it occurs in diabetics who are not by any means alcoholic. Finally, neuralgias and neuritides are incomparably more frequent in diabetes than in alcoholism.

Briefly, there are three conditions to be met with—viz.:

1. Alcoholic neuritis in diabetes;
2. Diabetic neuritis in alcoholic diabetics;
3. Diabetic neuritis in diabetics without an alcoholic taint.

By what mechanism does hyperglycistia create neuralgia and neuritis? Is it the sugar in excess in the body fluids that irritates the nerves? Or is there besides the glucose in the body fluids of diabetics some toxic substance or substances deleterious to the nervous system?

It is certain that the central and peripheral nervous systems are deeply impregnated with glucose. Widal's researches, and those of Sicard, have shown that glucose enters the cerebrospinal fluid in large amounts, this fluid generally resisting invasion by soluble substances circulating in the blood.

Attempts have been made to produce neuritis by injecting glucose or acetone compounds into the cellular tissue of animals or in the neighbourhood of nerve trunks. Auché and Eichhorst were unsuccessful, while Dopter provoked local changes in nerves by placing the blood-serum of diabetics in contact with the sciatic nerve in guinea-pigs.

Experimental failures do not imply that hyperglycemic neuritis does not exist, but only that it is not easy to produce experimentally. It cannot obtain by local injection of glucose, because this is rapidly absorbed; it is only by creating a state of hyperglycemia similar to that met with in man that the experiments will be successful.

Angiopathies.

Among the painful complications of diabetes, a certain number are due to disturbances of the circulation from arterial spasm or arteritis. In their most typical form they assume the aspect of Raynaud's syndrome or intermittent claudication described by Charcot. Here are some examples:

Case I.—Female, æt. 59 years, has a diabetes without denutrition. For several years she has suffered from pain in the right arm—tingling, sensation of burning, and numbness when the patient works, and disappear with rest. They become so intolerable after a few minutes that she is obliged to stop sewing. They likewise occur at night in bed, and cease when the arm is allowed to hang over the bedside.

Pain of the same kind also occurs in the lower limbs—tingling, cramps in the legs, and numbness. These phenomena are exaggerated by walking. A sudden violent pain starts in the light leg, a tearing sensation or as if struck by a whip, obliging the patient to halt and to sit down if possible. This pain is so severe that the patient remains motionless.

After a few minutes' rest the pain subsides, and walking can be resumed, but sometimes it recurs and obliges the patient again to rest. During these paroxysms a burning sensation is felt in the limb, but when the leg involved is palpated it is found to be colder than the normal limb. No objective symptoms of sensibility in the lower limbs can be detected.

This is a case of intermittent claudication comparable to that described by Charcot. It indicates an insufficiency of the circulation in the limb due to arteritis.

Diet and medication with analgesics, especially aspirin, decrease the intensity of the painful phenomena, but do not cause them to disappear. Potassium iodide and various iodine preparations appear to me to have a similar favourable action when taken in time and in small doses.

Struck by the fact that pain of this type is calmed by a declivous position, which combats the anæmia from arterial miopragia and tends to cause congestion of the limb, I have attempted to treat these angiopathic paroxysms by the application of a rubber band at night when going to bed, and I have by this means obtained appreciable results.

In other cases a more marked arterial occlusion only makes itself evident temporarily when the limb is moved; it prevents nutrition of a segment of the limb, and after a time dry gangrene ensues.

The following case illustrates a focus of localized gangrene of arterial origin:

Case II.—Female, æt. 68 years, has had diabetes without denutrition for twelve years.

In 1903 she began to experience shooting pain in the lower limbs, especially in the left leg. On July 15 a small ulcer appeared on the side of the third left toe and deepened rapidly. Gangrene developed, and the toe sloughed off. After this incident the pain became more severe in October, to such an extent that the patient was obliged to remain in bed. She experienced alternating sensations of cold and heat in the left foot. The patellar and Achilles reflexes were absent; sensibility to pain and heat was normal in both legs. The vessels were somewhat hard and sinuous, the aortic sounds ringing; blood-pressure high (22 with Potain's sphygmomanometer).

Electrotherapy in various forms applied regularly for several years produced no relief. On the other hand, massage appeared to ameliorate the situation.

If arterial occlusion occurs in a large or medium arterial trunk, instead of developing in a small peripheral vessel, the result will be gangrene of a finger, hand, or even the leg or arm. This dry gangrene from arteritis, which is identical with that usually called "senile gangrene," is not uncommon in diabetes; it is met with much more often in the lower than in the upper limbs.

Besides these typical cases there are others in which the painful syndrome is rendered very complex by the association of neuritis with arteritis.

Case III.—Female, æt. 68 years, with diabetes without denutrition, has had pain in the back of the legs, cramps, shooting pains, with a sensation of cold for two years. These pains are fleeting and unstable. She suffers from the right shoulder when the arm is moved. Movement of the right thumb is also painful, and the patient experiences a sensation of temporary heat as well. The finger-joints are deformed by Heberden's nodes.

At present the tingling in the hands is less frequent than it was two years ago, but she sometimes experiences a burning sensation when the hands are put under the bed-clothes. The same burning sensation is felt in the soles of the feet when the patient gets up to walk, and during walking there are lightning pains.

Formerly the patient was regularly awakened in the night by cramps in the legs, but these have disappeared, and she no more has, as she did three years ago, a feeling of numbness when she slept on the side.

The superficial tactile pain and thermic sensation is normal in the upper and lower limbs, likewise the deep sensibility, muscular sense, and stereognostic perception. Muscular strength is weakened, and the muscular masses are slightly atrophied.

The reflexes are almost all abolished, but they can still be weakly perceived after several attempts at stimulation have been made.

The patient presents a special psychic state, characterized by defective attention, loss of memory, and a tendency to exaggerate all sensations.

Treatment by aspirin and antipyrine gave no marked results; both drugs decreased the pain, but the former caused headache with distressing deafness, while the antipyrine produced gastric disturbances which obliged it to be given up.

These algias are very difficult to classify; from certain characters—absence of objective, disturbances of the sensibility, angiosclerosis—they are similar to angiopathic pain, but they also possess the characters of neuritis. Finally, arthropathies of the fingers also complicate the clinical picture.

In all cases of this kind in which the painful phenomena are complex and difficult to dissociate, the diagnosis of angialgia should be based on—

1. The existence of pain in a limb or an entire segment of a limb, and not over the course of a nerve.

2. Increase of the pain on movement, working or walking.

3. Intermittent claudication.

4. Absence of objective disturbances of the sensibility.

5. Sensation of burning or heat coinciding with real coldness and pallor of the limb. In these circumstances search for arterial occlusion by means of a blood-pressure apparatus in one or two limbs, usually the lower, will reveal a decrease of the amplitude of the oscillations of the needle, and in serious cases the oscillations will not occur; besides, the maximum and minimum pressure will be low. In contrast with these indications of arterial impermeability, disturbances of the tendon reflexes—indications of nervous lesions—may be absent.

6. The coexistence of atheromatous or sclerous lesions of the vessels, especially the aorta, radial, and temporal.

These angialgias are principally met with in elderly diabetics, from 53 to 70 years of age.

Their pathogenesis is easily explained. Diabetics are very frequently angiosclerotic and atheromatous because the usual suralimentation and alcoholism, which created the glycoregulator disturbance, are also common factors of angiosclerosis.

According to the degree and seat of the vascular atresia and circulatory miopragia, the arteritis will assume one or the other of the clinical aspects I have mentioned.

The association of angialgias and neuralgias, which sometimes renders the diagnosis of the syndrome so difficult, can be explained, not only because diabetics are predisposed to both neuritic and arterial lesions, but also because the arterial lesions may, as Joffroy, Achard, Dutil, and Lamy have shown, involve the arterioles of the nerves, and thus set up neuritides of vascular origin.

Myalgias.

It is common for diabetics to complain of muscular pain. They will, for example, complain of the shoulders, but when carefully examined the joint itself is not painful either on pressure or movement, and the nerve trunks also are not sensitive to pressure. The pain is exactly in the deltoid and biceps, and is caused by pressure of the muscular masses. In the lower limbs these myalgias often assume the form of cramps or a sensation of fatigue. At other times the lumbar

or gluteal muscles are painful. The patient may even exhibit a true lumbago.

Muscular fatigue appears at the very onset of diabetes, rendering the patient lazy and preventing him from doing his work or indulging in his favourite sports. The sensation experienced is one of rather distressing muscular stiffness or as if the muscles had been bruised. It varies with the degree of the hyperglycistia.

The cause of these myalgias is a moot question; in certain cases it is unquestionably alcoholism, since cramps and pain on pressure of the muscular masses are prominent symptoms of chronic alcoholic poisoning. This was probably the condition in the following case:

A male with diabetes without denutrition, complicated with pulmonary tuberculosis, entered hospital for the diabetes as well as severe painful cramps in the left leg. Pressure over the muscles of the left leg was really very painful. The patellar reflexes were diminished, and there was a certain degree of cutaneous hyperesthesia. Patient moderately alcoholic, with an enlarged liver.

But usually it would certainly seem as if the myalgia depended directly upon the hyperglycistia; it exists in non-alcoholic diabetics, and subsides along with cure of the hyperglycemia. The muscles being one of the principal reservoirs of glycogen of the body, one can readily conceive that the glycoregulator disturbance makes itself known by muscular symptoms; the combustion of glucose in the muscle being the source of muscular energy, it is evident that when this combustion no longer takes place or is improperly carried out, as is the case in diabetes, muscular weakness ensues.

Arthralgias.

Pain in the joints is met with rather often in diabetes, and is of variable nature. In some patients it is due to quite ordinary morbid conditions, such as Heberden's nodes that become painful, or dry arthritis, and chronic arthropathies of the small joints whose pathogenesis is unknown.

Gout, with its chronic arthropathies and tophi, sometimes coincides with diabetes; this is not to be wondered at, because gout and diabetes are two syndromes resulting from habitual suralimentation.

Besides these affections, one occasionally meets with a special arthropathic syndrome which appears to be related to intestinal auto-intoxication, and from its hypercrinic aspect and general symptoms is much like gout, but differs from it by the absence of tophi.

Case I.—Female, æt. 66 years, diabetic for at least eleven years; always has had a large appetite, and at 50 years weighed 105 kilogrammes. She lost weight rapidly at the onset of the diabetes, and when first seen only weighed 71 kilogrammes. At this time there was intense thirst, polyuria, and 147 grammes of glucose in twenty-four hours. Her strength had diminished, there was somnolence during the day, and finally a cataract developed.

She also complained of rather sharp pain in the thumb and fingers of the left hand, with some swelling of the tissues; tongue coated, some nausea. The patient had experienced similar symptoms before, and described the attack of joint pain as gout, and although it did resemble it there were no tophi in the hands or face.

A year later the patient had another similar attack. She felt tired, and there was anorexia, nausea, and diarrhœa; tongue coated; complained of heat in the head and cold extremities. The joints of the fingers and hands were somewhat painful. This was an attack of intestinal auto-intoxication which somewhat recalled an attack of gout.

Here is another example:

Case II.—Male, æt. 46 years, an incorrigible large eater, alcoholic, obese, with diabetes without denutrition. He came to hospital upon several occasions on account of pain in the joints. The first time it was for dull continued pain in the vertebral joints, which subsided by diet and aspirin. Next there was pain in the joints of the large toe, with tumefaction and impossibility to walk. Finally, he had an attack of tingling and heat in the great toe, which forewarned the patient of an approaching paroxysm of arthralgia.

The pathogenesis of these rheumatoid accidents may be explained as follows: As in gout, they occur in large eaters, especially excessive meat eaters, and of necessity diabetics are meat consumers. A state of uricemia and intestinal intoxication ensues which may create both gastro-intestinal and joint disturbances. It is a kind of attenuated gout, and one degree more would result in gout and tophi.

From these illustrative cases it is evident that diabetes is frequently a painful process, giving rise to neuralgia, angialgia, myalgia, and arthralgia.

Some of these painful syndromes are the result of associated

infections or toxic processes, as alcoholism, syphilis, tuberculosis, and uricemia, but the majority are due directly or indirectly to hyperglycistia.

The diagnosis of the painful syndromes in diabetics is often difficult to make on account of their association. However, the clinician should endeavour to make it, because upon it depends the proper treatment.

These syndromes, being due to hyperglycistia, should be treated by diet, which alone is of any use. Drugs are useful only as adjuvants.

CHAPTER VIII

EPILEPSY AND DIABETES*

THE subject of the relationship between epilepsy and diabetes is a moot one. To decide it, it must first be properly presented.

In the first place, one must distinguish the glycosurias occurring after paroxysms of epilepsy and epileptic paroxysms arising during diabetes. The former have nothing to do with diabetes; they are rather frequent, but temporary, and disappear in a few hours; they indicate an irritation of the bulbar centres during the epileptic paroxysm.

The attacks of epilepsy arising in diabetics may be of very different natures. In the first place, there may simply be a coincidence between the two affections, because an epileptic may perfectly well be a diabetic as well. Then, again, a diabetic may develop epileptic seizures the result of extrinsic causes, such as alcoholic intoxication, uremia, cerebral syphilis, tumour or abscess of the brain, cerebral softening, meningitis, etc. These epilepsies occurring accidentally in a diabetic subject, and which are not due to the diabetes, will not be considered.

We shall only refer to epilepsy arising during the evolution of diabetes, and which cannot be attributed to any other cause. It is usually met with in complete diabetic coma or in the premonitory phase of coma—at least, in diabetic acidosis. Therefore, it can be pathogenically connected with the acid intoxication.

The existence of these acidosic epilepsies has been discussed. In spite of his long experience with diabetes, Naunyn maintains that he has never met with an example. Lépine reports some instances, but he believes that individual predisposition plays a more prominent part than does the acidosis. Dufourt (*Province Médicale*, May 20, 1911) has

* *Paris Médicale*, May 1, 1920.

published a paper on diabetic epilepsy in which he reviews a good number of published cases and discusses their value. In the majority of cases he believes that the epilepsy is due to uremia or a cerebral lesion; in some he believes that there is a simple coincidence, and concludes that true diabetic coma is never accompanied by epileptiform manifestations.

There is reason to examine this too exclusive judgment. Although some of Dufourt's criticisms are well founded, there are others that are exaggerated. Thus, it is not just to deny that a Jacksonian epilepsy is a toxic manifestation, because there are unquestioned instances of localized epilepsies due to uremic or lead intoxication. Besides, it is an exaggeration not to recognize true diabetic coma in cases where the respiratory type described by Kussmaul does not exist, because we now know that diabetic coma is not always identical, and several times I have noted that deep respiration was absent in diabetics in the premonitory phase and in the phase of confirmed coma. What indicates true diabetic coma are the stigmata of acidosis—namely, Gerhardt's and Legal's reactions, ammonuria, urinary acidity, etc. It is upon them that one must base one's conclusion in respect to true diabetic coma. Now, these stigmata exist in some of the cases rejected by Dufourt, especially in Lossen's patient, in whom Gerhardt's reaction had been found very marked a few days previously.

Blum admits the existence of acidosic epilepsy, but believes it to be very rare, and he is inclined to suppose that the majority of epilepsies occurring in diabetic coma are due to a sodic intoxication provoked by intravenous injections of sodium bicarbonate. Of the four cases he observed, the epileptic paroxysms occurred rather soon after such injections, while, on the other hand, this writer states that he has never met with epilepsy in cases of diabetic coma treated with bicarbonate exhibited by mouth. He also bases his conclusions on Stadelmann's experiments, in which convulsions occurred in dogs after injections of sodium bicarbonate as soon as the dose of the salt exceeded a certain percentage.

It is quite possible that in acidosic diabetics epilepsy due to the toxic action of the sodium may occur, but there are also true diabetic epilepsies which do not appear to depend upon acid intoxication, and a certain number of such instances have

been recorded. We will review and discuss them, because all of them cannot be accepted.

Thus, Finlayson met with epileptic paroxysms accompanied by maniacal agitation in a case of diabetic coma, but Gerhardt's reaction in the urine was negative; hence it is doubtful that this case can be included among instances of coma from acidosis, so that the epilepsy might have been due to another cause. Blum also rejects one of Krauss' cases because of the absence of acetone compounds from the urine.

Abbe has seen convulsions and aphasia occur in a diabetic, but there was a left-sided otitis, and regardless of the fact that no abscess or other central lesion was found at necropsy, doubt is permissible in this case.

Pallasse and Roubier's case admits of doubt as to the acidosic nature of the convulsions, and these observers admit this themselves. The patient, a male, æt. 64 years, diabetic for eighteen years, was at the same time afflicted by albuminuria, and had recently presented stigmata of acidosis. The coma came on suddenly after a convulsive seizure; the seizures recurred twelve or fifteen times until death ensued; the respiration was not Kussmaul's type. The dosage of urea in the blood and an autopsy were unfortunately not made, therefore the hypothesis of uremic convulsions cannot be excluded.

In one of Lépine's cases, the patient, who became hemiplegic and aphasic a long time after the onset of the diabetes, and was also extremely acetonuric, presented major attacks of epilepsy for several months. At autopsy a minute lesion of cortical encephalitis was found in the motor zone. It is probable that the epilepsy was due, as were the hemiplegia and aphasia, to the encephalitis; its dependence upon acid intoxication is not proved. I believe the same may be said of Meynert's case of acetonuric diabetes, in which there were pain, paresis, and stiffness of the limbs on the right side in a subject who developed a sudden aphasia with convulsions. Although diabetic and acidosic, a subject is none the less exposed to organic lesions of the brain.

Kussmaul (*Deutsch. Arch. f. Med.*, Bd. XIV., 1874) relates a very demonstrative example. A girl of 16 years, diabetic, suffered for some time from repeated vomiting; the tendon reflexes were abolished, and Gerhardt's reaction was present

in the urine. The acidosis increased so that a bicarbonate treatment was given which made the urine alkaline. One night the patient was suddenly seized with headache, vomiting, and deep respiration; the urine was intensely acid. Active bicarbonate treatment was resorted to, and coma was averted. But two days later attacks of generalized epilepsy ensued, followed by loss of consciousness and death. No cerebral lesion was discovered at autopsy. Therefore, this is an instance of epilepsy from acidosis.

Lossen's case (*Zeit. f. klin. Med.*, Bd. LVI., 1905) seems to me to enter the bounds of acidosis. A female, æt. 25 years, with severe diabetes, offered a series of generalized epileptic seizures, commencing in the left arm and followed by loss of consciousness. These paroxysms ceased the day before death, when the coma developed. As prodromata, there were only some pain in the head and stomach, then agitation and sudden amaurosis. But during the days preceding death the urine presented a marked Gerhardt reaction. In spite of alkaline treatment—which was inadequate—the urine remained acid to the last. At autopsy no lesions of nephritis were to be found, so that the hypothesis of uremia can be completely eliminated.

A second case reported by Lossen is no less typical. A girl, æt. 16 years, seriously diabetic, was taken with headache, vomiting, and deep respiration; on the following day a paroxysm of generalized convulsions took place, followed by coma and death. No lesion of the nervous centres could be detected at autopsy.

Krause (*Deutsch. med. Woch.*, 1907) has likewise observed generalized epilepsy during the comatous phase. Grube met with an acidosic diabetic who, in the lapse of thirty minutes, presented four paroxysms of epilepsy followed by coma. In one of Hudson's cases (*Brit. Med. Journal*, February 7, 1908) the convulsions occurred three days before the advent of coma. Domausky and Reimann's patient presented epileptiform seizures of short duration a few hours before death. Scheube (*Zeit. f. Heilkunde*, 1878) observed convulsions of the left shoulder and arm occurring in paroxysms and followed by temporary loss of consciousness in an acetonemic diabetic 53 years old. Alkaline treatment resulted in a cure.

Soetbeer (*Monatschrift f. Psychiatrie*, Bd. XXII., 1907) reports the case of a 27-year-old diabetic female, with marked acidosis, who presented from three to twelve daily attacks of Jacksonian epilepsy for one week, with temporary loss of consciousness. In Lewis O'Connor's case the patient, a diabetic girl of 16 years, presented repeated epileptiform attacks, localized to the right half of the body, without loss of consciousness. No cerebral lesion was found at autopsy. This case is, however, more difficult to interpret than the preceding ones, because the acetonuria was transitory and there was a mild albuminuria. Jacoby has seen convulsions occur a long time before death in three cases of diabetic acidosis.

Lépine (*Revue de Médecine*, January 10, 1910; and *Progrès Médicale*, May 6, 1911) relates several cases of acidosis accompanied by convulsions. In one of them the convulsions appeared during diabetic coma in the form of sudden attacks, principally in the lower limbs; there was also general tremor. In another case, reported by Froment and Santy, the patient, a male, had had diabetes for twenty-eight years, and had lately complained of great prostration and persistent headache; the face was pale and the urine gave a strong Gerhardt reaction. The patient's wife had remarked that he had slight lapses of the memory and a tendency to somnolence for some time past. He was at once sent to hospital, and in the evening was suddenly seized with three epileptiform attacks and coma, and died with a high temperature. Autopsy revealed cerebral congestion, but no lesions.

Chauffard and Rendu (*Revue de Médecine*, March 10, 1912) have published the case of an alcoholic tuberculous diabetic patient, with cirrhosis of the liver and a low degree of acidosis, who, without any former menace of coma, suddenly developed generalized epileptic paroxysms and died in twenty-four hours. There was Cheyne-Stokes respiration, but no deep breathing. Chauffard excludes the diagnosis of uremia or cerebral lesion, and admits epilepsy from acidosis, basing this opinion on blood examination, which revealed a normal azotemia, and because autopsy did not reveal any nephritis or cerebral lesion.

I have met with four cases of attacks of epilepsy in diabetics.

In the first case the epileptic paroxysms occurred in diabetic coma.

Case I.—Male, very corpulent, had had diabetes for at least twenty years, treated irregularly. He entered hospital for an enormous carbuncle on the neck, which had been preceded for more than a month by a series of boils and a carbuncle in the same region. In spite of surgical treatment, a cure was not forthcoming. The temperature was a little subnormal.

February 2.—Urine examination revealed a polyuria (3 litres), a glycosuria of 100 grammes, and a very intense Gerhardt's reaction. The patellar reflexes were normal, likewise the pupils. No respiratory disturbances, no somnolence. Fifty grammes sodium bicarbonate were ordered by mouth.

February 3.—Same condition. Same treatment, in spite of which the urine remained acid with an intense Gerhardt's reaction.

February 4.—Ordered 100 grammes sodium bicarbonate. In the morning and during the day the patient developed several epileptiform attacks lasting one or two minutes, characterized by a slight torsion of the mouth to the right, some movements of the jaw, and shaking of the right arm. The mouth remained somewhat contorted after the attacks. The patient complained of general malaise, especially abdominal and gastric; there was no vomiting or special respiratory rhythm. He was plunged in a state of prostration and rather marked somnolence. The temperature reached 103° F. Death took place in coma on the morning of February 5.

In this case it seems to me quite natural to attribute the production of the epileptiform paroxysms to the acidosis complicated by a general infection to which the patient succumbed, since there was no symptom pointing to uremia. The following case is very typical:

Case II.—A somewhat corpulent male, æt. 45 years, had always been a large eater and drinker, and committed excesses of all kinds; was the subject of diabetes which had not caused denutrition. In November, 1911, he lost weight, felt very weak, and acetone was found in the urine. When I saw him on November 28, he was somewhat somnolent during the day with insomnia at night; he had lost the appetite completely; the urine presented strong Gerhardt and Legal reactions; no albumin. The liver was hypertrophied. No vomiting or constipation. Congestion at both pulmonary bases, but respiration was normal. Tachycardia at 120. At the first examination the patient's condition did not yet give the impression of great gravity. He was perfectly lucid, and had taken a little sodium bicarbonate. He was ordered milk, barley meal, and vegetable soup, with 10 grammes sodium bicarbonate every hour.

The night was quite bad with insomnia, and at 11 a.m. on

November 29 he had a severe attack of diarrhœa, while the respiration became difficult and noisy. At 5 p.m. there was a sudden loss of consciousness. The look was staring, the eyes upturned, and the limbs contracted; then slight twitching occurred in the face and limbs. In a few minutes the patient regained consciousness, but complained of an indefinite profound malaise. The respiration was sighing.

At 2 a.m. on November 30 the patient suddenly cried out; the face and limbs became contracted and then animated by a series of generalized epileptic twitchings. The attack lasted fifteen minutes, and was followed by coma of one-quarter of an hour's duration. Afterwards consciousness returned, but the remainder of the night was bad, due to dyspnœa.

At 8 a.m. the patient felt better, had a sudden pang of hunger, and devoured a beefsteak. At 9 a.m. his expression became fixed, syncope developed, and death took place.

In this case there can be no doubt as to the acidosic nature of the convulsions which took place in the precomatous phase at the same time that characteristic deep breathing developed.

Case III.—A vigorous male, æt. 19 years; no pathological antecedents. Diabetes commenced in 1918, and evolved with a desperate fatality, becoming progressively aggravated, and soon being complicated by acidosis. About the middle of December, 1919, he commenced to emaciate, and lost both strength and appetite; then on December 29 somnolence developed, and at the same time deep breathing ensued.

In spite of an intensive bicarbonate treatment (by mouth, per rectum, and intravenously), the urine remained very acid and the disease made rapid progress. On January 1, at 7 a.m., an epileptic attack took place with movement of the jaw, stiffness of the upper limbs, and clonic convulsions, stiffness without convulsions of the lower limbs, sphincteric incontinence. These attacks recurred four times at short intervals, the patient dying at 9 a.m.

Case IV.—This case lends itself more to criticism, because it was seen long ago before I was using Gerhardt's reaction; but in this case of serious diabetes with denutrition there was probably acidosis, because this is almost the rule.

Suddenly in the night the patient, a male, lost consciousness and developed an attack of epilepsy which recurred several times in the night. The following morning the patient awoke very depressed. Four days later the patient was seized in the night by vertigo and giddiness, but without convulsions. There was persistent headache and tingling in the hands and calves of the legs. For some time after the patient complained of vertigo and headache, but finally these symptoms improved.

Afterwards the patient was under the care of Professor Bard of Geneva. He never developed another epileptiform

attack or any nervous symptom, at length dying in a rapidly developing coma. At autopsy, no lesion of the nervous system was found which could explain either the diabetes or epileptiform attacks.

It is therefore probable that the vertigo, giddiness, and attacks of epilepsy were provoked by an outburst of acidosis arising during the diabetes.

From these several instances it becomes manifest that in cases of acidosis in which there is no reason to invoke uremia or other intoxication, attacks of epilepsy may sometimes occur which do not appear to me legitimate to consider as due to acid intoxication, and without being able to affirm, be it understood, which one among the agents of this complex intoxication plays the epileptogenous part.

These attacks are localized or general, followed by loss of consciousness, temporary or prolonged. They often are a prelude to diabetic coma, and they only cease to give place to diabetic coma. At other times they arise during coma, and, finally, they also appear to be capable of occurring quite a time before the end in death from coma, upon the occasion of an outburst of acidosis in a diabetic.

It is impossible to adduce any proof for or against the existence of this acidosic epilepsy from experimental work.

Under the name of acetonic epilepsy, von Jaksch has described convulsions occurring in rabbits intoxicated by inhalations of massive doses of acetone vapour.

On the other hand, André and Baylac, by acetone inhalations in rabbits, only produced dyspnœa, anesthesia, paralyses, and death in coma without convulsions or contractures.

Gouget has produced convulsions by injecting acetone compounds directly into the brain of guinea-pigs, but this manner of intoxication does not permit one to draw a firm conclusion in respect to the epileptogenous part played by acetone compounds.

When, with Violle, I poisoned rabbits with organic acids, we did not observe convulsions, but our experiments with oxybutyric acid are too few in number for concluding for or against its possessing an epileptogenous action, because it is most evident that the epileptic attacks do not take place in every case, and are a rare symptom in acidosis. Besides, we

did not experiment either with acetone or diacetic acid, yet it is possible that the epilepsy of diabetics results from the action of one or the other of the toxic substances intervening in the process of acidosis, and not from acid intoxication in general. For that matter uremic epilepsy has never been experimentally reproduced, the toxic element giving rise to it is not known, and nevertheless there is no doubt as to its existence.

In order to remain within the limits of our present clinical knowledge, I would conclude that diabetic epilepsy exists, and that it is a manifestation of acidosis, and not of hyperglycemia.

CHAPTER IX

DIABETES AND TYPHOID FEVER*

In spite of a certain number of published cases, the influence exercised by typhoid fever on diabetes and reciprocally is still not thoroughly understood. Having had the opportunity to observe a case of this morbid association, we have thought that it might be of interest to report it, and then endeavour to elucidate the following points:

1. The action of typhoid on diabetes, especially on the glycoregulator disturbance and the acidosis;
2. The action of diabetes on typhoid fever.

Case Report.—Female, æt. 33 years, entered hospital November 8, 1912.

Patient had been ill for ten days; she complained of general malaise, headache, tender and distended abdomen, cough and expectoration. There has been diarrhœa for five days, four to five fœtid yellow stools a day. Patient states that three years ago she had blood in the stools.

Patient looks ill, lips dry, tongue white in the centre, red on the border; anorexia, abdomen distended and sensitive to palpation. One rose-spot present, spleen hypertrophied, pulse well struck, 93 to the minute; the first heart sound slightly weak. Some râles could be heard over the left pulmonary base. Temperature 104° F.

Patient has been diabetic for a year. At the onset she suffered from intense thirst, polyuria, emaciation, and pruritus vulvæ, and glucose was found in the urine. Since then she has hardly followed any diet.

The urine contained sugar, but no albumin, urobilin, or reaction of acidosis. Treatment: Cold baths, injections of sparteine, and milk diet.

November 11.—Diarrhœa has ceased, stools formed, rose-spots over abdomen. Temperature 102° F.

November 14.—Rose-spots have disappeared. Congestion of left pulmonary base persists. First heart sound prolonged. Pulse 84.

November 18.—Systolic souffle over precardiac region. Physical depression more marked. Temperature again 104° F.

November 20.—Abdomen very distended. Pulse 96. Blood-

* In collaboration with Dr. Gendron, *Presse Médicale*, January 14, 1914.

pressure: Max. = 13·5, min. = 10. Saline injections with adrenalin, injections of camphorated oil.

November 22.—Second eruption of rose-spots. Generalized bronchitis and congestion of left base.

November 23.—Pulse 102. Some liquid brownish-coloured stools.

November 25.—Pulse 104. One stool containing blood.

November 26.—Slight intestinal hæmorrhage. Pulse 110. Heart weak, souffle at apex. Congestion of right pulmonary base. Treatment: Calcium chloride.

November 27.—Delirium. Hæmorrhages have subsided. Urobilin in urine. Temperature 100·5° F.

November 28.—Pulse 96. Congestion of both pulmonary bases.

December 2.—Pulse 110. Cardiac souffle has disappeared. Quiet delirium continues.

December 4.—No delirium. Abscess in left gluteal region. General condition better.

December 12.—For the past three days patient has complained of pain in right hypochondrium and epigastrium. Liver hypertrophied and sensitive on palpation. Urobilinuria continues.

December 14.—Incision of gluteal abscess, giving exit to ½ ounce of pus containing Eberth's bacillus. Temperature 100·5° F.

December 16.—Patient complains of bladder pain and a frequent desire to micturate.

December 22.—Temperature 102° F. Diet.

December 26.—Incision (second) of gluteal abscess, after which the temperature progressively dropped.

January 6.—Temperature about normal.

January 11.—Blood-pressure: Max. = 16, min. = 11.

January 17.—Urobilinuria absent. Patient discharged well.

December, 1913.—Patient was seen. Still diabetic, but presents a flourishing condition of health. She refuses to follow any régime, and consumes a large amount of bread, and about 230 grammes of carbohydrates a day. Glycosuria = 80 grammes.

During the patient's entire illness the urine was carefully collected each day, and a dosage of the glucose made. We summarize the evolution of the glycosuria at the various phases of the illness in the table on p. 109. The amount of glucose given represents the average daily excretion during the period indicated in the first column.

Briefly, the typhoid occurring in this diabetic patient, although ending in recovery, presented characters of notable gravity and various complications. The temperature underwent a recrudescence with the appearance of a second crop of rose-spots. Intestinal hæmorrhages occurred for three days. For about one month there was hepatic congestion with

urobilinuria and delirium lasting a week. Finally, there was suppuration due to Eberth's bacillus.

The action of the typhoid on the glycosuria is difficult to estimate in this case, because the amount of glycosuria previous to the typhoid was unknown.

Date.	*Phase.*	*Diet.*	*CH in Gr.*	*Glucose in Gr.*
Nov. 8-13	Stationary period	Milk, 2,000 c.c.	106	47·0
,, 13-23	Recrudescence	*Id.*	106	46·2
,, 23-26	Intestinal hæmorrhage	*Id.*	106	46·0
Nov. 26 to Dec. 4	Delirium. Urobilinuria	*Id.*	106	49·0
Dec. 4-14	Improvement. No delirium. Abscess	*Id.*	106	29·0
,, 14-18	Abscess. Fever. Hepatic congestion	Mixed diet, including meat	74	29·0
,, 18-22	Fever. Incision of abscess	*Id.*	60	37·7
,, 22-28	Improvement. Normal temperature.	*Id.*	52	37·0

During the first part of the disease the glycosuria was constant, an average of 46 grammes per day with a diet containing 106 grammes of carbohydrates, thus giving an apparent tolerance of 60 grammes. At the time of hepatic congestion with urobilinuria and delirium the glycosuria underwent a slight recrudescence; the apparent tolerance fell to 45 grammes. Afterwards, at the time of the gluteal abscess, the glycoregulator disturbance increased, because the glycosuria was 37 grammes with a diet containing 52 grammes of carbohydrates—that is to say, the apparent tolerance was only 15 grammes. Thus, during the first phase of convalescence the glycoregulator disturbance offered no tendency to decrease.

The patient was seen a year after recovery, at which time there was a glycosuria of 80 grammes with a diet containing 230 grammes of carbohydrates, hence representing an apparent tolerance of 150 grammes. Therefore, the tolerance is notably higher than at the end of the typhoid, and the glycoregulator disturbance considerably decreased. There is every reason to suspect that the Eberth infection temporarily aggravated the glycoregulator disturbance, and that this took

place from the onset to the end of the infection; but after complete recovery from the typhoid had taken place, the glycoregulator disturbance again diminished, perhaps falling to the same degree as before the illness.

The Action of Typhoid Fever on Diabetes.—The majority of writers mention a decrease of the glycosuria during typhoid. In Bamberger's case it greatly diminished, in Gerhardt's case it lessened, while in Ryba and Plumert's patient it disappeared. In Marfan and Iscovesco's case it fell from 230 to 67 grammes, then to 22 grammes.

Such decreases do not belong to typhoid fever exclusively; this has been noted in pneumonia (von Noorden, Leube), in variola (Prayer, Pavy, Carvalho), and in other infectious diseases. Minkowski has met with it in dogs, having had the pancreas removed, during febrile attacks.

Naunyn admits that a diminution of the quantity of food may play a part in the reduction of glycosuria, but he does not believe that this is the only cause. He states that he has had patients who, during typhoid infection, were able to support amounts of starch which would have previously given rise to an abundant excretion of sugar without causing glycosuria.

Minkowski has proposed two explanations: (1) Either the bacteria provoke fermentation in the tissues which destroy the glucose, as is seen *in vitro ;* or (2) the destruction of proteins during infections takes place normally, and does not give rise to carbohydrates, so that the organism has only the carbohydrates introduced in the foods to work on. Naunyn does not admit the latter hypothesis. Other hypotheses have been proposed, but seem to me useless to discuss.

None of them are convincing. In the majority of cases no record was made of the diet before and during the disease, so that it is impossible to affirm whether or not the decrease was due to an exaggerated combustion of sugar. It is more than probable that the reduction of the food intake during the infectious disease is the natural cause in most cases in which decrease of the glycosuria has been noted.

For that matter, an infectious disease does not always bring about a reduction of the glycosuria. In some instances it increases it or causes it to reappear when it had not been present for some time.

In a child of ten years with serious diabetes diet had caused the glycosuria to disappear, but a varicella developed, and Naunyn found that the glycosuria appeared although no change had been made in the régime, while Gerhardt's reaction was positive. A fortnight later there was a glycosuria of 100 grammes, and a few days later the child died in coma. This is a good example of rapid aggravation of diabetes resulting from an infection.

Naunyn has seen pneumonia produce a considerable increase of the glycosuria in a diabetic, and von Noorden has observed the same phenomenon in a case of angina.

In quite a number of cases the appearance of glycosuria has been noted in furunculosis, abscesses, and gangrene, and then to disappear after recovery from the septic process.

Mohr's experiments, in which he kept a precise record of the patients' diet, show that at least in the majority of cases the infection increases the glycosuria, and I here give a summary of his cases:

(1) In a case of mild diabetes the glycosuria had subsided, but recurred during an attack of influenza and ceased after recovery. (2) In another case the glycosuria reappeared during a febrile disturbance, after which it subsided. (3) In a third case a febrile cervical adenopathy caused the glycosuria to increase from 1 to 12 grammes, in spite of the fact that the intake of food was reduced. (4) During a mild diabetes, an angina caused the glycosuria to return and afterwards to disappear. (5) In a case of serious diabetes a phlegmonous angina increased the glycosuria from 15 to 75 grammes, and the acetonuria from 0·30 to 1·50; after this the diabetes progressively increased. (6) During a mild diabetes a pleuro-pneumonia caused a return of the glycosuria; it reached 60 and then 138 grammes; then after recovery it fell to 96, 41, and 26 grammes, but afterwards, with the same severe régime, the glycosuria persisted at 6 grammes. Therefore there was an aggravation of the diabetes.

The case we have reported is to be classed in the group of diabetes temporarily aggravated by an infectious disease.

This increase of the glycoregulator disturbance is not constant; we found it absent in the following case:

In a diabetic without denutrition whose limit of tolerance was maintained by a reduced diet, several paroxysms of malaria did not cause temporary glycosuria; on the other hand, a febrile congestion of the liver, resulting from suralimentation

with meat, resulted in a glycosuria of several days' duration. It would therefore seem that infections involving the liver aggravate the glycoregulator disturbance more than others.

Serious diabetes seems to be more sensitive to the action of infectious diseases than other forms of this morbid process. I have encountered similar instances to those reported by Mohr. In a girl of ten years with diabetes with denutrition a pneumonia increased the diabetes; the glycosuria passed from 18 to 60 grammes per 1,000 c.c. Nevertheless, the child resisted the pneumonia, and some time later contracted measles, from which she recovered. But since then the diabetes became much worse, with acidosis, and she died a few months later in coma.

Briefly, a febrile process often aggravates the glycoregulator disturbance in diabetes. It may even create a glycoregulator disturbance in a normal subject, and be the origin of a post-infectious diabetes, as Schmidt, Heine, Stern, Zinn, Holsti, Laignel-Lavastine, and myself have reported examples. There is no reason to be astonished at this, since we know from the writings of von Noorden, Poll, Klemperer, Campagnolle, and Paris that the test of alimentary glycosuria often reveals a disturbance of the glycogenic function during the evolution of fevers.

But the mechanism of this functional disturbance is not understood. May and Hergenhahn have noted that infected animals became poor in glycogen, although they did not develop glycosuria. Colla found that anthrax infection caused the glycogen to disappear from the liver and increase the glucose in the blood, while Roger has noted the same phenomenon in experimental anthrax infection. On the other hand, it is quite true that Kauffmann and Charrin have seen glucose decrease in the blood of animals infected with the staphylococcus, and Roger has found that streptococcal infection lowers the percentage of glycogen in the liver and blood. Noël Paton found that the sugar in the blood increased when animals were artificially heated, but it diminished when bacteria were injected. Richter believes that infection and the increase of temperature which accompanies it act in an inverse way, thus explaining the discordant results obtained.

Therefore, it is evident that one is far from being in a way

to settle the question of the mechanism by which infections produce disturbance of glycoregulation, and only the existence of this disturbance can be admitted.

The Action on the Acidosis.—In the case here reported the typhoid fever did not give rise to reactions of acidosis; at no time during its evolution were Gerhardt's, Légal's, or even Lieben's tests positive. It is rather curious to note this negative reaction in a diabetic subject when one knows that even in normal health infectious diseases may give rise to acetonuria. This clearly shows, as I have more than once pointed out, that the reactions of acidosis and even simple acetonuria are not as frequent or as easily provoked as certain writers would have us believe.

The appearance of acidosis in an infectious disease is influenced by the nature and degree of the diabetes. In diabetes with denutrition, or near to denutrition, it is probable that the patient will not escape this complication, as is shown by Mohr's cases mentioned above. Likewise, in my case of infantile diabetes it is probable that the pneumonia and measles both played a part in the rapid development of acidosis.

The finding of acidosis during an infectious process in a diabetic subject is an element of prognosis. In fact, it rapidly occurs in severe diabetes, and not in the milder cases; besides, with its tendency to a progressive evolution, it is from this fact a factor of gravity.

The Action of Diabetes on Typhoid Fever.—The gravity of infections occurring in diabetics is a well-known fact. Bouchardat said that pneumonia never was recovered from in diabetes, but clearly this pessimistic view is exaggerated. I could mention examples of serious pneumonia occurring in diabetics in which recovery has ensued. As to typhoid fever, statistics show that the process is aggravated by diabetes. Of seven published cases which I know of, there were five deaths and two recoveries only. This makes a mortality of 71 per cent., so that the prognosis is three times more serious than in typhoid in general.

Among the complications, intestinal hæmorrhage seems especially frequent; this took place in Marfan's, Rénon's, and my patients. Teissier has emitted the opinion that the rise

in the blood-pressure of diabetics might favour hæmorrhage, but in my patient this could not have been the cause, as the pressure was no higher than what is usual in most typhoid cases. For that matter, one must not suppose that the blood-pressure is raised in all diabetic subjects. This does occur in obese patients, because they often have renal sclerosis as well, but it does not exist in diabetes with denutrition.

Another complication which might be expected is abscess formation, because tissues infiltrated with sugar offer an eminently favourable soil for the development of pyogenic bacteria. Therefore, every aseptic precaution must be taken when giving injections.

In the case reported at the beginning of this chapter large abscesses developed where subcutaneous injections had been given, and suppurated for a long time, thus delaying convalescence. Defective asepsis cannot here be incriminated, because the pus contained Eberth's bacillus. It is possible that the injections merely played the part of a place of rendezvous for the bacteria circulating in the organism.

CHAPTER X

THE ŒDEMAS IN DIABETES—THE ACTION OF SODIUM BICARBONATE

DIABETICS easily develop œdema, which is not always of the same nature.

In diabetics *without* denutrition the œdemas are generally due to a renal or cardiac lesion, and have the same pathogenesis and evolution as brightic or asystolic hydropsies. They offer no peculiarity.

In diabetics *with* denutrition œdemas are frequent. They are not dependent upon a lesion of the heart or kidney; from their clinical evolution and manner of production they deserve a place by themselves in the pathology of diabetes.

Stäubli described these œdemas in 1908, and in a study on diabetes published in 1910 I included them among the symptoms of serious diabetes, and thought that they might be attributed to chloride retention.

However, in 1909 Blum, having observed œdemas in diabetic patients undergoing massive alkaline treatment, thought they were the result of the sodium bicarbonate. F. Widal, Lemierre, and Cotoni, in 1911, studied the œdemas provoked by bicarbonate in diabetics, and attributed them to chloride retention due to a suspensive action of the alkaline salt.

These data correspond to two distinct categories that will be successively studied:

1. The spontaneous œdemas of diabetes with denutrition;
2. The œdemas of diabetics ingesting sodium bicarbonate.

(*a*) **The Spontaneous Œdemas of Diabetes with Denutrition.**—One quite frequently meets with slight, soft, white œdema in diabetes with denutrition, although the patient is not taking alkalines. The œdema preferably develops in the declivous parts—ankles and legs—but may also involve the eyelids and face. Occasionally there may be fluid in the joints.

In one of my patients the body weight increased upon

several occasions at the same time that the œdema and hydrarthrosis developed.

In another patient, as soon as the scales showed an increase of 2 kilogrammes in weight a swelling of the ankles and face could be noted; inversely, when the weight decreased the œdema subsided.

These œdemas occur without apparent cause, and subside in the same way. They never attain the same degree as the œdema of Bright's disease, and rather more recall the œdema of cachexia.

Their evolution is parallel to the curve of the body weight. What is remarkable is that a slight increase of weight—2 kilogrammes, for example—is enough to reveal the œdema, while in Bright's disease the œdema hardly appears before there is an increase of 6 kilogrammes. It would seem that these thin cachectic subjects would be more in imminence of œdema than those with Bright's disease, which leads to the suspicion that a profound change in the composition of their tissues exists.

Even when diabetics with denutrition do not present any œdema their weight offers rapid and considerable variations without any apparent cause. One of my patients in a state of acidosis increased 7 kilogrammes in one week, although no change had been made in diet or treatment, and then lost 6 kilogrammes in six days. Another increased 4 kilogrammes in four days, and then the weight decreased spontaneously; however, during the first few days there was chloride retention, followed by a considerable excretion of salt.

Although not usually so marked, instability of the body weight is the rule in these patients. This instability is important for clinicians to be aware of; it shows these rapid increases and losses of body weight in diabetics with denutrition cannot be attributed to an amelioration or an aggravation of the patient's general condition. It is correlative to a no less remarkable instability of the mineral equilibrium; without any therapeutical or diabetical influence, these subjects spontaneously undergo demineralization, or, on the contrary, remineralization occurs.

(*b*) **The Œdemas of Diabetics undergoing Bicarbonate Treatment**—*Clinical Evolution.*—The œdemas arising in dia-

betics treated with sodium bicarbonate in large doses attain a far greater development. Hence, they have attracted attention.

Blum observed a diabetic increase 9 kilogrammes in six days, and presented on the third day of alkaline treatment an infiltration of the face and legs. Widal met with a diabetic who put on 10 kilogrammes of weight in fifteen days.

I have observed a diabetic who for one week ingested 40 grammes of sodium bicarbonate per day, and increased 8 kilogrammes during this time; œdema developed in the lower limbs. Another patient with acidosis, submitted to the ingestion of 30 grammes of bicarbonate *pro die*, increased 4 kilogrammes in weight in five days, and already on the second day presented œdema of the lower limbs. Still another patient, having taken 30 grammes of bicarbonate *pro die* for four days, increased 5 kilogrammes during this time, while œdema developed in the lower limbs.

The increase in weight is generally rapid; it is often as much as 500 grammes to 1 kilogramme, or even 3 kilogrammes a day. It is in direct relation to the dose of bicarbonate ingested. For doses of 20 to 30 grammes it is mild or even *nil*, while with doses of from 40 to 60 grammes or more a day it is ordinarily rapid and considerable.

For that matter, all patients do not react in exactly the same way to the absorption of bicarbonate; some are very sensitive to the salt, others appear to be uninfluenced by it. Thus, one of my patients did not present any increase of weight, although he took from 40 to 50 grammes of bicarbonate for ten days. F. Widal also has noted this fact.

When the bicarbonate treatment is stopped, the œdema subsides, the weight falls to that before treatment was begun, and sometimes it may drop below it. This return to the former weight is rapid, and takes place in a few days.

Those who have observed this increase of weight from the bicarbonate treatment at first supposed that it indicated an improvement in the general health, and fattening of good omen. I had the impression at one time that alkalines prevented saline and nitrogenous denutrition in diabetics, but the rapid drop of weight that follows cessation of alkaline treatment shows that fattening does not occur, but merely hydration of the organism.

With such rapid variations of the body weight one should, in this hypothesis, observe concording variations in the excretion of the urine; it might be thought that the increase of weight resulting from retention of water should be accompanied by a decrease of the diuresis, while the diminution of weight should have polyuria as a corollary. But the urine curves are not at all demonstrative in this respect; there is no oliguria or polyuria. This is because the intake of liquid varies in amount, and that usually it is greater during alkaline treatment. In order to ascertain if sodium bicarbonate exercises a suspensive action on diuresis, one must examine the situation more closely and take into consideration the coefficient of diuresis. I have thus found in one of my cases that the coefficient of diuresis, which before alkaline treatment was 0·70, dropped to 0·67 during treatment, and then went up to 0·72. This was worked out by averages, each one comprising ten days. These figures bring into evidence a retention of water during ingestion of sodium bicarbonate and an excretion after cessation of treatment. The œdemas resulting from the ingestion of bicarbonate are therefore due to hydration.

Physiological Mechanism.—The physiological mechanism of hydration has given rise to various interpretations. Blum believes that the bicarbonate exercises a direct hydropigenous action; the organism of diabetics being poor in alkaline salts, on account of acid intoxication, is very avid for them, and retains them energetically. He bases his opinion on the fact that in a normal subject absorption of sodium bicarbonate does not give rise to œdema, while in a subject artificially deprived of alkaline salts by means of prolonged milk diet the organism becomes more sensitive to bicarbonate.

Pfeiffer supposed that the bicarbonate exercises a greater hydrating action than sodium chloride in disease, and even in normal individuals. He attributes the action, not to chlorine, but to the sodium retained in the tissues. This property belongs, according to Pfeiffer, exclusively to sodium, and other metals, such as potassium or calcium, do not possess it whatsoever.

Widal, Lamierre, and Cotoni, having several times observed chloride retention after absorption of sodium bicarbonate, believe that the alkaline salt exercises a suspensive action on

the chloride excretion of the kidneys, and that the chloride retained in the tissues is in turn the cause of the water retention. Hence the bicarbonate œdemas enter into the general class of œdema from chloride retention.

These same observers have also experimented with the action of sodium bicarbonate in an acidosic diabetic. They found that an equivalent ration of sodium does not produce the same effects of hydration when given in the form of bicarbonate (20 grammes), chloride (15 grammes), or a mixture of these two salts (bicarbonate 10 grammes, NaCl 7 grammes), and that the mixture of the salts has a greater hydrating action. They conclude that the chlorine and not the sodium causes the œdema.

Rathery states that he has observed œdema with anasarca accompanied by chloride retention result from a moderate dose of bicarbonate (80 grammes in four days) in a diabetic without denutrition; unfortunately, he did not control the amount of NaCl ingested by the patient.

With my collaborators H. Bith and Fertyk, I have experimented with the action of sodium bicarbonate in three diabetic subjects. The first, who had diabetes without denutrition, increased in weight and developed chloride retention; the second, with diabetes with denutrition, taking from 40 to 50 grammes of sodium bicarbonate for ten days, did not increase in weight or develop chloride retention; the third, a case of diabetes with acidosis, consuming from 30 to 40 grammes of sodium bicarbonate a day, presented an increase of weight of 5 to 6 kilogrammes upon two occasions, but without chloride retention. The test of chloride ingestion showed that he eliminated this salt perfectly.

From these experiments we concluded that the œdemas produced by ingestion of sodium bicarbonate are certainly bicarbonate œdemas, that they may be accompanied by chloride retention, but that this is not essential for the production of the œdema.

In order to precisely investigate the pathogenesis of bicarbonate œdemas, and to compare the hydropigenous action of the sodium ion and the chlorine ion, I undertook with Guérithault a study in the cases of three diabetics with denutrition by dosing the sodium and chlorine eliminated in

the urine the entire time during which they were under observation. Thus we found that chloride retention is not constant, even when there is an increase of weight due to bicarbonate treatment; that, on the contrary, a more or less considerable retention of sodium occurs, followed by a corresponding elimination when the alkaline treatment is stopped; and that even if there is chloride retention, the non-chloride retention combined with bicarbonate retention, is always more important than retention of sodium chloride.

Hence *the œdemas provoked in diabetics by ingestion of sodium bicarbonate are due to retention of sodium, and not to that of chlorine ;* when the latter occurs it only plays an accessory part.

The hydrating action of sodium bicarbonate is not confined to diabetics; it is also met with in Bright's disease. Hayem has observed it in dyspeptics undergoing alkaline treatment, and Pfeiffer has seen it occur in normal subjects. In a case of Bright's disease I produced an increase of the body weight of 3,400 grammes and œdema without chloride retention by giving the patient 20 to 40 grammes of bicarbonate of soda a day; in the same patient the ingestion of 12 grammes of NaCl produced a much more rapid and marked hydropigenous action.

Achard and Ribot have also noted in a case of Bright's disease that sodium bicarbonate in large and prolonged doses exercises a hydropigenous action, although less than NaCl.

On the other hand, Widal was only able to obtain a moderate hydration with chloride retention by large and long-continued doses of sodium bicarbonate in a case of Bright's disease.

What is to be remembered about the hydrating action of sodium bicarbonate is that even in diabetics with denutrition, who are particularly sensitive to the salt, it is fleeting; the sodium combined in the bicarbonate is less prone to lodge in the tissues than is the sodium combined with chlorine.

By what mechanism does retention of sodium bicarbonate determine hydration of the tissues ? Does it act, as is generally admitted in the case of chloride œdemas, by a secondary aqueous retention from increase of the molecular concentration of the body fluids according to the laws of osmosis ? Or, as Heubner supposed, is it a phenomenon of hydro-

syntasis—that is to say, an increase in the affinity of water for colloid matters composing the tissues from the influence of sodium, which in this respect seems to possess much more activity than other metals ? In this second hypothesis, the accumulation of water in the tissues which have become more hydrophile would necessitate a secondary retention of the chlorides in order to re-establish the equilibrium of molecular concentration, following the mechanism an example of which was furnished by Achard in his experiments. These consisted of injecting a gelatinous substance or some saline matter into a serous cavity.

Thus could be explained the œdemas in diabetes with acidosis spontaneous or induced by sodium bicarbonate. In the first case it is the acidity of the body fluids; in the second, it is their alkalinization by the sodium which exaggerates the hydrophilia of the colloids of the tissues.

Thus, the study of the œdemas in diabetics, besides being of practical interest, reveals curious data concerning the mineral equilibrium of the organism and the pathogenic mechanism of œdemas in general.

CHAPTER XI

DIABETES AND TUBERCULOSIS*

THERE is no disease that predisposes the patient to tuberculosis as does diabetes mellitus, and the frequency of this occurrence did not escape the notice of the older clinicians. Bardsley (1807) and Copland even regarded tuberculosis as the chief cause of death of diabetic subjects. Nicolas and Gueudeville, struck by its almost certain end in phthisis, gave the name of *sugar phthisuria* to diabetes.

It is needless to consider the contrary opinion maintained by Pavy and Wilks, who not only denied the frequency of tuberculosis in diabetes, but even doubted such a possibility. Their mistaken opinion was due to the fact that, being partisans of Virchow in respect to the duality of phthisis, they attributed the pulmonary ulcers found in diabetics to non-tuberculous caseous pneumonia.

At present everyone admits this frightful predisposition of diabetics to tuberculosis. Griesinger states that 43 per cent. of all diabetics die tuberculous, while the combined statistics due to Frerichs, Seegen, and Williamson, based on autopsies, give 43 per cent. as the death-rate of tuberculosis in this affection. During life Williamson found, out of a total 100 diabetics examined, that 14 had advanced tuberculosis, 14 had incipient tuberculosis, and 1 was recognized tuberculous at autopsy only.

Although tuberculosis is a constant menace to diabetic subjects, all are not equally exposed to it. The frequency of this complication varies according to the three following conditions—namely, the midst in which the subject lives, his age, and the form of his diabetes.

Social Midst.—The majority of statistics have been made up of hospital cases, hence explaining the apparent extreme

* A clinical lecture delivered at St. Antoine Hospital, and published in the *Gazette des Hôpitaux*, July 30, 1908.

frequency of tuberculosis. The results are quite different when one studies diabetics living in easy circumstances.

Bouchardat, Durand-Fardel, Griesinger, and Mandl are unanimous in this respect, and they almost conclude that tuberculosis as a complication of diabetes is almost exclusively confined to the poor. Von Noorden's statistics, derived from well-to-do patients in a sanatorium and elsewhere, give a relatively low proportion of deaths from tuberculosis in diabetic subjects. Out of a total of 140 cases observed at various ages of life, he found 6 who died from pulmonary and 1 from intestinal tuberculosis, while in 80 diabetic coma was responsible.

Such frequency of tuberculosis in hospital cases, as opposed to its relative rarity in the well-to-do, is not merely related to misery and privations, as the older observers supposed; it is principally due to the fact that the diabetic is hypersensibilized in respect to Koch's bacillus, and he cannot resist contagion when exposed to it, as he inevitably is in hospital.

Age of the Patient.—No age has any preventive influence in respect to tuberculosis. Bertail erroneously put forward the idea that tuberculosis is rare in diabetic children and elderly people. Bouchardat considered tuberculosis as practically certain to develop in diabetics under 15 years of age. Traube and Durand-Fardel likewise admitted that diabetes in young subjects became much more frequently complicated by tuberculosis than in elderly individuals. In my opinion, this relationship is due to the form of diabetes, which in young people is almost always a diabetes with denutrition.

The Form of Diabetes.—Bouchard supposed that albuminuria made the predisposition to tuberculosis greater in diabetics, and personally he found diabetic phthisis almost exclusively in subjects with albuminuria. Dieulafoy did not attach the same prognostic value to albuminuria; out of 12 tuberculous diabetics that he mentions in one of his clinical lectures, 8 did not present albumin in the urine.

Tuberculosis is met with in all forms of diabetes, no matter what may be the ætiology or the gravity.

Charcot and Brouardel have seen it complicate "gouty" diabetes—that is to say, a mild form of diabetes. It is frequent

to see tuberculosis become grafted on obese diabetics—that is to say, in that form of diabetes which the classic writers relate to arthritism. Hutinel has even reported a very demonstrative example of tuberculosis with a rapid evolution in a young man with traumatic diabetes following a railway accident. Mild or severe, the glycoregulator disturbance invariably predisposes to tuberculosis. This predisposition does not belong to intense diabetes, as Dieulafoy has pointed out; it often occurs in robust diabetics with a mild glycosuria or even an unsuspected diabetes.

Assuredly, tuberculosis may develop in all diabetes, mild or severe, but it is not correct to say that all are equally exposed to it. On the contrary, the intensity of the glycoregulator disturbance appears to measure the degree of predisposition. Lancereaux had already noted that in pancreatic diabetes death was generally due to phthisis.

The frequency of tuberculosis is considerably greater in diabetes with denutrition than without denutrition.

In my personal statistics (1908), comprising 71 cases, it results that of 61 cases without denutrition there were only 16 complicated by tuberculosis. Of 10 diabetics with denutrition, there were 5 manifestly tuberculous; 3 others presented signs of probable tuberculosis at the time I examined them, and are to-day most likely tuberculous. In one of them the signs were slight dullness over the right apex, with weak granular respiration in front and rough respiration behind; in another there were mild dullness and respiratory obscurity behind over the left apex, slight dullness over the right apex in front, cough, and mucopurulent expectoration.

From these data one may conclude that tuberculosis is incomparably more frequent in diabetes with denutrition, and that it is even almost the rule.

The Origin of the Tuberculosis.—A diabetic subject frequently contracts tuberculosis by contagion; his receptivity in respect to the bacillus makes it very dangerous for him to cohabit with a tuberculous patient. Likewise a sojourn in a general ward of a hospital is risky. Rénon has published a fine example of familial contagion—that of a diabetic who contracted tuberculosis while nursing his daughter. One of

my diabetics became tuberculous after the death of his wife from phthisis.

However, it would be inexact always to regard the tuberculosis of diabetics as the result of contagion; oftentimes the bacillosis existed in the patient before the advent of the diabetes, but it had become cured or was in a latent state, the diabetes having merely awakened it and favoured its extension. Thus in a male diabetic who became tuberculous at the age of 45 years there was a history of Pott's disease at the age of 5 years. This patient married a healthy wife, but lost three children from meningitis. Another diabetic had lost a child from tuberculous peritonitis, and still another lost two offspring from meningitis and convulsions. Given such family antecedents, it is impossible not to suspect a tuberculous infection in the parents.

The very curious predisposition to tuberculosis in diabetic subjects may be explained by the action of glucose, which favours the development of Koch's bacillus. We now know that this bacillus grows better when glycerine or glucose is added to the culture medium. Hence hyperglycistia creates an admirable medium for the development of bacillary infection.

Nitrogenous denutrition, which characterizes the serious forms of diabetes, appears to add its predisposing action to that of the hyperglycemia. It is known that tuberculosis becomes readily implanted in subjects in a state of inanition, and that a certain amount of suralimentation, with meat especially, on the contrary, increases the resistance of the soil. Now, a diabetic with nitrogenous denutrition is in a state of true inanition.

Evolution of the Tuberculosis.

Pulmonary tuberculosis in diabetics is susceptible to assume various forms. Its evolution presents certain peculiarities that case histories bring into relief.

The Ordinary Caseous Type.—In the Moïana ward we have recently had a diabetic woman with tuberculosis.

Case I.—After having been very obese, this patient became diabetic at the age of 30 years. At the onset she presented a syndrome of very intense hyperglycemia with an abundant glycosuria of 62 grammes per 1,000 c.c. Upon various occasions treatment and diet had resulted in

an improvement, so that she had maintained a relatively fair state of health for thirty-five years. In October, 1906, at the age of 65 years, her strength declined very rapidly, likewise the body weight; in five months she lost 40 pounds.

Becoming still weaker, the patient decided to enter hospital on October 8, 1907. At this time there was polydipsia, glycosuria, and polyphagia, with a temperature oscillating from 98·6° to 100·5° F., while examination of the lungs only revealed rough respiration over the left apex without change of sonority.

The glycosuria was quickly stopped by diet, but the patient did not regain strength, and continued to lose weight, and at the same time the temperature was going up.

One month later, November 7, the patient complained of a distressing, suffocating cough, and it was noted that the tuberculosis had made rapid progress. The left apex had softened, large moist râles could be heard in front and behind, while behind the respiration was also whistling. The right apex was also undergoing softening; moist râles could be heard behind, and some subcrepitant râles in front.

On November 20 the left apex was in the same condition, while over the right apex a souffle with a metallic ring was detected.

On November 23 the respiration was whistling over the right lung.

After this the patient's condition became worse. The tuberculosis progressed, and the patient left hospital, preferring to die at home.

This is a typical example of tuberculosis grafted upon an old diabetes, with rapid torpid evolution ending in death. Two months were enough to result in a caseous melting of both lungs. The following case is similar:

Case II.—Male, æt. 53 years, having formerly indulged excessively in alcohol, and diabetic for some years past, although the exact date of the onset of the affection cannot be determined. Four years ago he lost his teeth from gingivitis, and seven years previously he had sciatica. It is possible that he was diabetic at this epoch. At any rate, the diabetic symptoms had become aggravated of late.

The patient had lost his wife two years previously from pulmonary phthisis. He himself had been afflicted by influenza, so called, a year ago, and since this epoch he has coughed and lost both weight and strength.

When he entered hospital on December 5, 1905, the patient had a moderate glycosuria. He was thin, fatigued, with a temperature oscillating between 98·6° and 100·5° F. He coughed and freely expectorated. Signs of pulmonary tuberculosis in an advanced state were noted. There was a cavity in the right apex, and infiltration with softening in the remainder of the lung. The left lung was infiltrated with tuberculous lesions which had commenced to soften.

Diet rapidly put a stop to the glycosuria, and it was found that the patient had a tolerance for 125 grammes of carbohydrates. In twenty

days he had gained both strength and weight (5 kilogrammes), coughed and expectorated less, while the râles became less numerous. Forty days after entering hospital the improvement was considerable; there were few and less moist râles, while cough and expectoration had subsided.

On February 22 patient was discharged in a relatively good condition, and it was only over the right apex that a few subcrepitant râles could still be heard.

He did not continue his diet after leaving hospital, and it was not long before the symptoms of tuberculosis and diabetes returned.

On March 13 he again entered hospital in a weak state, a loss of 5 kilogrammes in body weight and a glycosuria of nearly 100 grammes. Numerous râles could be heard over both lungs.

Again a diet was successful; it stopped the glycosuria, improved the pulmonary condition, increased the patient's strength and weight (4 kilogrammes). At the end of a month the patient again left hospital.

He returned one month later in a very serious condition. He was pale, weak, and had lost 7 kilogrammes. Respiration was very difficult, cough distressing, and expectoration abundant; temperature ranged between 100·5° and 102° F. Signs of tuberculous bronchopneumonia were detected in both lungs. Glycosuria was abundant.

This time diet was powerless to control the glycosuria or change the pulmonary condition. The patient died on June 13 in coma, and autopsy revealed both lungs riddled with cavities and a tuberculous meningitis.

Briefly, this case is an example of diabetes without denutrition; the tuberculosis was contracted from the patient's wife, and at first had a torpid evolution which soon became caseous. Upon two occasions diet controlled the situation, but the patient died two months after the onset of the pulmonary process.

The evolution appears to be still more rapidly fatal in diabetes with denutrition.

Case III.—Male, without any personal or hereditary antecedents of tuberculosis, and had never had any serious illness, fell ill at the age of 34 years. He lost weight and strength, and suffered from intense thirst and polyphagia. He became nervous and irritable. A physician consulted found a glycosuria of 86 grammes per 1,000 c.c., and ordered a meat diet without sugar or starches.

The general health then seemed to improve, but soon the patient began to cough. This was at first dry, but soon was accompanied by expectoration. There was nocturnal sweating, and emaciation was rapid. A stay in the country resulted in temporary improvement, then the temperature went up, the strength declined, and emaciation progressed.

On November 5, 1905, patient entered hospital. There was serious diabetes; total amount of urine ranged between 2,500 and 3,500 c.c., containing from 200 to 300 grammes of sugar with a diet containing 110 grammes of carbohydrates.

Appetite very capricious, liver hypertrophied, tongue coated. Tendon reflexes very diminished. Patient complained of myalgia and pruritus. . Muscular strength greatly decreased, and there were attacks of narcolepsy and temporary diplopia. There was little albumin in the urine. Blood-pressure was low (13 with Potain's instrument), Fever moderate.

Cough frequent, expectoration free. There was tuberculous infiltration, with softening and multiple small cavities in the left apex. In the right apex there was infiltration with slight dullness and subcrepitant râles.

A fortnight later the condition was the same, and after this it became worse. The patient could not leave his bed, there was œdema of the legs, appetite almost *nil*, and there was an aphthoid stomatitis.

On December 8 the patient was very weak, somnolent, the breath and urine gave off an odour of acetone; Gerhardt's reaction was positive. Pulse 112; blood-pressure low, = 11. Sodium bicarbonate was ordered in large doses, but the somnolence continued.

On December 13 a left-sided pyopneumothorax was found, also a slight ascites, and the patient died the next day.

At autopsy there was a purulent peritonitis, a left pyopneumothorax, and a lung so riddled with cavities and adherent to the thoracic wall that it could not be removed. The right lung was filled with tubercles.

Case IV.—Female, developed diabetes of mild aspect in November, 1905. In August, 1906, she began to cough, and complained of pain in left chest; lost weight and strength rapidly.

When she entered hospital a glycosuria of from 200 to 300 grammes per day was found in spite of a reduced carbohydrate diet, a polyuria of 5,000 c.c., liver hypertrophied, and patellar reflexes absent.

Examination of the lungs showed the beginning of tuberculosis in the left apex: increased vibrations, rough granular respiration, prolonged expiration; some dry crackling after coughing. Some subcrepitant râles over right base. Temperature ranging from 98·6° to 100·5° F.

In spite of treatment the tuberculosis made rapid progress; both lungs softened and cavities developed. The patient died on October 11. At autopsy a caseous pneumonia was found in the right lung with a cavity in the apex; in the left lung there were disseminated tuberculous lesions and œdema.

Case V.—Female, æt. 29 years, had had diabetes with denutrition for only one month. She began to cough at the beginning of December, 1906, and entered hospital, where sibilant and moist râles were found over both lungs, with a very slight dullness over the right apex.

The pulmonary lesions rapidly became worse, the patient emaciated, severe night sweats, cough, and expectoration. Mild dullness was

found over the right apex, blowing respiration, and some râles at the end of respiration. The left apex in turn became involved; dry crackling could be heard after coughing. The sputum contained large numbers of Koch's bacilli.

Weakness was extreme; appetite *nil*; glycosuria ranging between 200 and 300 grammes per day. Albumin in urine. Temperature varying from 100·5° to 104° F.

The moist râles became general throughout the lungs, caseation made rapid progress, and the patient died on February 7, 1907—a little more than two months after the onset of the pulmonary tuberculosis.

These cases are typical. They depict the *usual aspect* of pulmonary tuberculosis in diabetes.

The onset is insidious; there is no pleuritic pain, no febrile reaction, and no hæmoptysis. It is only marked by cough, expectoration, and rapid emaciation. Hence the diagnosis of tuberculosis at its initial phase in a diabetic subject is particularly difficult. A prolonged cold should cause the physician to be suspicious, and every diabetic with a cough should be carefully auscultated.

Examination of the sputum, when it reveals the tubercle bacillus, will clinch the diagnosis. Unfortunately it is often negative in tuberculous diabetics. Von Noorden has insisted upon the frequent absence of bacilli in the sputum even when the tuberculosis is undeniable. Such is the case in a female patient now under observation. For the past few days she has emaciated, lost strength, has a slight febrile state, coughs and expectorates large purulent masses of sputum. Auscultation reveals disseminated sibilant râles in both lungs and soft friction sounds over both apices; in the right subspinous fossa percussion sonority is diminished. In spite of this syndrome, which imposes the diagnosis of tuberculosis, there are no bacilli in the sputum.

Absence of bacilli is very awkward for the diagnosis, because the clinical signs obtained from the pulmonary apices in diabetics frequently lead to erroneous conclusions. I know of two cases of this kind—one a diabetic with denutrition at the Laennec Hospital who was examined by a number of physicians; some affirmed that there was tuberculosis in the right apex, where they found slight dullness and rough jerky respiration, while others declared that the disease was in the left apex with quite as much assurance.

In the second case autopsy showed the clinical mistakes made. The subject, a diabetic without denutrition, died from infectious rheumatism. During his illness some mild dullness with decrease of the vesicular murmur and rough inspiration was noted over the left apex. Autopsy showed that there was not a trace of tuberculosis anywhere; there was an œdematous congestion at both pulmonary bases with recent pleural adhesions; nothing in the apices.

Emaciation is an important symptom, which should lead one to suspect tuberculosis, but there is nothing specific about it, because a diabetic may emaciate from other causes. Very often it is because the diet is improperly ordered, in which case all that is necessary is to regulate the food intake to stop the loss of weight.

The *evolution* of tuberculosis in diabetics is rapid; it is a phthisis that consumes. The onset is sometimes difficult to detect, and when the patient consults his physician one is often astonished at the ravage tuberculosis can accomplish in so short a time. From one examination to the next the tuberculosis will be found to have progressed. In one of my patients at the first examination I only found a slight degree of dullness over the right apex; eight days later crackling could be heard, and three months later the patient died with progressive caseation in both lungs and a cavity in the right apex.

In spite of this rapid progress the temperature is very moderate; often it does not exceed 100·5° F. throughout the illness; there may not be any sweating, and sometimes a rise of temperature is unsuspected until the thermometer is used; but only exceptionally is it wanting. As Pidoux used to say, the tuberculosis of diabetics is a *cold* process without reaction.

No matter what may have been said, tuberculosis usually never acts on the diabetic process itself. Lecorché and many others have noted the disappearance of the glycosuria during the final phase of the disease. The reason is quite natural; it is due to the diminished appetite, the ingestion of the carbohydrates falling below the patient's tolerance. My observations have shown that neither tuberculosis nor fever increases the tolerance of the diabetic; quite on the contrary, they cause it sometimes to diminish. In diabetics with denutrition the glycosuria persists without decreasing to the end.

Phthisis of diabetics has almost invariably a fatally progressive evolution. It kills in one or two years, sometimes in only two or three months. Its progress is more rapid in diabetes with denutrition than when there is no denutrition. Thus, the first three cases I have here reported belonged to the second category, and died in from eighteen months to two years, while the three last cases of diabetes with denutrition died within hardly two months.

However, the rapid progress is not always evident, and the evolution may be prolonged and undergo temporary arrests. The cases published by Lecorché, Bouchardat, Griesinger, and Trousseau show that tuberculosis is susceptible of becoming arrested, and may even be recovered from. Lépine not long since insisted on the relative benignancy of certain cases.

I have observed that by treating the hyperglycemia an already advanced tuberculosis might undergo an arrest, retrogress apparently, and mislead the serious prognosis given. I also have some case records of diabetics whose pulmonary lesions seemed to have no tendency to progress.

However, I have never seen recovery from tuberculosis in a diabetic, and I believe that one must be very reserved in reference to cases of so-called recovery, given the great difficulty of making a diagnosis of tuberculosis at its onset in diabetic subjects.

From the pathological view-point phthisis of diabetics is distinguished by no peculiarity from tuberculosis having a caseous evolution with infiltration, softening, and cavity formation. At the terminal phase there is a tendency to generalization, and in two of my cases there was a meningitis and tuberculous peritonitis with tubercles in other viscera.

Tuberculosis with a caseous evolution is the most frequent form met with in diabetics, but it is not the only one. The *broncho-pneumonic*, *acute miliary*, *hæmoptoic*, and *pleuritic* forms are met with as well.

Broncho-pneumonic Form.—Dieulafoy has reported one case of tuberculous broncho-pneumonia in a diabetic, and I can add another.

Case VI.—Female, æt. 61 years, with a moderate diabetes which appeared to have commenced at the age of 52 years. At the age of 54 the patient underwent an operation for uterine fibroma. Two years

later she again underwent an abdominal operation, and at this time sugar was found in the urine; there was also gingivitis, which caused the loss of teeth. At the age of 59 years the patient was operated on for an abscess in the neck, probably a suppurating tuberculous adenitis.

She came to hospital on May 7, 1907, complaining of oppression and dry cough without expectoration; at the middle of the right lung souffles could be heard, as well as a focus of fine subcrepitant râles.

In ten days the symptoms were improved; only a few subcrepitant râles could be detected over the apex in the right axilla, with some friction sounds along the spine.

After a temporary improvement the patient returned to hospital on June 7. The cough had increased; the expectoration was free and nummular, containing the bacillus of tuberculosis. Respiration was difficult, accelerated, and the patient was obliged to remain almost all the time seated in bed. A focus of broncho-pneumonia was detected in the upper right lobe: dullness, increased thoracic vibrations, subcrepitant râles, and a souffle having an almost amphoric ring. In the left lung the breathing was whistling. Temperature ranged between 100·5° and 102° F.

On June 12 the lesions had progressed. The souffle persisted in the apex, and was accompanied by a splashing sound. In the lower two-thirds large subcrepitant râles could be heard, and some fine râles at the base. Cardiac beats = 110 to the minute. Tongue very dry. Temperature still high.

On June 20, a cavity had developed in the right apex, and percussion elicited the " cracked-pot " sound.

The temperature at length reached 102° to 104° F., the dyspnœa and asphyxia increased, and diarrhœa developed. Prostration became marked, and death occurred on July 5.

At autopsy an enormous cavity filled with pus was found in the right apex, foci of tuberculosis, and pleural adhesions in the remainder of both lungs.

The Acute Miliary Form.—Letulle has published two cases of acute miliary tuberculosis occurring in diabetics. This is very uncommon.

The Hæmoptoic Form.—All observers agree that the pulmonary tuberculosis of diabetics is rarely accompanied by hæmoptysis, but Christison, Marchal de Calvi, Lecorché, and von Noorden have met with instances. The loss of blood may acquire a considerable importance, and was the cause of death in Dieulafoy's, Richardière's, and Sicard's cases.

At other times the hæmoptysis recurs so frequently and in such quantity that it imparts a peculiar aspect to the tuberculosis.

Rénon has met with a fine example in a patient that he

followed for several years, and whose condition had not become aggravated at the end of five years; he believes that this hæmoptoic form is more superficial and more inclined to remission than the other forms.

I have had one case occurring in a diabetic without denutrition.

Case VII.—The onset of the diabetes was uncertain, but the disease appeared to be of long standing. The onset of the tuberculosis dated back to the age of 18 years; it was marked by expectoration of blood, lasting three days, and fever. However, the subject was able to go through three years of military service without being ill, and afterwards went to work.

At the age of 40 years his health began to decline; he became emaciated, coughed, and felt very weak. However, he continued his work as tailor.

At the age of 43 years his wife remarked that the patient's breath had the odour of acetone; he coughed frequently, the sputum was purulent, and he sweated at night. In June, 1907, he was seized with hæmoptysis and entered hospital.

He was discharged improved a month later, but on August 8 another hæmoptysis occurred, and the patient again entered hospital. During August the temperature ranged around 100·5° F.

At the end of August the temperature rose to 102° F., cough was distressing, breathing difficult, sputum purulent and blood-stained, nights were bad.

During September the strength declined. On September 18 a cavity was detected in the right apex and a tuberculous infiltration of the left apex. Scattered moist râles were heard in both lungs.

A few days later the patient died from a violent hæmoptysis.

Autopsy revealed a cavity the size of a walnut in the right apex filled with blood-clot, and about 300 c.c. of hæmorrhagic fluid in the right pleural cavity.

The Pleuritic Form.—Pleurisy is rare in diabetics, and Dieulafoy brings this rarity into relief by comparing it with the frequency of pulmonary tuberculosis. He was only able to find one example of serofibrinous pleurisy, this terminating in death, and published by Bigou (Thesis, Paris, 1888).

The Fibrous Form.—Fibrous phthisis and its various clinical modalities do not seem to occur in diabetics. I know of no instance. Given the frequency of this form when tuberculosis in general is considered, it must be supposed that the diabetic soil is particularly unsuited for a sclerous evolution of the tubercle, while, on the contrary, it favours caseation.

Principles of Treatment.

From what we know of the predisposition of diabetics to tuberculosis a distinct line of treatment is evident. First of all, these subjects should avoid exposure to contagion; this is prophylaxis.

When a diabetic develops tuberculosis the soil must be changed, and cause the hyperglycistia, favourable to the development of the bacillus, to disappear.

This is not the classical doctrine. Most writers maintain that a severe treatment is more harmful than useful in tuberculous diabetics. Dieulafoy says that "it is not necessary, but, on the contrary, rather harmful, to endeavour to cause the glycosuria totally to disappear by resorting to drastic diet"; he believed that "by an exacting régime nutrition is vitiated, and that the diabetic is exposed to albuminuria, emaciation, and tuberculosis." Rénon at first maintained this point of view, but at present he believes in the usefulness of treatment.

The cases that I have brought forward in this lecture show how needless is this fear. It is by diet only, without drugs of any kind, that I have upon two occasions made one of my patients fatten and produce a considerable amelioration of the pulmonary symptoms. On the contrary, when this patient left hospital and neglected his diet, the glycosuria reappeared and the tuberculosis made more progress.

Since it is the hyperglycistic soil that favours the development of Koch's bacillus, it is logical to cure the hyperglycistia in order to control the tuberculosis, and it is by diet only that this can be accomplished.

For that matter, properly ordered reduced carbohydrate diet should not cause a diabetic subject to emaciate; on the contrary, he will fatten on it. To carry this out, one must not blindly prescribe a *diet of proscriptions*, which in most cases will be found impossible to follow. If the case is one of diabetes without denutrition, the physician should progressively reduce the carbohydrates by exactly indicating the various foods that may be permitted.

Should the case be one of diabetes with denutrition, the treatment must be different. Here the hyperglycistia cannot

be done away with. Therefore, all that can be done is to reduce the carbohydrates without eliminating them completely from the diet. On the other hand, in order to prevent nitrogenous denutrition, an alimentation rich in albuminoids and fats should be ordered.

Treatment with drugs has only a secondary importance. These will have no more action on the diabetes than on the tuberculosis. Arsenic is useful to tone up the patient; the alkalines for their action on the hepatic disturbances, as well as for acidosis and to prevent demineralization. As to antipyrine and aspirin, they are ineffective and sometimes harmful.

CHAPTER XII

THE TREATMENT OF TUBERCULOSIS IN DIABETES*

TUBERCULOSIS is one of the most frequent and redoubtable complications of diabetes.

It is serious, rapid, and fatal in evolution, whether it be the caseous, broncho-pneumonic, miliary, or hæmoptysic forms of the disease. It usually ends in death in a few months; rarely does it last more than two years, while in some cases death ensues within two or three months. The prognosis is regarded by Jaccoud, Dieulafoy, and the classic writers in general as absolutely fatal.

However, some recoveries have been mentioned. Griesinger, Bouchardat, Lecorché, and Trousseau have recorded instances. Lépine has met with cases of tuberculosis in diabetics which improved, but all such cases are rarities.

The rapid and fatal evolution of tuberculosis in diabetes is in part due to the fact that the majority of physicians are fearful of employing an antidiabetic diet, which they regard as pernicious in tuberculosis. This is a mistaken opinion. On the contrary, I have noted that *each time the hyperglycemia was dealt with in a tuberculous diabetic the bacillosis was improved, and that it helped it to be recovered from.*

CASE I.—Male, æt. 50 years, diabetic, with a cavity in the apex of the right lung and signs of softening in the left apex, was seen in 1908. The glycosuria was abundant—150 grammes per day. By diet the glycosuria rapidly lessened, the patient put on weight, and the pulmonary lesions improved considerably. After leaving the hospital he ceased to follow the diet, and was obliged to return a month later, having lost 5 kilogrammes of body weight and presenting a glycosuria of 100 grammes and aggravated pulmonary lesions. While in hospital the second time he gained 4 kilogrammes, and the pulmonary condition was very considerably ameliorated. But the patient again left hospital, and did not follow his diet. The diabetes returned, and the patient soon died of the tuberculosis.

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* A clinical lecture delivered at the Charité Hospital, February 16, 1911.

In this case the tuberculosis was twice held in check by a diet for the glycosuria, but as soon as the patient ceased his regimen it continued its evolution.

The following case also shows that the evolution of tuberculosis is controlled when the diabetes is dealt with:

Case II.—Male, æt. 41 years, entered hospital in a very serious condition, November 5, 1906. He had had diabetes for about two years, and his urine at the onset contained 119 grammes of sugar, thirst was intense, and he was very weak. For the past six months the diabetic symptoms had become more severe; polydipsia, polyuria, and polyphagia were very marked, and the patient also had amblyopia and impotency.

Finally, for the last two months pulmonary tuberculosis had been present, and he had emaciated considerably. His antecedents were burdened. He was alcoholic, had contracted severe malaria in Guiana, he was syphilitic, and had suffered from an attack of acute articular rheumatism. Five years ago he had ascites, from which he recovered.

When he entered hospital he was very thin and weak, he looked old, the hair was becoming grey, and the conjunctivæ were yellow. Tongue coated, liver hypertrophied, spleen enlarged and could be palpated. Patellar reflexes very diminished. Glycosuria abundant—319 grammes.

There was cough and purulent sputum, and in the right apex there was dullness with numerous moist râles revealing the presence of a cavity. Subcrepitant râles could be heard over the rest of both lungs. No temperature.

Given the gravity of the general condition, the advanced development of the tuberculosis, the weak state of the patient, and the high degree of glycosuria, I at first thought that treatment would be without avail and diet illusory.

However, an attempt was made to reduce the hyperglycemia by diet. At the end of three weeks the result was marvellous; the syndrome of hyperglycemia had disappeared, the glycosuria had subsided. The patient had gained both weight and strength. The râles had decreased in the lungs, and the symptoms of a cavity were about all that remained.

During the following months the patient was kept on a diet corresponding to his tolerance for carbohydrates. The glycosuria had not returned, he had gained 5 kilogrammes in weight, and the general condition had remained relatively good; however, the pulmonary lesions progressed, and the lung slowly became excavated.

During the summer hectic fever with great oscillations occurred, and the patient declined. He died some months later from tuberculosis.

Here, therefore, is a diabetic in whom tuberculosis developed insidiously, and progressed so rapidly that two months after the onset it had already produced a cavity in the right lung.

In spite of the extent of the pulmonary lesions and the gravity of the general condition, a reduced diet was successful; the patient put on weight. And this subject, who was brought to hospital in a state of extreme weakness and cachexia, incapable of getting out of bed, finally was able to be up and about, and came to hospital for advice and treatment. It would seem as if the evolution of the tuberculosis had been controlled momentarily.

Case III.—In 1910 I saw, with Dr. Bezançon, a young man with diabetes and abundant glycosuria, who presented a tuberculosis having a broncho-pneumonic evolution and softening of an entire lung. An early death was the only prognosis that could be given. Nevertheless, by diet strength returned, the temperature fell, and the tuberculosis underwent a much slower evolution than was to be expected.

Case IV.—The patient that I show you to-day is 58 years old. Her antecedents are laden. Her mother died of tuberculosis, as did her daughter. Her sister is diabetic. It would appear that the tuberculosis developed early in the patient's life. At 18 she had pulmonary congestion and pleurisy at 20. However, from 20 until 52 years of age the patient felt well, although she frequently had colds, but for the past six years she has had bronchitis each year which has lasted from two to three months. This year she has coughed more than usual and expectorates, there has been fever, and finally last April she had hæmoptysis.

She entered hospital on March 5. Some dullness was found over the left lung, and an amphoric souffle with moist râles indicated the existence of a cavity. Over the right apex a tubal souffle with subcrepitant râles could be detected. Râles of bronchitis existed in both lungs. The temperature oscillated around 101° F., sometimes reaching 102·3° F. in the evening. Cough was frequent, and the abundant expectoration contained Koch's bacillus.

At the time she entered hospital the glycosuria was 158 grammes per day; with the exception of rather great thirst, the functional signs of diabetes were not very evident, although the teeth had fallen out from gingivitis. The reactions for acidosis in the urine were negative.

The patient was put upon a reduced carbohydrate diet. The following day the glycosuria had dropped from 69 to 8 grammes, and afterwards remained at about 10 grammes.

On May 10 the improvement was notable; the patient coughed and expectorated less, and the temperature was lower; the dyspnœa had subsided. Auscultation of the right apex revealed a less intense souffle and fewer râles; the râles had decreased over the left lung, and it seemed as if the cavity was drying up.

On May 20 the patient's weight had increased from 43 to 44 kilogrammes 200 grammes, and she had more strength; she walked and

could go upstairs without being too much out of breath. She slept well, the temperature oscillated between 98·6° and 100·5° F. Only a few râles could be heard after coughing over the right apex; on the left only some subcrepitant râles existed.

Therefore, this patient's general condition is at present satisfactory, and it is to be hoped that the improvement may continue.

Such results are not uncommon. I will give two others.

Case V.—Male, æt. 53 years, has been diabetic since the age of 25. He belongs to a tuberculous family. For the past year he has coughed; sputum purulent, containing Koch's bacillus; no hæmoptysis. There is some dullness over the right apex with diminished respiration; no râles. A little albumin in the urine.

He was put upon a diet and rest. The glycosuria fell from 159 to 25 grammes; the temperature also dropped; while the body weight rose from 72 to 78 kilogrammes. The stethoscopic signs did not change.

Briefly, although the tuberculosis persisted, a great improvement took place; the evolution was very slow.

Here is another very characteristic example that was under my care in hospital in 1910:

Case VI.—The patient, a young woman, with serious diabetes with denutrition, had during 1910 an outbreak of tuberculosis with emaciation, moderate fever—not much above 100·5° F.—and Koch's bacilli in the sputum. When she entered my ward, both lungs were involved; there were slight dullness, souffle, and subcrepitant râles over the left apex; over the right apex were signs of infiltration, and a little later there were evidences of the onset of softening.

Anorexia prevented the patient from properly feeding; an improvement could not be expected; but, in spite of the very reduced diet, the body weight did not drop off, but rather increased a little, strength returned, and the menses appeared. Gerhardt's reaction was no longer positive.

After a summer in the country the patient returned fattened to the extent of several kilogrammes, and no signs of sclerosis could be found in the right apex. To my great astonishment the evolution of the tuberculosis had become arrested in spite of the diabetes and insufficient feeding.

You have also seen in my wards a young woman under treatment for the past year for diabetes. There was a rough, granular respiration over the right apex. Radioscopy showed opacity at this level. Nevertheless, she has now recovered, and can be regarded as cured.

These cases prove that when diabetes is properly treated

the tuberculosis can be arrested. Much harm is done to diabetics by suralimentation, and this unfortunate practice is certainly one of the reasons for the rapid evolution of tuberculosis in them. If, on the contrary, the patient is put on a reduced carbohydrate diet intended to reduce the hyperglycemia, the tuberculosis will also improve, the fever ceases, the weight increases, strength returns, the pulmonary symptoms improve, and the lesions retrogress. After a few weeks of treatment the change wrought is surprising, and the improvement is such that the patient can be discharged and return to work. In the fortunate cases, in patients who understand how to take care of themselves, a real cure may ensue. On the contrary, if the patient neglects his diet, the hyperglycemia recurs, and with the tuberculosis continues its evolution.

The mechanism of régime is easy to understand. When suralimentation is essayed in a tuberculous diabetic and the tolerance for carbohydrates exceeded, the result will be a hyperglycemia and hyperglycistia which are eminently favourable for the development of the bacillus of tuberculosis. Inversely, when by a reduced diet the body fluids and tissues are made normal by the disappearance of the hyperglycistia, the patient will be able to set up a defence against the tuberculosis just like any other individual.

This result, which can be obtained in diabetes without denutrition with more or less ease according to the patient's degree of tolerance, is impossible to bring about in a diabetic with denutrition, because the hyperglycistic state is irreducible, and this is what explains the exceptional gravity of tuberculosis in this form of diabetes. However, a relative improvement may ensue if a diabetic with denutrition can be prevented from resorting to exaggerated suralimentation.

At the same time that one reduces the carbohydrate diet, attention must be paid not to reduce the albuminoid and fat intake. It is essential not to place a diabetic with denutrition in a state of nitrogenous inferiority by a defective regimen, and to limit as far as possible the nitrogenous waste by a proper diet. The paucity in albuminoids which is characteristic of the organic soil of inanition, cachexia, enteritis, and serious diabetes, is without doubt, along with the hyper-

glycistia, one of the causes of the seriousness of the evolution of tuberculosis in diabetes with denutrition.

As much can be said of demineralization, which is considered as one of the predisposing factors of tuberculosis. The instability of the mineral equilibrium in diabetes with denutrition undoubtedly contributes to decrease the force of resistance of the soil against invasion of the tubercle bacillus. Hence, one should endeavour to mineralize these patients, and for this purpose alkaline treatment may be utilized.

From what I have said I want you to especially remember that *tuberculous diabetics should be treated in the same way as if they only had diabetes*, and that reduction of the carbohydrate intake, by causing the hyperglycistia to cease, places the diabetic in quite as good a posture as any other subject for combating the inroads of the bacillus of tuberculosis.

CHAPTER XIII

THE TREATMENT OF INTERTRIGO AND ERYTHEMA OF THE VULVA

INTERTRIGO and especially vulvar erythema in the female are to be counted among the most frequent complications, as well as the most disagreeable, of diabetes mellitus.

These cutaneous lesions are more prone to occur in obese subjects. By favouring contact and friction of the skin, obesity predisposes to erythemata; these are very tenacious, become excoriated, and easily suppurate in diabetics. Underneath the breasts, in the axillæ and groins, in the intergluteal region, and especially in the genital region—the glans and prepuce in the male—and vulva, the production of erythema is facilitated by the fermentation of glucosic urine.

Vulvar erythema is one of the disclosing symptoms of diabetes, one that is the most likely to lead the patient to seek medical advice. It begins by distressing itching and an irresistible desire to scratch, prevents sleep, and disturbs the pudency of some women. By scratching the irritation increases; the pruritus is replaced by a sensation of heat; an erythematous redness occupies the region of the vulva, and extends beyond towards the groins and upper portion of the thighs. It is soon accompanied by a thickening of the mucosa, and then of the skin. Small excoriations occur on the surface of the mucous membrane. A serous fluid, staining the linen yellow, is continually oozing forth; occasionally abnormal fermentation developed in the folds of the region gives off a foul odour.

Eczema succeeds erythema, and if this continues a thickening and lichenification of the skin ensues. The indurated labia minora drop down between the labia majora, which themselves are swollen. The irritation and pain resulting from these lesions are sometimes such that the patient completely loses sleep, and life becomes intolerable.

The ordinary treatments of erythema fail in these cases. Baths, powders, ointments, and electricity all remain without avail so long as only local treatment is given. This is because the erythema of diabetics is caused and kept up by the hyperglycemia, and will only subside when the latter is dealt with. Hence general treatment is essential. When the hyperglycemia ceases by an appropriate diet, the tissues, becoming relieved of the sugar they contain, assume the vitality of normal individuals. The applications that were unsuccessful at the beginning will then quickly restore the parts to the norm.

Here are a few examples:

Case I.—Female, æt. 60 years, diabetic and obese, was seized by an erythema under the breasts which for several weeks had resisted all local treatment—even the application of a solution of silver nitrate. However, she only offered a mild glycosuria. A reduced carbohydrate diet caused the hyperglycemia and glycosuria to subside in a week, and the intertrigo was completely cured as well.

Case II.—Female, æt. 55 years, obese and a large eater, became diabetic at the age of 50. Since then the glycosuria has varied between 250 and 300 grammes per day. The teeth had fallen out, she had had neuritis of the lower limbs, and now had erythema of the vulva. She had taken drugs, but had never submitted to a diet, as she believed the diabetes to be incurable. However, the vulvar pruritus was so intolerable that she decided to come from Poitiers to Paris for consultation.

Some starch baths were ordered with a zinc oxide powder, and she was made to follow a reduced carbohydrate diet comprising only 25 to 39 grammes of carbohydrates.

In a week the glycosuria fell from 250 to 7 grammes, the pruritus of the vulva completely subsided, and the vulvar region had become normal.

Case III.—Female, æt. 48 years, had had diabetes for eleven years. She had had repeated attacks of furunculosis and styes. The teeth had fallen. She had taken several cures at Vichy and various drugs, but had never followed a diet, or, rather, she had thought she had taken a "parmentière cure" by eating a kilogramme of potatoes a day with large quantities of gluten bread.

The glycosuria had varied, but had never ceased, the last analysis showing 175 grammes of sugar. For the past sixteen months the patient has had a vulvar erythema, which caused intense suffering both day and night. The perineal region, the upper part of the thighs, and inguinal regions were red and moist, the labia majora and minora were thick and indurated, the vagina inflamed, and a prolapsus uteri with a discharge from the uterus contributed to keep up the local irritation.

She consulted me for relief from her suffering. A diet comprising 30 grammes of carbohydrates was at once ordered, a cure with Vichy water, and the local application of a zinc oxide ointment.

After three days' diet the glycosuria had fallen from 175 to 10 grammes, while the pruritus and vulvar pain had decreased. Six days later the glycosuria had completely ceased and the local improvement was rapidly continuing; the redness was less, the pruritus had almost subsided, the patient slept well—a thing that she had not done for months. After a six weeks' rest with diet and local treatment the vulvar eczema was completely cured, the tissues had recovered their softness, and only some pigmentation of the skin remained.

These cases are typical examples. They show the primordial importance of treating the hyperglycemia in order to cure the vulvar erythema and intertrigo in diabetics.

The treatment of erythema of the vulva in diabetics comprises two parts—viz.: (*a*) Cure of the hyperglycemia; and (*b*) local treatment of the erythema.

(*a*) **Cure of the Hyperglycemia.**—The treatment of hyperglycemia reposes upon three very simple principles, which can be summarized as follows:

1. Place no credence in medicaments, such as antipyrine, opiates, salicylates, etc., which are generally without effect.

2. For the hepatic disturbances frequent in diabetics, prescribe alkaline treatment with Vichy water (Grande Grille) heated to 104° F., and taken at the dose of one glass before each meal. This treatment should last fifteen to twenty days.

This is followed by an arsenical treatment destined to counteract the cutaneous lesions and to stimulate the patient's nutrition. About fifteen subcutaneous injections of sodium cacodylate at the dose of 5 centigrammes each are given every second day.

3. Reduced carbohydrate diet is the basis of treatment. It is to be ordered taking into consideration the form of the diabetes, the former habits and taste of the patient.

If there is reason to obtain a very rapid reduction of the hyperglycemia, an inanition treatment can be essayed for two to three days, but usually it is better to proceed less brusquely, and to be content to reduce the total intake of food and the amount of carbohydrates in the diet.

By this treatment the glycosuria rapidly decreases and then ceases in the majority of cases. It is well to continue

the reduced diet for some days after the cessation of the glycosuria in order to further remove the glucose infiltrating the tissues.

(*b*) **Local Treatment.**—For intertrigo of the skin, drying and astringent powders are to be prescribed, and as curative medication alkaline and astringent lotions should be ordered; and if the process resists this treatment, recourse may be had to daily applications with a 2 per cent. solution of silver nitrate.

For the vulvar pruritus hot lotions are to be applied in the morning and evening, using boiled starch water or bran water.

After the lotion, the parts are thoroughly dried with absorbent cotton without friction, and a little of the following ointment is applied:

℞. Zinci oxid. .. .. .. 2 grammes.
Cocain. hydrochlor. .. 50 centigrammes.
Lanolini } .. .. .. āā 10 grammes.
Vaselini }

The region may also be powdered with the following:

℞. Pulv. camphor. .. .. 40 centigrammes.
Pulv. iris .. .. .. 1 gramme.
Pulv. amyli } .. .. āā 10 grammes.
Pulv. talcum }

In the above ointment the cocaine can be replaced by carbolic acid 1 gramme. The use of menthol should be guarded, as it is sometimes irritating.

When the pruritus and erythema resist this treatment, the starch lotion may be replaced by an alkaline lotion containing 2 per cent. sodium borate, or by a daily application of a 2 per cent. solution of silver nitrate.

When the local inflammation is very considerable, good results may be obtained by spraying the parts with boiled water two or three times a day with some apparatus similar to that devised by Lucas-Championnière.

Finally, in very obstinate forms, especially in neuropathic individuals, if the pharmaceutical treatment does not give sufficiently rapid results, physical procedures are to be essayed, such as hydro-electric static douches and high-frequency currents; radio-therapy or radium-therapy may be resorted to with prudence.

When the vulvar erythema is very irritated, it will be necessary to impose rest in bed or on a lounge, at least for the first few days of treatment, in order to avoid friction, which is inevitable during walking.

Finally, in neuropathic subjects it is indispensable to calm the irritability of the nervous system by the use of antispasmodic remedies: potassium bromide, 2 grammes daily, or camphor bromide in capsules at the dose of 50 centigrammes. Various preparations of valerian in pill form will be of great service.

When combined with diet, which is the basis of treatment, I have never seen these various therapeutical measures fail to cure the most stubborn intertrigo and vulvar erythema.

CHAPTER XIV

DIABETES OF INFECTIOUS ORIGIN

THE ætiological relationship between diabetes mellitus and the acute infectious diseases is still a moot subject. However, the problem has been discussed many times, and a certain number of observations would seem to admit an affirmative reply. Thus, cases of diabetes following typhoid fever have been reported, likewise after whooping-cough, measles, and influenza; but, according to Naunyn, none of them can be regarded as decisive.

Zinn met with an acute diabetes following scarlatina in a child of four years of age which underwent its evolution in two months and a half, ending in recovery; Naunyn denies the relationship between the glycosuria and scarlatina, because it was only discovered ten weeks after the infectious disease. This criticism appears to me to be exaggerated, because an albuminuria occurring in the same circumstances would certainly be regarded as scarlatinal.

Holsti has related the case of a male, æt. 41 years, who developed an acute diabetes with a sudden onset following an attack of influenza: Thirst was severe; there were polyuria, a glycosuria of 22 grammes per day, and emaciation to the extent of 17 kilogrammes in two months. The process only lasted two and a half months, and complete recovery ensued.

Galippe has maintained that certain diabetes are the result of bucco-pharyngeal infections and the continued absorption of pus from chronic gingivitis; he believes that the latter is rather more the cause than the consequence of diabetes. With Debré, I have reported the case of a young man who developed a curable acute diabetes following mumps complicated by pancreatitis. Other observers have recorded similar cases.

Achard and Loeper have published the case of a patient with pneumonia who developed a spontaneous diabetes during

the evolution of the pulmonary process; the glycosuria disappeared during convalescence, and then recurred several months afterwards, accompanied this time by polyuria and polydipsia.

Numerous instances of diabetes have been encountered following carbuncle. An adversary of the infectious origin of diabetes, Naunyn does not believe that carbuncle is ever the cause of this morbid process. He, on the contrary, maintains that the diabetes is only a predisposing factor for the carbuncle, and that the latter causes a latent diabetes to be discovered, as it gives rise to an analysis of the urine. He interprets in the same way all glycosurias met with during or following various suppurative processes, such as furunculosis, gangrene, and erysipelas. Von Noorden is practically of the same opinion. He thinks that one frequently reasons *post hoc, ergo propter hoc*, and that glycosuria observed after an infection is not necessarily a sequela.

The ætiological relationship between glycosuria and infection is often very difficult to establish, and mistakes can readily be made. Von Noorden reports a striking example. One of his diabetic patients stated that the disease began after a very severe attack of influenza; during the influenza the urine was examined and albumin was found, but no sugar. After the influenza the urine was voided in large amount, so that sugar was looked for and found, since which time it had remained present. But in going over the papers of a life assurance company, to which the patient had applied before the attack of influenza, von Noorden found that sugar had at this time been found. The influenza, therefore, was not the cause of the diabetes; on the contrary, it had interrupted the glycosuria, as is seen in other infectious diseases occurring in diabetic subjects.

Hence the problem is not solved. It is only by detailed and precise case histories, escaping all possible criticism, that it can be shown that acute infectious diseases are susceptible to create diabetes.

This pathogenical notion is distinctly evident in the two following cases:

Case I.—Male, 45 years old, obese, but with general good health, took a chill in February, 1903, followed by an herpetic angina with

fever. I saw him on February 16, and as a precaution the urine was examined. There was no albumin or sugar.

The angina was recovered from, and the patient went to rest up in the country, but from this time on he began to complain of a dry mouth and perpetual thirst which daily increased. He drank a good deal, and the urine was voided in large amount. The hands were dry and the skin hot. He complained of extreme lassitude and weakness in the legs. Emaciation was rapid. The sight, which had been excellent, progressively diminished, and on February 26 he found that he could not read a sign that was posted up on the opposite side of the street.

Frightened by this condition of affairs, he came to see me; and although a fortnight before the urine contained nothing, on March 4 the report was as follows: Urine = 5,000 c.c., with 83 grammes of sugar per 1,000 c.c., hence 415 grammes of glucose per twenty-four hours. On the same day he was weighed, and it was found that from 114 kilogrammes his weight had fallen to 104 kilogrammes; in less than three weeks he had lost 10 kilogrammes.

Examination of the eyes by Dr. Terrien revealed no change in the fundi. The glasses prescribed gave back his normal vision, but for one day only. On March 5 they were insufficient, and the patient saw persons around him in a confused way. He said that it was impossible for him to distinguish any object 2 metres off; at 5 metres he could distinguish between a man and a woman, but could not recognize the face.

March 6.—Sight still less.

March 7.—Could only read at the distance of 50 centimetres with letters 10 centimetres high. Thirst had become intolerable; he could not remain five minutes without drinking, the mouth was burning, and he could not speak for more than two minutes at a time.

Treatment was begun in the afternoon of March 4: diet deprived of sugar and starch, two glasses of Vichy water before each meal, and injections of sodium cacodylate.

By March 8 improvement was already manifest. Thirst was less, sight was better, and he could see with his glasses as well as on the first day.

March 9.—Glasses were no longer necessary. Thirst much less, skin less dry. Legs stronger.

March 19.—Great improvement. Urine = 2,500 c.c. per twenty-four hours, containing 53 grammes of sugar per litre, hence a total of 133 grammes in twenty-four hours. Stopped injections of cacodylate, Vichy water continued.

March 27.—Only 75 grammes of sugar in twenty-four hours.

April 3.—Great improvement. Ordered antipyrine and sodium bicarbonate. A little bread and potato added to diet.

April 10.—Absence of sugar from urine, likewise on April 20.

April 25.—Alimentary glycosuria test. The patient ingested while fasting 150 grammes of glucose. Sugar was not found in the urine.

Since this time the urine, examined from time to time, never

revealed a trace of sugar. Even after large meals rich in carbohydrates sugar was never detected by Fehling's solution. Therefore, the diabetes was completely cured.

Here is a typical instance of diabetes following an infection. The subject had never presented glycosuria before the advent of the herpetic angina, nor was there any during the disease. It was only two weeks later that an intense glycosuria was found.

Unlike von Noorden's case, this case cannot be explained by the existence of a latent diabetes aggravated by an angina. The patient never had any previous symptoms of diabetes, and for several years since recovery from the diabetes he has not developed any. Finally, the onset was sufficiently violent, the symptoms and evolution quite characteristic, and the duration short enough for one to be certain that the case was unquestionably a diabetes with an acute evolution, and not an aggravation of a chronic diabetes.

Such a glycosuria makes one think of certain albuminurias arising after acute diseases in which no doubt is entertained as to the pathogenic relationship of the infection.

Case II.—Female, æt. 67 years, became obese early in life, and in spite of her shortness weighed 90 kilogrammes. Ten years ago she began to lose weight, and at present only weighs 64 kilogrammes. At no time in her life has she experienced symptoms of diabetes, and glycosuria has never been detected.

In the winter of 1905, during an acute febrile nasopharyngeal infection, the patient began to experience intense thirst; she drank much and presented a polyuria. I then had the urine examined, and a large amount of sugar was found, although her diet was restricted.

She was placed upon a rather severe regimen containing only 15 grammes of carbohydrates and a Vichy water treatment.

At the end of three weeks the sugar had disappeared from the urine. A month later the patient could tolerate 50 grammes, and two months later 65 grammes, of carbohydrates without giving rise to glycosuria.

This diabetes, a sequela to an infection, is on the road to recovery.

In both the cases here reported the infectious origin of the diabetes cannot be questioned. The first patient certainly had never had glycosuria; in the second, glycosuria had never been detected upon the occasions when the urine had been submitted to analysis.

However, infection, perhaps, is not the sole factor to be

invoked in the pathogenesis of the diabetes in these subjects. Both patients, in fact, were obese—that is to say, they offered the morbid soil upon which diabetes ordinarily undergoes its evolution. It is possible that the metabolic disturbance resulting in obesity predisposed them to the other nutritive disturbance which results in diabetes, and that the infection all the more readily created glycosuria because the soil for it was prepared.

But although obese subjects are predisposed to diabetes, they do not necessarily become diabetics, and in the two cases under consideration the infection certainly seems to be the determining cause of the glycosuria.

A goodly number of clinical facts and experimental findings produce arguments in favour of the infectious origin of certain diabetes, as they show that infection always determines disturbances of the functions of the glycoregulator apparatus.

In many diabetics an intercurrent infection aggravates the disease; von Noorden has seen glycosuria increase during an acute angina in spite of a reduction in diet and the amount of sugar ingested. He has frequently observed that the diabetes became more intense after acute diseases, especially after anginas and influenza. In a diabetic subject who only had a mild glycosuria and tolerated 100 to 150 grammes of bread per day, he found that the glycosuria had become serious following influenza, and that it maintained this character in spite of a very severe diet followed for many months.

Mohr has collected many cases of this kind, and two are to be particularly noted. In one a pneumonia, in the other a phlegmonous angina, increased the glycosuria and caused an aggravation of the diabetes.

On the other hand, the cases related by Poll, Campagnolle, Richter, Klemperer, and Strauss show that alimentary glycosuria is rather easily produced in acute infectious diseases. Poll gave from 100 to 150 grammes in the morning before breakfast to patients with pneumonia, scarlatina, diphtheria, septicemia, and angina, and he frequently noted the occurrence of glycosuria. In two cases of pneumonia, from 7 to 8 per cent. of the sugar ingested was excreted in the urine.

Heintz, Samoje, Buhl, Huppert, Gubler, and Naunyn have met with temporary glycosuria during the phase of reaction

in cholera; Burdel has frequently observed glycosuria in acute paludism—a fact that my personal experience does not allow me to accept. Achard and Loeper have noted a slight degree of glycolytic insufficiency in pneumonia and rheumatism.

Hence, infections appear to cause disturbance of the functions of the glycoregulator apparatus.

The disturbance is ordinarily moderate; it does not show itself when an average diet is being given. It is only when an excess of sugar is furnished the organism that insufficiency of the glycoregulator apparatus will be detected, and that glycosuria appears. But it can readily be conceived that the functional disturbance may be more or less considerable according to the nature of the infection, its localization, as well as individual predisposition.

The limit of tolerance of the organism for carbohydrates, which usually remains high, may fall considerably. Instead of only being produced by an excess of sugar, the glycosuria will appear after the ingestion of a moderate amount of carbohydrates, or even after a very small quantity, which in ordinary medical language constitutes true diabetes, and not merely alimentary glycosuria. One can conceive that the disturbance brought about by infection of the glycoregulator apparatus may be yet more considerable, and that the patient will eliminate in the urine not only the sugar intake from the food, but the sugar manufactured from albumins and fats of food or tissues, as in serious diabetes with denutrition.

Between alimentary glycosuria provoked by an excess of sugar and serious diabetes with glycosuria of organic origin there is only a difference of degree. An infection may realize these degrees from the most trifling—which is the rule—to the most serious—which is the exception.

By what mechanism does the infection act? Is it by influencing the liver, pancreas, nervous system, or some portion of the glycoregulator apparatus? It is impossible to say. In point of fact, we know that by various procedures an infection may attack all the viscera of the economy.

Charrin believes that the infection can create lesions of the pancreas susceptible of causing diabetes; the bacteria of the intestine travel up Wirsung's duct and infect the pancreas. Of nine dogs in whom he infected the pancreatic duct, one

presented a glycosuria for several days. P. Carnot's researches, as well as those of others, have established the existence of infectious pancreatitis, which may account for certain glycosurias following infections. On the other hand, all infections react on the liver, either by way of the general circulation or by ascending infection of the biliary tract—a fact that may explain the disturbance wrought in the glycogenic function and the production of hepatic diabetes of infectious origin. It may be quite the same if the infection brings its action to bear upon the nervous system, and principally on the bulb in which the glycoregulator centre is supposed to exist since the writings of Claude Bernard.

Thus, by various mechanisms infection seems to be susceptible of creating diabetes; although this may yet seem to be relatively uncommon, it nevertheless remains that this is an ætiology that should never be lost sight of.

CHAPTER XV

GLYCOSURIA IN DISEASES OF THE LIVER—HEPATIC DIABETES*

Ever since the memorable experiments of Claude Bernard no doubt has subsisted that the liver plays a fundamental part in glycogenesis. Bernard even went so far as to say that diabetes should be located in the liver. Following Bernard's teachings, many observers attributed the production of diabetes to hepatic disturbances, or at least certain forms of diabetes were referred to the liver. Lecorché supposed that this affection was due to exaggerated hepatic functions. Seegen, Pavy, and Schiff admitted the existence of hepatogenous diabetes. Glénard has also insisted upon the lesions of the liver in diabetes, and attributes the preponderant part to them in the genesis of the disease. Finally, Gilbert has distinguished two types of diabetes due to functional disturbances of the liver—the first due to insufficiency, the second to excessive functional activity.

However, other observers, noting the frequent integrity of the liver in diabetic subjects, do not attribute an important part to this viscus in the production of diabetes.

It is for this reason that we have thought it interesting to revert to this subject from the clinical view-point, and to determine the relationship existing between diseases of the liver and diabetes.

We distinguish five categories of cases:

1. Glycosuria arising in hepatic lesions.
2. Hepatic congestion in suralimentation.
3. Post-infectious or toxic hepatic disturbances.
4. Diabetes without denutrition in suralimented subjects with a large liver.
5. Hepato-pancreatic cirrhoses with serious diabetes.

* Read at the International Medical Congress, London, August, 1913, in collaboration with Dr. Ambroise Bouchage.

I. Glycosuria in Hepatic Lesions.—During hepatic cirrhoses or other lesions of the liver (cancer, cardiac liver), the glycoregulator function is usually disturbed, but not to the extent that one speaks of diabetes. Usually the alimentary glycosuria test must be resorted to in order to reveal the existence of any glycoregulator disturbance. Occasionally there is a more advanced degree, the glycosuria being spontaneous, but it is intermittent, moderate, and is not accompanied by any other symptoms of hyperglycemia.

This glycosuria is met with at the onset of the cirrhoses much more frequently than at a later phase of the process; several of our cases prove this fact. It does not increase with the progress of the lesions.

II. Hepatic Congestion of Suralimentation.—In subjects who eat to excess, especially meat, a glycosuria is sometimes met with accompanied by congestion of the liver and various disturbances of the hepatic functions. A few case histories will illustrate this type of disease.

Case I.—Male, æt. 29 years, has lost weight for the past year, suffers from lumbar pain and loss of strength, and, fearing tuberculosis, consulted Dr. Labbé in June, 1911. There was mild jaundice. Tongue coated, stomach dilated. Two soft stools daily. Liver enlarged, measuring 14 centimetres in the nipple line. The other viscera were normal. Urine = 1,000 c.c., containing a large percentage of total N (18·2 grammes) and urea (35 grammes), a large amount of urobilin and indican, traces of bile pigment, and 6 grammes of glucose. The patient stated that he was a large meat eater.

A lacto-vegetable diet and Vichy cure were ordered.

In July he was better. Urine = 3,000 c.c., with 7 grammes total N, 15 grammes of urea, little urobilin and indican; glycosuria absent. Liver smaller, 12 centimetres in nipple line.

In September he was decidedly better; weight increased 2 kilogrammes; no glycosuria.

In December improvement had continued; weight had increased 5 kilogrammes; liver still decreasing in size, measures 11·5 centimetres in nipple line.

The condition then remained stationary; an excess in eating caused the hepatic disturbances to return. The liver again became hypertrophied, while urobilin, glycosuria, and a trace of albumin were present in the urine. These symptoms subsided when the patient was again put upon a lacto-vegetable diet.

Case II.—Male, æt. 34 years, had a beginning of tuberculosis in 1900, and by medical advice took a rest cure in the South of France

with suralimentation. Besides an ordinary diet he consumed twelve raw eggs, 700 to 800 grammes of raw meat, and two wine-glasses of cod-liver oil daily. With this regimen he rapidly fattened.

In 1902 there was a second outburst of tuberculosis, and suralimentation was again resorted to. Since this event the patient has eaten a large amount of meat.

At the commencement of 1907 the patient began to suffer from the stomach, and presented symptoms of muco-membranous entero-colitis. Severe pain over the ascending colon led to the suspicion of appendicitis, and the question of operation was discussed. The urine was then examined and found to contain glucose.

He then consulted Dr. Labbé. Tongue coated, bitter taste in mouth, strong odour of breath. Stomach normal, liver slightly hypertrophied, urine contained a reddish-brown pigment. Cicatrization of the pulmonary lesions appeared to be complete. Diagnosis = gastro-enteritis with hepatic congestion caused by suralimentation.

A moderate mixed regimen resulted in a complete recovery.

Case III.—Male, æt. 45 years, having a sedentary profession, was a large eater and drinker, although this did not affect the health for some time.

For some little time past, however, the patient complained of lameness in the renal regions and noted œdema of the ankles. Examination of the urine revealed glycosuria and reddish-brown pigment. There was some corpulency, some jaundice, and the patient looked prematurely old. Liver hypertrophied. Some evidences of high blood-pressure.

The glycosuria ceased very quickly by a lacto-vegetable diet and a Vichy cure. He lost weight and felt generally much better. At the end of forty days the liver had become normal in size. The blood-pressure, too, became normal. Glucose was absent from the urine.

The evolution of the symptoms was identical in these cases. A patient resorts to suralimentation, especially meat; after a variable lapse of time congestion of the liver ensues, accompanied by functional hepatic disturbances with glycosuria, and he assumes that he is diabetic.

In these circumstances the glycosuria is moderate and is not accompanied by the major symptoms of hyperglycemia. A point to be especially noted is that it gives in to a lacto-vegetable diet and a Vichy cure at the same time as the other hepatic disturbances. In other words, this regimen and treatment places the liver at rest and increases the functional activity of the hepatic cell.

It would be a mistake to treat such a glycosuria by a meat diet and reduction of carbohydrates, because, instead of making

it disappear, this regimen would, on the contrary, tend to increase it.

Such cases do not deserve the name of diabetes. However, they occupy the frontiers of the disease, and it may well be questioned whether or not certain instances may not end in true diabetes in case the patient should persist in suralimentation.

III. Post-Infectious and Toxic Hepatic Disturbances.—Following infectious processes a group of hepatic disturbances with glycosuria recalling diabetes may develop.

Case IV.—Female, æt. 32 years, had a pseudo-membranous angina with a temperature; at the onset there was epistaxis and bilious vomiting. At the decline of the process a slight glycosuria was found, accompanied by notable urobilinuria, ammonuria, and some bile pigment. For some days the urine contained reductive substances in notable amount. Finally the symptoms disappeared.

Case V.—Male, æt. 56 years, asthmatic and dyspeptic, and a large sugar consumer, developed measles. He lost weight rapidly during his illness, and the urine was found to contain 5 grammes of glucose, 10 centigrammes of albumin and urobilin; the liver was slightly hypertrophied and sensitive to palpation. He feared diabetes, but other than for the glycosuria there was no symptom of hyperglycemia. A moderate lacto-vegetable diet was enough to cause the glucose to disappear.

These cases can be explained in the following way: The infection involves the liver in its various functions, principally that of glycoregulation; hence the glycosuria, which, for that matter, remains usually moderate.

There is only an exaggeration of what is observed in infections in which the alimentary glycosuria test usually shows the existence of glycoregulator disturbance. An analogous condition is encountered in infections arising in diabetics whose glycoregulator disturbance generally undergoes a temporary or definitive aggravation.

Every transitional type can be met with between simple alimentary glycosuria and true infectious diabetes, and one can readily conceive that, in a predisposed subject or one already moderately attacked by the disease, an infection may determine a true diabetes, examples of which I have recorded.

IV. Diabetes without Denutrition in Subjects subjected to Suralimentation with an Enlarged Liver.—Diabetes without denutrition arising in habitually large eaters is frequently accompanied by hypertrophy of the liver and functional disturbances of the organ.

Case VI.—Male, æt. 45 years, very large eater, sedentary life with an abdominal obesity, suffered from what was apparently gouty arthralgia and nephritic colic.

For some years past he has had diabetes and a glycosuria averaging 100 grammes. From time to time after an excess at table has a bilious diarrhœa. Liver a little enlarged, icteric tint.

A reduced carbohydrate intake caused the glycosuria rapidly to subside, and produced a slight loss of weight; the digestive disturbances also subsided.

Case VII.—Male, æt. 51 years, sedentary habits, very obese, large eater, and consumed 1 litre of wine daily. He has weighed 104 kilogrammes, now weighs 96 kilogrammes.

In 1901, upon the occasion of a furunculosis, a glycosuria of 69 grammes was discovered. This disappeared in one month by diet, but it returned afterwards, and in spite of hydromineral cures it remained at between 5 and 15 grammes in twenty-four hours.

Digestion slow; liver hypertrophied, reaching below the ribs. Analysis of urine indicated suralimentation; it contained 44 grammes of urea, uric acid 1·10 grammes, NaCl 18 grammes, and a trace of albumin.

A moderate reduction of the regimen easily controlled the glycosuria and albuminuria, and caused the patient to lose some weight.

Case VIII.—Male, æt. 49 years, large eater and drinker, obese and diabetic. At the age of 39 years he applied for a life insurance, and glycosuria was found, which rapidly subsided.

At the age of 46 years the glycosuria was 30 grammes per day, and then, in spite of certain precautions in diet, it varied between 30 and 60 grammes.

The patient was corpulent, short of breath, fatigued, and continually complained of dryness of the mouth. He had two soft stools daily. Liver enlarged, extending 5 centimetres below the costal border; slight jaundice; hæmorrhoids. Urine contained 4 grammes of glucose, some urobilin and albumin.

A reduced carbohydrate diet caused the glycosuria to disappear in four days and reduced the albumin to a trace. He lost a little weight, and his general condition improved.

After this his condition remained stationary. The liver was enlarged and hard, and the urine contained traces of urobilin and albumin. Whenever he committed any excess at table a glycosuria of severa grammes invariably ensued.

V. Hepato-Pancreatic Cirrhoses with Serious Diabetes.—Finally, there is a group of diabetes related to hepato-pancreatic cirrhosis. Bronzed diabetes enters into this category. The diabetes is serious, with denutrition and frequently acidosis. Cirrhosis of the liver is very characteristic; that of the pancreas is made evident by symptoms of more or less marked pancreatic insufficiency.

Therefore, in these cases there is a simultaneous evolution of a serious diabetes and a lesion of the liver and pancreas, but it is impossible to decide whether the liver or the pancreas plays the chief part in the pathogenesis of the diabetes.

Such are the facts. They show that during the evolution of hepatic affections one may meet with all degrees of glycoregulator disturbance, from simple alimentary glycosuria to perfectly characteristic diabetes.

The limit between diabetic glycosuria and non-diabetic glycosuria is difficult to define. By an insensible transition one transforms into the other. Achard and Weil have shown that certain arthritic subjects, who later in life become diabetic, begin with alimentary glycosuria.

Inversely, we have seen frank diabetics who, after having presented the major syndrome of hyperglycemia, will only have the slightest glycosuria—the only indication of a glycoregulator disturbance—when they follow a proper diet, and may even have their glycosuria disappear unless it be provoked by the ingestion of glucose.

Should these various cases be regarded as hepatic diabetes? Assuredly one can always discuss this interpretation, because although glycosuria is a sign of hepatic insufficiency, it is likewise a sign of pancreatic, thyroid, or nervous functional disturbances. Besides, it appears to be a difficult matter to affirm that the liver alone is involved, and that the other organs of the glycoregulator apparatus are not. However, it appears to us that the term of hepatic diabetes can be reserved for certain cases in which the morbid changes in the liver are evident.

Hepatic diabetes usually supervenes in large eaters and drinkers. It is often preceded by obesity, sometimes by gout or renal lithiasis. The process is moderate without nitrogenous denutrition, and corresponds to the classical obese or arthritic diabetes.

It is accompanied by the habitual signs of morbid changes in the liver. The organ is hypertrophied, the patient is slightly jaundiced. The urine contains bile pigment, reddish-brown pigment, and urobilin, while ammonia and the amino-acids are in excess. The N ratio is low. Finally, the patient occasionally presents hæmorrhages and changes of the blood coagulation.

The cause of hepatic diabetes is occasionally a general infection which hits the liver, or an intoxication, like alcoholism, which has a predilection to attack the hepatic cell. Still more often, according to our observation, suralimentation, and above all the abuse of meat, are the factors.

Usually moderate, the glycoregulator disturbance is susceptible to completely disappear if the anatomical and functional integrity of the liver can be restored. This shows how important is the treatment of hepatic diabetes.

The treatment is principally directed to the liver. Cures at alkaline mineral water spas, such as Vichy, Brides, Vals, and Pouges, hepatic opotherapy, and lacto-vegetable diet, form the basis. Although avoiding excesses in carbohydrates, one should especially reduce the intake of meat—the principal factor of the morbid process.

CHAPTER XVI

BRONZED DIABETES*

FOR several weeks there has been in the wards a patient with bronzed diabetes. This affection, described for the first time by Hanot and Chauffard in 1882, is rare to the extent that Chauffard himself has not met with another example, and only about fifty other cases have been reported. Hence I believe that we should make the most of the present case.

The patient is a woman, æt. 63 years, and until recently has always enjoyed good health. There are no antecedents of diabetes, and she has never sustained any serious illness. Her labours have been easy; her corpulency superior to the norm.

In January, 1911, she began to be tormented by ardent thirst, marked loss of strength, and progressive emaciation. A physician at this time found an abundant glycosuria. Was this the onset of the diabetes? Possibly so, but at all events it was not the onset of her illness, because for already some months she had been losing strength and had emaciated, her weight having dropped from 67 to 62 kilogrammes.

She was put on rather severe diet, and at the end of a fortnight the glycosuria had almost completely disappeared, but the patient still felt weak.

Upon two occasions an attempt had been made to add some potato to the diet, but each time it caused the glycosuria to reappear, and this subsided when the strict diet was returned to. It would, for that matter, seem that the glycoregulator disturbance had increased, because at the end of some months the glycosuria became permanent in spite of the almost complete suppression of carbohydrates in the diet.

During the year a bronzed tint of the hands and face slowly developed, and then on other portions of the body. The mouth was dry, the lips rough, while their internal surface slowly became coloured by a blackish pigmentation. The teeth decayed and fell out.

The case finally came to hospital, at which time she walked with great difficulty. The bronzed aspect of the integuments, the hypertrophy of the liver, and the abundant glycosuria at once led to the diagnosis of bronzed diabetes, while the depression, somnolence, and a positive Gerhardt's reaction made us fearful of acidosis and imminence of coma.

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* A clinical lecture delivered at the Charité Hospital, and published in the *Archives des Maladies de l'Appareil Digestif*, July, 1912.

A searching examination of the patient confirmed the first diagnosis, revealing the existence of the three primordial symptoms—namely, pigmentation, hepatic cirrhosis, and diabetes.

The expression was that of fatigue, the lips were slightly cyanosed, the cheek-bones red, and the mucosæ offered a slight icteric line. The patient was considerably emaciated, and from 67 kilogrammes the body weight had now fallen to 42 kilogrammes.

The integuments were dark-coloured, looking like mercurial ointment, but rather less bluish and more swarthy. The pigmentation was everywhere over the body, but more marked on the face and hands. An important point to be noted is that it involved the mucous membrane. Over the internal aspect of the cheeks one could detect minute blackish spots the size of a lentil; there also were some on the internal aspect of the lips, corners of the mouth, on the under surface of the tongue, and even on the free border of the lower left eyelid.

The hard, smooth, indolent liver was easy to palpate; its lower edge reached the level of the umbilicus; the organ was greatly hypertrophied.

The spleen did not seem to be very much enlarged.

The digestive disturbances consisted especially of a profound anorexia; the mouth and lips were dry; the breath had a slightly aromatic odour; there was neither vomiting, diarrhœa, nor constipation.

The heart was not hypertrophied, pulse 80, blood-pressure 17.

There were some signs of bronchitis, and the right apex was suspicious from the view-point of tuberculosis.

Pupil and patellar reflexes normal. Temperature normal.

The urine, which was rather dark, measured 2,000 c.c. in twenty-four hours. Examination showed a glycosuria of 65 grammes, a very small amount of bile pigment, a large quantity of urobilin, and absence of albumin. Gerhardt's, Legal's, and Lieben's reactions all positive.

Briefly, the patient had a rather intense diabetes, because the glycosuria (65 grammes), small in appearance, was, nevertheless, higher than the ingestion of carbohydrates, and the process was complicated by a mild degree of acidosis.

I will rapidly relate the incidents arising during the evolution of the case, in order to show the dangers to which such patients are exposed. In these cases the diabetes and acidosis dominate the symptomatology.

The patient was put upon a mixed diet comprising meat, eggs, cheese, butter, and 50 grammes of carbohydrates in the form of potatoes, milk, and green vegetables. The glycosuria oscillated between 130 and 65 grammes per day.

After a few days, as the state of depression and signs of acidosis were causing me to be fearful as to the outcome, 40 grammes of sodium bicarbonate *pro die* were ordered, and two intravenous injections of a 5 per cent. solution of the bicarbonate were given. The first was 160 c.c., the second 500 c.c.

A slight improvement ensued from this treatment: the strength increased and somnolence subsided; the appetite slowly returned; the liver decreased in volume, and only reached two fingers'-breadth above the umbilicus.

A curious thing was that a depigmentation occurred in the hands, commencing at the finger-tips, and slowly reaching the dorsal aspect of the hands, forming a very marked contrast with the rest of the integument, which was very brown.

The urine became alkaline, but the diaceturia persisted. Finally, the sodium bicarbonate provoked two incidents—namely, a rather frequent diarrhœa and œdema of the lower limbs extending up to the knees; the weight rose from 42 to 51 kilogrammes. However, the patient could not yet get on without the bicarbonate, because when it was stopped there was a tendency to somnolence.

On July 1 the patient was put upon my oatmeal diet, which was fairly well supported, but did not give any result.

On July 14 she was put on a milk diet (2,000 c.c. of milk and a bottle of kéfir) and the bicarbonate was stopped. The diarrhœa ceased, the œdema subsided, and in a few days the body weight fell from 51 to 41 kilogrammes. The somnolence disappeared, Gerhardt's and Legal's reactions were less marked and then disappeared, while the ammonuria decreased. But the glycosuria increased from 45 to 110 grammes.

At any rate, the patient was stronger, the appetite better, and during the two months of August and September the improvement obtained persisted. When I took up my hospital service again early in October, Gerhardt's reaction was negative.

Unfortunately the patient contracted an angina on October 8, accompanied by a stomatitis and slight bronchitis, and complained of much lassitude. Acid intoxication recurred; the ammonuria reached 2·48 grammes per day, and Gerhardt's reaction was very intense.

The symptoms became worse. On October 11 a paralysis of the velum palatinum developed, with a menace of periostitis of the lower jaw.

On October 13 an erysipelas appeared over the nose, the temperature went up, and the diaceturia was very intense. The erysipelas extended over the face on the following days, producing a considerable painful swelling of ears; temperature 104° F.

However, on October 17 some improvement could be detected, the erysipelas was cured, the temperature had fallen, and the stigmata of acidosis had diminished. I hoped that the patient had weathered the storm.

In the middle of the day she was suddenly seized by a paroxysm of dyspnœa and cyanosis, and after a phase of progressive somnolence, coma ensued.

On October 18 coma was complete, with a rapid respiration (34) and pulse (104), and contracted pupils; and in spite of an intravenous injection containing 50 grammes of sodium bicarbonate, the patient did not rally.

Let me now compare this case with the description of bronzed diabetes given by Hanot and Chauffard, and completed by other writers, as Letulle, Brault and Galliard, P. Marie, Rendu and de Massary, Gilbert and Surmont, Opie, etc.

The disease is more prone to occur in males; it is an exception to observe it in a female, as in this case. It arises in adults from the age of 35 to 51 years. Our patient, æt. 61 years, offers an example of tardy development of the process.

It is characterized by three symptoms—namely, pigmentation, hepatic cirrhosis, and diabetes.

According to the classical description, the pigmentation would appear to be limited to the cutaneous surface. Gilbert and Surmont state that absence of pigmentation from the mucosæ is an important sign by which to distinguish the melanodermia of bronzed diabetes from that occurring in Addison's disease. However, Jeanselme had already met with a slight pigmentation on the free border of the gums in one case. Potier and de Massary have seen pigmentation of the lips. Gouget has noted three slate-coloured spots on the edge of the tongue, and, collecting all cases published up to 1911, found that pigmentation of the mucous membranes was mentioned in eleven instances.

Adding the case here reported to this list, it will be seen that the pigmentation of bronzed diabetes may extend to the mucous membranes and assume the intensity of that met with in Addison's disease. An association with Addison's disease cannot be invoked in the cases under consideration, because autopsy showed that in our case the suprarenal glands were intact. As Rendu and Triboulet have already observed, the melanodermia decreased during the disease; depigmentation had proceeded, as in vitiligo, over a special area bounded by a distinct border.

Following the rule, to which only one exception is known (the case of Hanot and Schachmann), the cirrhosis in our case was accompanied by hypertrophy of the liver, and, as has been noted by Rendu and de Massary, the organ underwent a decrease in size during the disease.

Occasionally signs of hepatic cirrhosis are made evident by ascites and an abdominal collateral circulation. These were absent in our case.

In some instances the digestive disturbances are rather marked, especially by anorexia and attacks of diarrhœa. The lesions of the pancreas present in bronzed diabetes explain these disturbances. In our case anorexia was profound; Schmidt's test revealed an absence of digestion of fruit-stones, indicating an insufficiency of the external pancreatic secretion, but the diarrhœa I believe to be due to the bicarbonate.

Writers state that the diabetes in this process is of medium intensity, the polyuria varying between 3,000 and 4,000 c.c., and the glycosuria between 150 and 200 grammes. In our case the glycosuria was generally above 100 grammes, and nevertheless the glycoregulator disturbance was intense, because the glycosuria was not merely due to the carbohydrate intake, but to other foodstuffs as well. It was a diabetes with denutrition. In practice it is not by the amount of the glycosuria that the intensity of the diabetes is judged, but by the ratio existing between the glycosuria and the food intake. If the glycosuria does not attain a very high degree in bronzed diabetes, it is because of the digestive disturbances, which prevent the patient from eating much. It is for the same reason that a decrease or disappearance of the glycosuria has been noted at the end of the disease; the anorexia and insufficient feeding are the cause. It is likewise probable that acidosis complicates most cases and explains the weakness, anorexia, and rapid physical collapse.

Death results from tuberculosis, infection such as peritonitis (Letulle), miliary tuberculosis (Barth), pneumonia (de Massary and Potier), and still more frequently from coma. In our patient it was the erysipelas that was indirectly the cause of death; occurring in a subject threatened with acidosis, it provoked the sudden development of coma.

The prognosis is very serious; the evolution is quickly fatal; the duration varies between a few weeks and months: in our case it was ten months.

In reality, treatment should never be neglected. It will prolong life, and above all will relieve suffering. The two dangers to combat are the hyperglycemia and especially the acidosis. Milk diet, cereal and vegetable regimens, or a mixed diet containing a certain amount of carbohydrates,

pancreatic and hepatic opotherapy, and the exhibition of sodium bicarbonate, form the basis of treatment.

The lesions found at autopsy of our case are in accord with the classic findings.

All the viscera were pigmented; even the serosa, especially the peritoneum, offered blackish spots.

The liver was large, weighing 1,870 grammes; it was slightly hob-nailed, reddish in colour, and hard. Microscopically a very intense bivenous cirrhosis was found; thick bands of sclerosis surrounded the lobules and even penetrated them; they offered very numerous neo-formed biliary canaliculi.

The ochre pigment, in the form of fine granulations, infiltrated all the hepatic cells, whose nucleus was intact. In the connective-tissue bands it was seen to form thick masses, contained in the degenerated cells or even in the midst of the fibrous tissue.

The pancreas weighed 65 grammes. It presented an intense peri- and intralobular sclerosis, both perivascular and pericanalicular in type. The cells of the acini were greatly altered and infiltrated with pigment granulations, especially in the areas adjacent to the bands of sclerosis. As in the liver, masses of pigment were found in the midst of the sclerous tissue. The islands of Langerhans had disappeared.

The hypertrophied spleen presented less advanced lesions of sclerosis than those of the liver, with hæmorrhages in the pulp. The macrophages of the pulp were gorged with ochre pigment.

There was a slight sclerosis of the kidneys, with an intense congestion and hæmorrhages in the cortex. The pigment infiltrated the epithelium of Henle's loops and respected the tubuli contorti. It was much less abundant than in the liver and pancreas.

The heart was small and soft; the muscle fibres were loaded with ochre pigment in the state of fine granulations.

In the suprarenals the pigment was principally seated in the more superficial cells of the cortex.

The thyroid presented chronic inflammation, with development of interstitial tissue and destruction of most of the colloid lobes. It was infiltrated with pigment.

Finally, pigment was present in the hypophysis.

Briefly, the lesions were characterized by an intense sclerosis of the liver and pancreas, and a milder sclerous process of the spleen and thyroid, and by an accumulation of pigment in all the viscera, especially the liver, pancreas, and heart. The pigment was in a state of fine granulations in the parenchymatous cells, and in more or less large masses in the connective tissue.

As Gilbert has shown, this ochre pigment is ferruginous in nature. Besides, there was an increase of the normal melanic pigment of the skin.

The pathogenesis of bronzed diabetes has given rise to much discussion. The early writers on the subject regarded it as a morbid entity, and endeavoured to establish a close relationship between the three characteristic elements of the process—viz., pigmentation, hepatic cirrhosis, and diabetes.

Hanot and Chauffard admitted that by the combined influence of hyperglycemia, the determining lesion, and diabetic endarteritis, the hepatic cell became the seat of pigment hypergenesis, and that by emboli the pigment was distributed throughout the organism.

Letulle, and Brault and Galliard afterwards, criticized this theory, and admitted that the destruction of hæmoglobin and the formation of pigment took place in the entire organism.

The study of numerous pathological conditions bordering on bronzed diabetes, but less distinct than this process, showed the relative independence of the three characteristic elements, and led to the supposition that bronzed diabetes was not a morbid entity, but a combination of several syndromes.

Thus, we have pigment cirrhosis of the liver without any cutaneous pigmentation or diabetes (Letulle, Gilbert and Grenet), and pigment cirrhosis with melanodermia without diabetes (Brault); we have hepato-pancreatic cirrhosis without hepatic or cutaneous pigmentation, but with diabetes (Gilbert and Lereboullet, Monier); and, lastly, there are generalized pigmentations of the skin and viscera which are not accompanied by either hepatic cirrhosis or diabetes (Quincke, Recklinghausen, Gandy and Bornait-Legueule).

This dissociation of the three elements—pigmentation, cirrhosis, and diabetes—brings us to the study of each.

The ochre pigment which infiltrates the viscera is ferruginous in nature, and is derived from hæmoglobin. It seems to form everywhere in the body in contact with the cells in which it is found. These generalized pigmentations have been studied by Quincke and Recklinghausen, who gave them the name of hæmochromatosis. The German writers attributed

the pigmentation to a general hæmatic destruction, but do not seem to have noted its connection with diabetes.

More recently the researches of Chauffard and F. Widal on hæmolytic icterus have lent precision to these generalized pigmentations by revealing the first phase of hæmolysis which precedes the accumulation of pigment in the viscera. Finally, two recent cases have established the relationship between hæmolysis and pigment cirrhosis. Chalier and Nové-Josserand found the same predisposition to hæmolysis in a case of bronzed diabetes. These symptoms of hæmolysis are not constant, and they have been absent in other cases.

Briefly, generalized ochre pigmentation is the result of a hæmolytic process, apparently toxic in nature, but whose origin escapes us.

Is hepatic cirrhosis caused by pigmentation? P. Marie emitted the hypothesis that the pigment, by accumulating in the liver, sets up an irritation and connective-tissue reaction. But in his experiments on hepatic siderosis, Castaigne did not find that an accumulation of iron in the liver produced cirrhosis or decreased the functional activity of the cells. Besides, the cases of hæmochromatosis or hæmolytic icterus, in which cirrhosis of the liver and other viscera is wanting or only attains a very minute degree, do not allow one to establish a relation of cause and effect between pigmentation and sclerosis. The two lesions, although sometimes associated, seem to me to be independent of each other.

To what cause should visceral cirrhoses be attributed? In several instances alcoholism has been invoked. Perhaps tuberculosis or syphilis may be responsible for some cirrhoses. But none of these affections were to be found in the antecedents of our patient, so that the ætiology completely escapes us. At all events, the existence of some sclerosing organic poison must be admitted, possessing a powerful action and capable of simultaneously acting on the liver, pancreas, kidneys, and spleen. It is probable that this sclerosing poison is, in the case of pigment cirrhosis, at the same time endowed with hæmolyzing properties.

The diabetes is not the cause of either the pigmentation or the cirrhosis. It rarely pre-exists the two lesions; usually it ensues as a consequence. The changes in the pancreas, as in

our case, were sufficiently marked for one to regard them as entering into the pathogenesis of the diabetes, and this is all the more likely when an advanced cirrhosis of the liver be added. Bronzed diabetes, therefore, is a variety of diabetes from hepato-pancreatic cirrhosis to which another symptom—pigmentation—becomes added, this being merely a contingent phenomenon.

If one considers the entire evolution of the known data, one is led to admit three phases in the pathogenesis of bronzed diabetes—viz.: (1) A toxic process whose origin is unknown; (2) a hæmolyzing and sclerosing action resulting from this process, and giving rise to hæmolytic icterus followed by hæmosiderosis and hepato-pancreatic cirrhosis; and (3) these lesions clinically are made evident by cutaneous and cutaneo-mucous pigmentation and diabetes.

This interpretation is not a mere idea. In our case it well fits into the morbid evolution. The patient's history, in fact, revealed that a prolonged toxic process, characterized by emaciation and loss of strength, preceded the appearance of the pigmentation and diabetes by several months.

Undoubtedly, clinical observation will bring forward proof in favour of this theory by following cases of this kind, not only during the last phase of the process, but during the entire evolution of the disease.

CHAPTER XVII

PANCREATIC DIABETES*

THE first notion of the relationship existing between diabetes and lesions of the pancreas is now remote. Already, in 1788, Cawley related the case of an obese alcoholic man with diabetes, æt. 35 years, whose pancreas was found stuffed with calculi. Chopart reported a similar instance. In 1833, Bright found at the autopsy of a diabetic subject a lesion of the head of the pancreas which apparently was a cancer, if one may judge from the description of the case. In 1846, Bouchardat remarked with great justice that sometimes there were lesions of the pancreas in diabetics, although not always. All these were isolated data.

Lancereaux, in 1877, was the first to give an individuality to pancreatic diabetes. In opposition to diabetes without denutrition, with constitutional or arthritic obesity, and nervous diabetes, he described pancreatic diabetes caused by lesions of the pancreas, characterized by its sudden onset, the considerable emaciation, intense polydipsia and polyphagia, the peculiar type of fæces, and the rapidly fatal evolution. Lapierre exposed Lancereaux's ideas on the subject in his thesis (Paris, 1879).

A few years later experimental work brought much weight to bear in favour of the theory of pancreatic diabetes. In 1889, Mering and Minkowski performed pancreatectomy on dogs, followed by diabetes shortly after the operation, and which lasted for several weeks, when the animals died. This diabetes was accompanied by symptoms recalling those encountered in man—namely, the glycosuria persisted in spite of starvation; it increased with a meat diet, and especially with a sugar regimen; there was hyperglycemia; the glycogen disappeared from the liver and muscles; and a profound disturbance of the digestion of fats and albumins ensued.

In 1891 Hédon performed partial pancreatectomy, which

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resulted in chronic diabetes which was still more like that met with in man. Then, in 1895, Sandmeyer, repeating Hédon's experiments, produced a slowly developing diabetes which underwent its evolution in two months in one animal and eight months in another. To obtain these results it was only necessary to leave about one-ninth of the pancreas. Hédon, Thiroloix, and Jacob also induced the various types of chronic diabetes, with or without denutrition, after partial pancreatectomy, comparable with those met with in man.

Claude Bernard, Schiff, Gley, Hédon, and Thiroloix produced an atrophic sclerosis of the pancreas by injecting various substances into Wirsung's duct in order to occlude it, but the lesions of the gland thus produced were not always accompanied by diabetes. The same has been done with bacterial cultures or toxins. P. Carnot provoked an atrophic sclerosis of the pancreas accompanied by glycosuria by injecting cultures of the tubercle bacillus or tuberculin into the pancreatic duct.

Two different mechanisms have been proposed to explain the relationship of diabetes with excision or destruction of the pancreas.

In 1889, after von Mering and Minkowski's discovery, Lépine supposed that the pancreas behaved like a vascular gland; but in 1892 Thiroloix attributed diabetes to a traumatic lesion of the solar plexus, his conclusion being derived from a very complete experimental study on pancreatectomy. The same idea was emitted by Pfeiffer, who believed in the existence of a saccharific nervous centre which became irritated by the intermediary of the nerves of the pancreas. This opinion was not generally accepted.

The dispute was settled by Minkowski's experimental work. This observer, in the first place, showed the integrity of the nervous plexus after pancreatectomy. He next carried out an operation in two steps. The pancreas was first removed, and then a portion of the gland was grafted under the skin of the abdomen. Diabetes did not result, but when later on the pancreatic graft was removed diabetes developed. Therefore the pancreas acts by its internal secretion given off to the blood. Minkowski's results were confirmed by Hédon, Thiroloix, and others.

It now remained to ascertain by what physiological mechanism the internal secretion of the pancreas acted. Lépine supposed that the pancreas secreted a glycolytic ferment which not only acted on the blood by destroying the sugar it contained, but that this took place in the midst of the tissues as well.

Loewi, Zuelzer, Eppinger, Falta and Rudinger admitted that the pancreas secreted substances which acted as antagonists to the diabetogenous elements found in the organism; thus, according to Ghedine, the pancreas neutralizes adrenalin, which is susceptible of provoking glycosuria.

Gley and Lafon supposed that the internal secretion carried by the blood acted on the liver, and that it intervened in the transformation of sugars into glycogen in the hepatic cells, so that excision of the pancreas rendered the liver inapt to fix glycogen.

The intimate physiological relations which exist between the pancreas and liver—the two essential organs of glycoregulation—incline me to regard them as linked together functionally, and to admit the action exercised by the pancreas over the liver as probable.

The experiments with blood transfusion and vascular anastomoses between two dogs carried out by Hédon seem to have given a final demonstration of this mechanism; the internal secretion of the pancreas only acts upon the condition that it is thrown into the portal circulation and reaches the liver; thrown into the general circulation, it has no effect. The primordial cause of pancreatic diabetes is therefore a disturbance of the hepatic function resulting from an absence of pancreatic secretion brought by the portal vein.

More recently the question of pancreatic diabetes has been envisaged histologically. Already, in 1881, Baumel admitted the existence of lesions of the pancreas in all cases of diabetes, or at least physiological disturbances of this gland. Later on, Fleiner, Hansemann, Thoinot and Delamare, Dubs, Gellé, and others, also believed that all cases of diabetes were accompanied by lesions of the pancreas, and endeavoured to ascertain the nature of these morbid changes. But opinion is still moot on this subject.

Some, like Lemoine, Lannois, and Lépine, attribute the

preponderant part in the genesis of diabetes to lesions of the glandular acini; Gilbert and Lereboullet attach great importance to angio-pancreatitis from auto-infection that they have observed in the pancreatic glands of diabetic subjects.

Other observers—and they are the more numerous—attribute the external secretion to the acini and the internal secretion to Langerhans' islands; hence they consider lesions of the latter as the anatomical cause of diabetes. This opinion is upheld by Diamare, Opie, Ssobolew, Dieckoff, Weichselbaum and Stangl, Herzog, Wright and Joslin, Curtis, Thoinot and Delamare, Dubs, Sauerbeck, Finney, Steele, and others.

These observers describe various lesions of the islands, such as rarefaction, atrophy, sclerosis, vacuolar degeneration, hyalin infiltration, adiposis, hæmorrhage, etc., all of which have as a result the reduction or abolition of the functions of the islands. Gellé, who has contributed many interesting articles to this subject, characterizes diabetic pancreatitis by the scarcity of the islands, the importance of their lesions, and the predominance of the insulo-acinous transitional forms. In point of fact, it is known that, according to Laguesse's theory, there exists a sort of equilibrium between the acini and the islands—a living pancreas is in a state of continual renovation—and that, according to its needs, the acini transform into islands or inversely. Now, in the pancreas of diabetics a tendency for all the islands to transform into acini is observed, thus resulting in the rarefaction of the former with a consequent abolition of their function.

Certain observers—Guttmann, Hansemann, Herxheimer, Karakascheff, among others—accord a diabetogenous part only to lesions involving the entire glandular parenchyma. Therefore, the subject is still moot.

In order to ascertain the pathogenic signification of the pancreatic lesions, I carried out a histological study with Laignel-Lavastine and Vitry on nineteen pancreatic glands removed at autopsy from diabetic subjects, and thirty-seven pancreas obtained from non-diabetic subjects. In a general way we were able to confirm the findings of the above-mentioned observers, but there were many serious exceptions, as will be seen in Chapter XVIII., where the reader will find a detailed account of our results and conclusions.

Microscopically and macroscopically there is no clue to the diabetic processus; we know no specific lesion of diabetes, and therefore should be most reserved as to the histological interpretation of lesions of the pancreas.

But although one cannot affirm that all cases of diabetes have their origin in the pancreas, on the other hand it clearly appears that certain diabetides are related to morbid changes arising in this gland. There are cases in which the diabetes coincides with some gross lesion of the pancreas, such as sclerosis, lithiasis, or cancer, resulting in cessation of the functions of the gland. These cases are clinically characterized by a double syndrome—namely, a glycoregulator insufficiency from abolition of the internal secretion of the pancreas, and digestive insufficiency from suppression of the external secretion. It is for such cases that the name of pancreatic diabetes should be reserved, and as examples I here append four typical instances:

Case I.—Female, æt. 25 years, without any notable morbid antecedents, was seized in July, 1907, with polydipsia, loss of strength, and emaciation; one month later glycosuria was discovered. Patient entered hospital in January, 1908, at which time she was thin, depressed, with a dry skin and vulvar pruritus; the mouth was dry and the tongue stuck to the lips. There was a high degree of polyphagia, polydipsia, a polyuria of from 5 to 6 litres, and glycosuria of 260 grammes. There was no albumin, acetone, or diacetic acid in the urine. The patellar reflexes were absent, the menses suppressed. Liver and spleen normal.

By diet the glycosuria retrogressed, and then subsided. The patient regained strength, and was discharged from hospital.

In July, 1908, in spite of a diet not too strict, the glycosuria did not exceed 10 to 30 grammes, and the body weight had increased.

In July, 1909, the patient returned to hospital, greatly emaciated and weak. She presented the major symptoms of diabetes and a glycosuria of 100 grammes. She had lost her teeth. A new phenomenon had developed—namely, the stools were abundant and clay-like, with a butyric odour, red inside, and covered on the surface by fat and undigested muscular fibres.

After a period of temporary improvement, her condition became progressively worse; the glycosuria could not be reduced; double cataract with a rapid evolution developed; and then pulmonary tuberculosis, which resulted in death in a few months.

A study of the nutrition made in 1909 revealed the characters of a diabetes with moderate denutrition; the nitrogenous balance was in equilibrium upon the condition that nitrogen food intake was abundant

—170 to 228 grammes per day; it became negative when the intake of albumin descended to 141 grammes. There was a slight tolerance (about 30 grammes) for carbohydrates; the glycosuria was influenced both by carbohydrates and albuminoids. The fæces were abundant—1 kilogramme per day—and microscopically showed a large amount of muscular fibres, neutral fats, and grains of starch. Chemical analysis showed that the nitrogenous substances were only absorbed to the extent of from 16 to 50 per cent. The digestion test with fruit-stones, as well as with gluten capsules, revealed a complete pancreatic insufficiency.

Autopsy showed lithiasis with sclerous atrophy of the pancreas.

Case II.—Male, arthritic family history, obese, large eater and drinker, commenced to suffer from epigastric and abdominal colic after meals, followed by pasty stools, in 1912. He lost weight at the same time, likewise his strength; the urine presented a slight glycosuria.

The symptoms became worse the following year, and in 1914, when I saw the patient, his body weight had dropped from 84 to 60 kilogrammes; he complained of lassitude, with weakness of the legs and lumbar pain upon the slightest exertion. The appetite was capricious, intestinal digestion still painful, and accompanied by abdominal colic and distension. Thirst moderate. Sleep was difficult even with hypnotics. The abdomen was developed, the liver hypertrophied. The patellar reflexes were abolished.

Examination of the urine revealed a polyuria of 2,500 c.c., a glycosuria of 157 grammes, corresponding to a carbohydrate intake of 104 grammes, hence a defect in the carbohydrate tolerance and a glycosuria of mixed origin resulting from carbohydrates, fats and albumins, foodstuffs, and the tissues. The nitrogenous equilibrium was broken, there was a nitrogenous waste of 3 grammes per day; the urine also contained 1·44 grammes of acetone, a small amount of diacetic acid, and an excess of ammonia (1·73 grammes per day).

The fæces were enormous, pasty, grey in colour, fatty and oily over the surface. They contained undigested muscle fibres and fats (neutral, acid, and soaps), but very little starch. Chemical analysis showed a defective absorption of albumins (88·7 per cent.) and fats (84 per cent.); the splitting up of the fats was normal. The fruit-stone test of the digestion was incomplete.

Briefly, the case was one of chronic pancreatitis, perhaps due to lithiasis on account of the colic after eating, accompanied by a double syndrome—namely, diabetes with nitrogenous denutrition and acidosis, and insufficiency of pancreatic digestion. The chief symptom was an enormous and rapid emaciation.

The patient lived for several months, becoming more and more emaciated in spite of an excessive appetite that he was unable to satisfy. He died in a few hours in coma.

Case III.—Male at the age of 25 years developed violent paroxysms of pancreatic colic, following which he developed morphinism. In 1911

he cut himself; the wound was slow to heal, and it was then found that he had 235 grammes of sugar in the urine. Treatment caused the glycosuria to disappear. In 1912 he was again seized with colics and also jaundice, and glycosuria was found. The glycosuria continued to increase, so that in 1913 it had gone from 90 to 200 grammes. He first underwent a cure for the morphinism, and then in 1913 he took two cures in succession at Vichy for the painful paroxysms, which were supposed to be due to gall-stones. In December, 1913, he still suffered. He was distended after meals, and pressure over the pancreatico-duodenal area gave rise to pain; pressure over the lower border of the liver and false ribs was painful, although less so than over the region of the pancreas.

The patient was very emaciated; his height was 1 metre 80 centimetres, and the weight was only 53 kilogrammes. The stools were soft and fatty. Intestinal absorption of albumins was very defective (67 per cent.), as well as of fats (68 per cent.); the splitting up of fats was normal. Microscopical examination of the fæces showed muscle fibres, granulations of neutral fats, and a large quantity of crystals of fatty acids.

The symptoms of diabetes were complete. The patient voided 2,900 c.c. of urine, with a glycosuria of 51 grammes, corresponding to a carbohydrate diet of 52 grammes. The nitrogenous equilibrium was not disturbed. Acidosis was already very marked; there was a large proportion of diacetic acid, 3 grammes of acetone, and 2·95 grammes of ammonia; the ratio of ammoniacal nitrogen to the total nitrogen was 13 per 100; the nitrogen ratio was reduced to 73 per 100.

Diet and pancreatic opotherapy slightly improved the intestinal digestion and the general condition, but the glycosuria and acidosis persisted, likewise the pain in the right lumbar region.

Briefly, this was a case of pancreatic lithiasis with repeated colic, which I believe was more pancreatic than biliary on account of the site of the pain and the coexistence of the diabetes, and regardless of the icterus, which may very likely have been due to compression of the cholodochus by the head of the pancreas. The pancreatic lithiasis was accompanied by diabetes with denutrition and acidosis.

Case IV.—Male, æt. 60 years, diabetic, with pancreatitis and locomotor ataxia. A persistent painless diarrhœa began two years previously; the fæces were soft, whitish in colour, and greasy on the surface; at the same time the patient rapidly emaciated. In eighteen months his weight fell from 84 to 60 kilogrammes. There was no jaundice, and the urine was normal.

A year after the onset of these digestive disturbances very intense thirst developed, and there was a glycosuria of 85 grammes daily, which disappeared with a diet. Then it recurred, attained 300 grammes per

day, and could not be reduced. The patient presented the major symptoms of hyperglycemia; the teeth fell out. Obesity and diabetes existed in his family. In his personal antecedents there was a history of repeated attacks of gout since the age of 40 years. There was a distinct tabes dorsalis, but no history of syphilis.

On a reduced carbohydrate diet analysis of the urine showed 1,500 c.c. urine with 43 grammes of glucose, 7 centigrammes of acetone, no diacetic acid, the ratio $\frac{AN}{TN} = 6{\cdot}2$ per 100, and azoturic ratio $\frac{UN}{TN} = 67$ per 100. The nitrogenous equilibrium was broken; there was a waste of nitrogen daily to the extent of 3·89 grammes. The glycosuria (43 grammes) was superior to the amount of carbohydrates (30 grammes) ingested. Therefore, there was diabetes with nitrogenous denutrition.

Examination of the fæces revealed a considerable proportion of undigested muscle fibres and fat. Nitrogenous absorption only reached 55 per cent.; that of fat was about *nil*. However, the splitting up of fats was very complete. Opotherapy resulted in some improvement of the intestinal absorption.

In this case there was a double syndrome: (1) A severe diabetes with denutrition and no acidosis; (2) a considerable insufficiency of pancreatic digestion. The painless lesion of the pancreas without icterus, already of two years' standing, appeared to be a pancreatitis; the existence of locomotor ataxia should lead one to suppose the probable existence of syphilis, hence perhaps the case was syphilitic pancreatitis.

Case V.—Male, æt. 41 years. Paternal heredity of diabetes and obesity. Has always been a large eater and drinker, and became corpulent; weighed 96 kilogrammes at the age of 30 years. Had enteritis during childhood and adolescence, and jaundice at the age of 20 years. At 32 years had an attack of gout, which recurred the following year. At the age of 36 years suffered from extremely violent epigastric pain extending to right shoulder, occurring in paroxysms every three months, and requiring morphine for relief. Finally, at the age of 40 years he commenced to emaciate and had intense thirst; the emaciation was rapid and profound; from 96 kilogrammes the body weight fell to 63 kilogrammes. An examination of the urine made in March, 1914, revealed a glycosuria of 233 grammes.

In June, 1914, he presented the major diabetic syndrome. Urine, 3,600 c.c.; glycosuria, 70 grammes for a daily intake of 55 grammes of carbohydrates; acetonuria of 10 centigrammes, but no diaceturia. There was no nitrogenous denutrition. Two very large, soft, almost colourless stools per day, containing much fatty matter and undigested muscular fibres. Fat absorption only reached 57·3 per 100; that of nitrogenous substances was 67·6 per 100. Fat splitting in the intestine normal. The liver was not hypertrophied, the tendon reflexes

were absent, there were no disturbances of the pupils, the patient never had syphilis, and Wassermann was negative.

The patient died some months later.

This is a case of chronic pancreatitis of unknown cause, made evident by an insufficiency of the pancreatic digestion, a serious diabetes with irreducible glycosuria, an intermediary form of diabetes without nitrogenous denutrition or acidosis—at least, for the time the patient was under observation. The emaciation was considerable and rapid, a customary symptom at the onset of pancreatitides.

CASE VI.—Male, æt. 38 years, with a maternal diabetic heredity, himself becoming diabetic at about the age of 35 years, but only noticed it himself at the age of 38 years. At the same time digestive disturbances developed, characterized by numerous daily, large, pasty stools; no pain. Since the onset he has lost considerable weight. The diabetes was of a severe grade. The glycosuria was 55 grammes daily, with an intake of 34 grammes of carbohydrates, hence a deficient tolerance and a deficit of 21 grammes. The nitrogenous equilibrium was upset, with a daily deficit of 4·9 grammes of nitrogen. Acidosis was moderate at 53 centigrammes of acetone per day, and intermittent traces of diacetic acid; there was no excess of ammonia (96 centigrammes), and the azoturic coefficient (85 per 100) was normal.

Examination of the fæces revealed a defective absorption of fats and muscle fibres. The coefficient of fat absorption was only 78·2 per 100, that of proteins 83 per 100. Fat splitting in the intestine was normal.

Briefly, we have here a double syndrome: (1) A serious diabetes with nitrogenous denutrition and commencing acidosis; (2) insufficiency of the pancreatic digestion. These symptoms should be attributed to a chronic pancreatitis of unknown nature and origin. Both cancer and syphilis can be eliminated from the pathogenesis in this case.

Pancreatic opotherapy gave good results; the emaciation was arrested and the stools became less fluid.

Clinical Considerations.

The six cases of pancreatic diabetes that I have here related will serve to characterize this clinical type. It is composed of two associated syndromes: (1) A syndrome of internal pancreatic insufficiency—the diabetes; (2) a syndrome of external pancreatic insufficiency—the digestive disturbances.

1. **The Diabetic Syndrome** offers different degrees:

(*a*) Sometimes it is only a minute glycoregulator disturbance which merely gives rise to a temporary glycosuria upon the occasion of an excess at table or the ingestion of glucose as a test. This condition of affairs may be observed in certain chronic pancreatitides, and does not merit the name of pancreatic diabetes in the strict sense of the term.

(*b*) In other cases there is a rather abundant permanent glycosuria, but which is susceptible of subsiding under the influence of a reduced diet, and spontaneously disappearing at the end of the disease on account of a diminished appetite. The hyperglycemia is occasionally sufficiently important in these cases for the glycemia to be accompanied by other symptoms of diabetes, such as polydipsia, pulyuria, looseness of the teeth, and suppurative processes. Such was the condition of affairs in a case of cancer of the pancreas studied by Brault and Ameuille, and in a case of cancer of the body of the pancreas observed by Gendron and myself, in which the glycosuria, which still existed when the patient was admitted to hospital, disappeared and did not return up to the time of death.

(*c*) In the more typical cases the diabetes is of high grade, often accompanied by nitrogenous denutrition and acidosis. Of my six cases there were three in which nitrogenous denutrition was absent, while in the remaining three it reached a high degree, the daily nitrogenous waste attaining from 3 to 4·9 grammes. On the other hand, in these diabetides undergoing a progressive evolution the nitrogenous denutrition may only appear at a more advanced phase of the process, or it may, as I have observed in the first case reported, arise if the nitrogenous diet is insufficient, and cease when the absorption of albumin is increased. Given the great waste in intestinal absorption, it can readily be conceived that the alimentary needs of the patient must be fulfilled by a larger amount of food.

It is the same for the curability of the glycosuria. In moderate cases without nitrogenous denutrition, the glycosuria can generally be reduced by diet; there is a more or less considerable tolerance for carbohydrates. In the serious cases with nitrogenous denutrition, the glycosuria is, on the

contrary, irreducible; it is superior to the daily carbohydrate intake, and in my cases was represented by a negative balance of from 13 to 53 grammes.

The acidosis goes hand in hand with the gravity of the diabetes. Some cases may undergo their evolution to the end without acidosis, but the majority will develop acidosis. At first there is only acetonuria, and later on diaceturia develops, and the acidosis reaches a high degree to the point of coma.

2. **The Digestive Syndrome** is characterized by a peculiar low-grade dyspepsia; at times the appetite is abolished, at others it is preserved. The digestive period is accompanied by vague distress, but the only characteristic it presents is the large, fatty, soft stools with a butyric odour, in which it is easy to detect undigested food with the naked eye. Occasionally there is diarrhœa. Microscopical examination reveals a large number of intact muscle fibres, drops of neutral fats, crystals of fatty acids, soaps, and an exaggerated amount of starch. Chemical analysis confirms these findings by showing that the coefficient of albumin and fat absorption is very low; from 90 to 95 per 100 the coefficient of nitrogenous absorption falls to 88 per 100, or even 42 per 100 in my cases. From an average of 95 per 100 the coefficient of fat absorption fell to 84 or even 16 per 100. In one case it was almost *nil*. On the other hand, it is to be remarked that, contrary to Muller's and Gaultier's statements, the chemical splitting up of unabsorbed fat was always found to be quite as complete as in normal subjects.

The fruit-stone test of the digestion is also an excellent procedure for characterizing the insufficiency of the external pancreatic secretion. In these cases the nuclei of the muscle fibres and connective tissue remain undigested in the ball of meat ingested by the patient; but in order that the result shall have any value, the passage of the ball through the digestive tract must not be too short or too prolonged—it should take twenty-four hours. I gave this test to five patients; in two the results obtained indicated pancreatic insufficiency, while in the remaining three the results were perverted by the excessive duration of the transit through the digestive tract, which lasted from thirty-nine to forty-four hours.

With such defective digestive absorption one can readily conceive that the organism will not resist for any length of

time. Rapid and profound emaciation is one of the principal symptoms of pancreatitis. One of my patients lost 24 kilogrammes in three months; another, 24 kilogrammes in six months; while a third lost 35 kilogrammes in about one year; finally, a fourth patient was reduced to the state of a skeleton, weighing 53 kilogrammes with a height of 1 metre 80 centimetres. The considerable emaciation in cancer of the pancreas has long been known; it is not less in pancreatitides with or without diabetes, and it may be said as a general rule that rapid severe emaciation should always lead one to suspect a lesion of the pancreas.

The emaciation is accompanied by considerable loss of strength, and the patient is incapable of doing any work.

Pain is not a constant symptom. It was present in three of my cases and absent in the other three. It usually occurs in violent paroxysms seated in the epigastrium, extending towards the right shoulder, back, and right hypochondrium; lasts for several hours, recurs more or less frequently, sometimes every year, or three or four times a year, with or without regularity. The severity of the pain is occasionally such that morphine must be given. These painful paroxysms are not accompanied by icterus, which distinguishes them from hepatic colic, with which they are commonly confounded, especially at the onset; however, in one case under my care pancreatic colic was accompanied by icterus, either because there were calculi or because of compression of the cholodochus from tumefaction of the head of the pancreas. In certain cases pancreatic colic is attenuated, and is only made evident by moderate pain occurring during digestion preceding a copious pasty stool. Search for a painful spot in the pancreatico-duodenal area is another diagnostic means of precision, and was very distinct in one of my cases.

There is every reason to believe that these painful forms usually are due to pancreatic lithiasis; clinical observation, with one exception, leads me to this conclusion, so that I cannot be more affirmative. On the other hand, pancreatic lithiasis may be indolent, as in Case I., in which autopsy revealed the presence of calculi; while non-lithiasic sclerosis of the gland may be painful, as Loeper's cases testify.

The clinical type of pancreatic diabetes is not always as

distinct as in the cases I have reported. There are intermediary forms in which the disturbance of pancreatic digestion is sufficiently moderate to cause hesitation. One can readily conceive that, besides the complete destruction of the pancreas from sclerosis or lithiasis, there may be incomplete lesions only, giving rise to moderate digestive disturbances. In these circumstances resort must be had to all procedures for the study of pancreatic insufficiency, in order to establish the relationship between the diabetes and lesion of the pancreas.

This is what I have done by systematically studying the function of the pancreas by means of the fruit-stone digestion test in diabetics. I thus was able to confirm that in 19 cases of diabetes without denutrition there was complete pancreatic digestion of the stones in 12, incomplete digestion in 7; in 26 cases of diabetes with denutrition the stones were completely digested in 12, in 6 the digestion was incomplete, while in 8 it was *nil*. Hence the disturbance of pancreatic digestion is more often met with in serious diabetes than in the mild forms of the disease—53 per cent. in the former, 36 per cent. in the latter. From this statistic it is evident that pancreatic disturbance is more frequent than might be assumed from the general clinical aspect of these cases, and this is quite in accord with pathological findings.

On the other hand, if one considers diabetes accompanied or not by insufficiency of pancreatic digestion, it will be seen that the glycoregulator disturbance is in no way influenced by this external pancreatic insufficiency. It undergoes the same evolution, reacts in the same way to both diets and drugs, whether or not it be associated with external pancreatic insufficiency. Alone examination of the digestion will allow one to make the diagnosis of pancreatic diabetes, be this present in its complete forms or in its mitigated forms. There is diabetes with denutrition and serious acidosis which undergoes its entire evolution to death without ever manifesting the slightest degree of insufficiency of the pancreatic digestion; it corresponds to diabetes with denutrition which at autopsy reveals a pancreas hardly, or not at all, diseased.

The study of disturbances of the pancreatic digestion therefore leads to the same conclusion as experimental and pathological study does—namely, that the glycoregulator disturb-

ance, although fairly frequently related to a lesion of the pancreas or a disturbance of the external pancreatic secretion, nevertheless may be completely independent, and that its evolution and prognosis must be regarded separately, and quite independently from the pancreatic lesion or the secretory disturbance of this organ.

Pathology.

The *anatomical lesions* of pancreatic diabetes are in the majority of cases represented by sclerous pancreatitis or lithiasis; cancer is sometimes responsible. Less frequently there is an inflammatory or hæmorrhagic pancreatitis with slow evolution. Syphilis can be incriminated only in exceptional cases, and for the most part doubtful; excepting Steinhaus's case, in which there was an ulcerated gumma in Vater's ampulla and a gumma in the liver, the others were sclerous atrophy of the gland in syphilitic subjects (Lenhartz, Manchot), although it could not be affirmed that syphilis was the cause of the sclerosis. Diagnoses based upon the results of specific treatment are usually lacking in precision, so that no conclusion can be arrived at. I have met with a case of pancreatic diabetes in a syphilitic, but it is quite impossible for me to say whether the pancreas was involved by specific lesions, because there was no autopsy, and intensive specific treatment persistently carried out was absolutely without effect. I know of no case of tuberculous lesions of the pancreas.

The question arises as to whether ordinary sclerosis of the pancreas may not be due to syphilis or tuberculosis; this is possible, since experimentally injections of cultures of bacilli or tuberculin into the pancreatic duct may bring about sclerosis and atrophy of the organ, but it has not been demonstrated. Syphilis does not appear to be especially frequent in diabetic subjects, and was absent in the majority of my cases. As to tuberculosis, the arguments in favour of the specific origin of pancreatic sclerosis are still less solid. Hence the question is still a moot one.

There is another syndrome in which the pancreas intervenes along with the liver in the production of diabetes. This is the *hepato-pancreatic type*, rather frequently assuming the

form of bronzed diabetes. Anatomically the affection is characterized by an intense sclerosis of the liver and pancreas, clinically by serious diabetes, to which hepatic and pancreatic symptoms become superadded. Therefore, this is another form of pancreatic diabetes of a more complex nature. I mention it without describing it, as I am only envisaging the pure forms of pancreatic diabetes.

Prognosis.

Pancreatic diabetes is invariably serious. It is not because the evolution is always very rapid, but it is continued, progressive, and the association of the diabetic and digestive syndromes soon leads to a state of emaciation, weakness, and cachexia.

Diagnosis.

It is neither the form nor the intensity of the diabetic syndrome that will indicate the pancreatic origin of the process. It is the association of the syndrome of external pancreatic insufficiency with the syndrome of diabetes. Therefore, this should be thought of in all cases of diabetes, and examination of the digestive functions should never be neglected, especially the quality of digestion and intestinal absorption. Chemical and microscopical examinations of the fæces are indispensable for the diagnosis.

Treatment.

The diagnosis of pancreatic diabetes is necessary, because it has a therapeutic sanction. Not only treatment for the syndrome of hyperglycemia is essential, as well as for the syndrome of acidosis according to ordinary rules, but opotherapy should be resorted to for the pancreatic insufficiency. Pancreatic extracts, pancreatin, pancreato-kinase in gluten or keratin capsules, are exhibited in order to supply the insufficiency of the digestive pancreatic juice and stimulate the activity of the internal secretion. In some cases I have obtained an amelioration of the intestinal digestion with this treatment, but it is not invariably efficacious.

The action of opotherapy on the internal secretion and on

the diabetic syndrome has as yet not been demonstrated. Capparelli and Vanni say that they have succeeded in causing the glycosuria to disappear in diabetic dogs by injecting pancreatic extract in suspension in physiological salt solution. But Hédon gave subcutaneous or intravenous injections of pancreatic extract without any success whatsoever. Sandmeyer fed diabetic dogs on fresh pancreas, and found that the glycosuria increased at the same time as the digestive disturbances. Zuelzer, Dohrn, and Marxer seem to have obtained positive results in experimental diabetes in dogs and in diabetes in man by having recourse to particularly active pancreatic extracts.

Personally, I have never seen any effect on the diabetic syndrome from opotherapy; it does not decrease the glycosuria or increase the tolerance; on the other hand, I have occasionally observed a temporary but important increase of the glycosuria at the beginning of treatment, as if an unusual quantity of sugar had suddenly been set free from the tissues and fluids of the organism.

CHAPTER XVIII

THE PANCREAS IN DIABETES*

SINCE Lancereaux published his works on the pathology of the pancreas, since the physiological experiments of von Mering and Minkowski, reproduced by Thiroloix, Hédon, Lépine, and many others, no doubt any longer exists that there is a relationship between morbid changes in the pancreas and diabetes. But the nature of these diabetogenous changes is still unknown.

Their study has given rise to numerous researches. Some proposed to discover the physiological disturbance of the pancreas which resulted in diabetes, while others tried to demonstrate the lesions of the pancreas belonging especially to this morbid process. I shall only refer to the study of the anatomical lesions of this gland that I have undertaken during the past few years with Laignel-Lavastine and Vitry. I will describe the lesions of the pancreas that we found at autopsy of sixteen diabetics, and will discuss their pathogenic value by comparing them with lesions encountered in non-diabetic subjects; finally, I shall attempt to expose the subject as it stands to-day.

Lesions of the Pancreas in Diabetics.

I here give a description of the pancreatic glands that I have had the opportunity of studying histologically, classifying them according to the decreasing importance of their lesions; only a very brief summary of the lesions is given, as a more complete discussion can be found in other of my writings on the subject.

CASE I.—*Diabetes with Denutrition.*—Atrophy and sclerosis of the pancreas. Around a dilated Wirsung's duct filled with calculi, only a dense sclerous tissue can be found, in the midst of which numerous

* Société Médicale des Hôpitaux de Paris, April 25, 1913.

nerve branches and some cell collections, which can be regarded as the islands of Langerhans, are disseminated.

CASE II.—*Bronzed Diabetes complicated with Acidosis.*—Pigmentary bivenous hepatic cirrhosis. Very intense cirrhosis of the pancreas, isolating the lobules and even the acini. Lesions of the acini. Absence of the islands of Langerhans and the forms of transition. Excessive pigmentation.

CASE III.—*Acute Diabetes with Denutrition and Acidosis.*—Pancreas sclerous, brownish, hypertrophied. Perilobular and intralobular cirrhosis, especially marked around the excretory ducts. Islands very rare; peri-insular and intra-insular cirrhosis. Ochre pigment infiltration in the cells of the acini, and bands of sclerosis under the capsule and in the lymphatic spaces. Hepatic cirrhosis with ochre pigment infiltration.

CASE IV.—*Lipogenous Diabetes, complicated later by Denutrition and Acidosis.*—Intense perilobular and intralobular pancreatic cirrhosis. Fat very abundant. Langerhans' islands surrounded by sclerosis, sclerosed or hyaline.

CASE V.—*Diabetes with Denutrition and Tuberculosis.*—Interacinous sclerosis of pancreas. Numerous small islands, mostly normal, some sclerous or hyaline. Numerous acino-insular transitional forms.

CASE VI.—*Diabetes without Denutrition; Gangrene of Foot.*—Hepatic sclerosis. Renal sclerosis.

Marked sclerosis of pancreas around and in the interior of the lobules; perivascular sclerosis especially marked. Abundant fat. No islands of Langerhans. Numerous insulo-acinous transitional forms.

CASE VII.—*Diabetes and Hemiplegia.*—Marked intralobular sclerosis of pancreas. Islands very sclerous.

CASE VIII.—*Diabetes; Alcoholism; Tuberculosis.*—Perilobular and intralobular sclerosis of pancreas. Islands normal or sclerous. Some acino-insular transitional forms.

CASE IX.—*Diabetes.*—Very slight sclerosis of pancreas, at places vascular, at others canalicular. Little fat. Acini normal. Islands very numerous, and not large. Very slight thickening of the connective tissue of the islands. Many transitional forms.

CASE X.—*Diabetes without Denutrition; Acidosis; Peritonitis from Perforation.*—Slight perilobular, intralobular, pericanalicular, and perivascular pancreatic sclerosis. A very few islands surrounded by a slight sclerous ring. Slight hepatic sclerosis.

CASE XI.—*Diabetes without Denutrition.*—Pancreas shows little change. Slight thickening of the pericanalicular and perivascular connective tissue. Rare islands, quite a good size, with slight thickening of the capillaries. Rare acino-insular transitional forms.

Case XII.—*Diabetes with Denutrition and Acidosis.*—Slight pancreatic changes. Fine intralobular and peri-acinous sclerosis. Few islands, some sclerous or presenting hyaline infiltration.

Case XIII.—*Diabetes with Denutrition and Acidosis.*—No marked sclerosis; no visible Langerhans' islands.

Case XIV.—*Diabetes with Acidosis.*—Mild fine sclerosis. Islands very scarce.

Case XV.—*Diabetes with Denutrition and Acidosis; Pulmonary Tuberculosis.*—Aspect of pancreas normal. No sclerosis. Acini normal. A few healthy Langerhans' islands. Rare transitional forms.

Case XVI.—*Diabetes with Denutrition ; Pulmonary Tuberculosis.*—No sclerosis of pancreas. Islands not numerous; a few acino-insular transitional forms.

Case XVII.—*Diabetes with Denutrition and Acidosis ; Tuberculosis.*—Aspect of pancreas normal. Very slight thickening of perilobular and intralobular connective tissue. Numerous large islands. A few acino-insular transitional forms.

Case XVIII.—*Diabetes without Denutrition ; Pulmonary Tuberculosis.*—No sclerosis of pancreas; islands normal.

When one examines these eighteen cases, it becomes evident that the pancreas of diabetic subjects presents very varied lesions, principally involving the interstitial tissue and islands—namely: (1) Perilobular and intralobular sclerosis, having a canalicular or vascular starting-point; (2) few islands of Langerhans, sclerosed or infiltrated with a hyaline substance; (3) pigmentation; (4) lesions of the acini.

The extent of these lesions is very variable. In some the pancreas is completely destroyed by sclerosis, in others the pancreas offers no trace of sclerosis or lesions of the acini or islands. The former are to be regarded as functionally *nil*, the latter as histologically normal.

Lesions of the Pancreas in Non-Diabetic Subjects.

Out of a total of 37 subjects dying from various acute or chronic affections, the pancreas was normal in 7; in all the other cases the gland presented more or less extensive lesions, more or less systematized, but unquestionable.

Sclerosis of the glandular acini is very common, since it was found in various degrees in 27 out of 37 autopsies. Adiposis was noted in more than 50 per cent. of the cases. As to Langerhans' islands, upon which discussion is especially

rife, they were normal 8 times out of 37 autopsies; in all the other cases there was some morbid change, even if only mild; the number or size differed from the norm, or the sclerosis invaded the islands to a certain extent.

The Pathogenic Value of the Lesions.

In order to appreciate the pathogenic value of the lesions of the pancreas in diabetic subjects, they should be compared with those encountered in the pancreas of subjects without diabetes.

Sclerosis.—In respect to sclerosis one must distinguish four different types: (1) Complete sclerosis having completely destroyed the gland, as in Case I.; (2) intense sclerosis, as in Cases II., III., IV., V., and VI.; (3) very mild sclerosis, as in Cases VII., VIII., IX., X., XI., and XII.; (4) complete absence of sclerosis, as in Cases XIII., XIV., XV., XVI., XVII., and XVIII.

In the first case, the sclerosis represents a complete destruction of the pancreas, and may be regarded as the cause of the diabetes. In the cases where the sclerosis was intense, one may assume that the process had destroyed the functions of the gland sufficiently to give rise to diabetes; but the sclerosis must be really very considerable, as in Case II., because one meets with very extensive pancreatic sclerosis in subjects with biliary lithiasis, hepatic cirrhosis, or other morbid processes, although it did not give rise to diabetes. Finally, animal experiments show that in order to produce diabetes the pancreas must be almost completely excised, and that if only a small portion of the gland remains—for example, about one-fifth—diabetes does not ensue. Hence the sclerosis must be very intense in order that an almost complete destruction of the gland shall take place.

In the numerous cases in which the sclerosis is slight, the morbid process cannot in any way be connected with the genesis of the diabetes. In the majority of cases pancreatic sclerosis cannot therefore be regarded as the cause of diabetes.

Adiposis.—Fatty infiltration of the pancreas has still a lesser signification; it is quite as common in non-diabetic subjects as in those with diabetes. Even when the adiposis is

considerable, when the pancreas is completely buried in fat, so that the development of the latter greatly reduces the amount of pancreatic tissue, I do not believe that it can be a cause of diabetes. In point of fact, I found at the autopsy of a corpulent woman a pancreas in such a state of adiposis that the glandular lobules were nothing else than disseminated masses of fatty tissue, and nevertheless this woman never had diabetes. In reality, fatty infiltration of the pancreas is a casual phenomenon, just as is fatty infiltration of the lymph nodes. The pancreas will be fatty in obese individuals, and free from fat in those who are thin, whether or not the subject be diabetic.

Lesions of Langerhans' Islands.—I have noted the *rarity* of these islands in the pancreas of diabetics; occasionally it has even been impossible to find a single one. Dieckoff, Curtis, Sauerbeck, and Gellé have made the same remark. This is a character which differentiates diabetic pancreatitis from the non-diabetic pancreatitis, in which the islands are more prone to be numerous.

But this paucity of the islands is not constant; in two of my cases I found, on the contrary, numerous large islands, and Parmentier and Chabrol have made the same remark.

The same may be said of the *size* of the islands, which are frequently very small in diabetes, as Weichselbaum, Stangl, and Schmidt have pointed out; as an exception I found them enlarged in one subject (Case XVII.). Lépine, Thoinot, and Delamare have reported similar instances.

Like other observers, I have rather frequently met with *lesions* of the islands, especially sclerosis and hyaline infiltration; but these lesions do not appear to me characteristic, because I have seen an insular sclerosis quite as well developed in non-diabetic pancreatitis, while in other instances I have met with hyaline infiltration of the islands when no diabetes was present. Carnot, Amet, and Gellé have made the same remark. And what is more, the lesions never involved all the islands, and the development of diabetes cannot be accounted for by a lesion of only a few.

The insular hæmorrhages observed by Weichselbaum, Stangl, Delamare, and Gellé are inconstant lesions, and were absent in all my autopsies.

This likewise may be said of pigment infiltration and degeneration (Thoinot and Delamare), as well as of calcareous degeneration (Weichselbaum and Stangl).

Gellé has particularly insisted on the pathogenic signification of the *transitional forms*. He distinguishes two types, the first of which are the acino-insular forms, which represent the acini about to become transformed into islands, and which indicate the functional activity of the gland from the viewpoint of carbohydrate metabolism. The second are the insulo-acinous forms, which, on the contrary, represent the transformation of the acini into islands, and indicate a decrease of the functional activity of the pancreas. These two types can be recognized by the delicate histological characters described by Gellé.

Gellé has noted that the insulo-acinous forms are almost the only, if not the only, ones met with in the pancreas of diabetics, while the acino-insular forms predominate in non-diabetic pancreatitides. According to his way of thinking, the histological characteristic of the diabetic pancreas should be a lesion of the islands as well as a decrease of their number, the insulo-acinous retrogressive forms predominating—that is to say, everything that would seem to indicate a diminution and disappearance of the endocrine secretion of the pancreas, if it be admitted that Langerhans' islands are the organs of internal secretion, while the acini are organs of external secretion.

My histological researches have confirmed Gellé's views. I was also struck by the disappearance or scarceness of the islands in diabetic pancreatitides, the frequency of lesions of the islands, the rarity of the acino-insular transitional forms, and the relative frequency of the insulo-acinous forms.

But these findings suffer exceptions. There are cases of diabetes, and even diabetes with very serious denutrition, as in Case XV., in which the glycosuria reached 1,000 grammes per day, where the pancreas presented numerous, large, and perfectly normal islands.

On the other hand, the lesions of sclerosis or hyaline infiltration that I met with in the islands of a certain number of diabetics never involved all the islands of a given pancreas, and unless they were very intense they did not appear to be

such as to completely abolish the functions of the islands. Hence it is difficult to understand how a lesion of a portion only of the islands can bring about diabetes when it is known that one-fifth of the gland is enough to prevent the development of glycoregulator disturbance.

Even if the physiological signification attributed by Gellé to the predominance of retrogression to acini and the disappearance of the forms retrogressing towards island formation be accepted, I do not see that this is a sufficient characteristic to regard it as a diabetogenous pancreatitis. From the physiological view-point it makes very little difference if the islands are incapable of regeneration when a sufficient number of them exist for assuring the functions of the pancreas. Now, precisely what drew my attention in some cases of serious diabetes was the remarkable state of preservation of Langerhans' islands in cases where I expected to find advanced lesions of the pancreas.

I therefore believe that one should be *very guarded as to the physiological interpretation to be given to the histological lesions of the pancreas*, all the more so because this organ is one of those which most rapidly develops post-mortem changes, and that, on account of the auto-digestion that it undergoes, the specimens are often too changed to allow one to derive any knowledge of the true pathological condition present. One may in these circumstances detect gross sclerosis and the scarcity of the islands, but the fine cellular lesions escape observation.

Another thing claimed my attention—and on this point I entirely agree with Gellé—namely, *the want of correlation* between the gravity of the diabetes and the degree of pancreatic lesions. In obese diabetes of years' duration without denutrition and little glycoregulator disturbance one will find at autopsy very extensive sclerosis of the pancreas with fatty infiltration. On the other hand, in diabetes with the most serious forms of denutrition resulting in death within a short lapse of time, the pancreatic lesions will be trifling, the sclerosis is mild, while lesions of the islands are not constant.

But let me once more say these are not absolute rules, and histology, any more than clinical observation and physiology, does not permit one to establish a difference between

the nature of diabetes with and that without denutrition. There is simply a difference of degree between these two forms, therefore of the prognosis as well; a diabetes without denutrition may become aggravated, and finally nitrogenous denutrition ensues.

The Conception of Diabetic Pancreatitis.

What should be our conception of pancreatic diabetes, given the data we now possess ? A few years ago, in France at least, there was a tendency to establish an equation between diabetes with denutrition and pancreatic diabetes. At present this opinion is losing ground. Upon several occasions Ménétrier, Ramond, Chabrol, and myself have referred to the absence of important lesions of the pancreas in subjects dying from serious forms of diabetes.

Nevertheless, there certainly exists a clinical type of the disease to which the name of *pancreatic diabetes* may be logically given, and I have notes of several fine examples. The diagnosis can be made during life. This type can be recognized by digestive disturbances depending upon the insufficiency of the external pancreatic secretions which become superadded to a glycoregulator disturbance. For that matter, it is to be remarked that this pancreatic diabetes has an evolution which in no essential point differs from that of other serious forms of diabetes. The cases which can unquestionably be given the name of pancreatic diabetes are relatively rare, and only represent an infinite number of serious diabetes.

A last and more general question must be considered. Should one assume that the pancreas plays a part *in the production of all diabetes?* This is a seductive conception, and is based upon a certain number of solid arguments. Some observers, taking pathological data as a basis, reply in the affirmative; but I have already discussed the signification of these arguments, and have shown that they are not absolutely convincing.

Whether or not physiology will bring forth more specific arguments is a question that I propose to take up in the near future. For the time being our information is insufficient,

and a prudent reserve is in order. Diabetes appears to be one of those affections that formerly would have been called essential—that is to say, one that did not possess a constant pathological or ætiological substratum. Anatomically and physiologically we have not as yet been able to localize the functional disturbance, which clinically manifests itself by an imperfection of the carbohydrate metabolism.

CHAPTER XIX

DIABETES AND ACROMEGALIA*

THE relationship existing between diabetes and acromegalia has been proved by a large number of cases. Hansemann's statistics show a proportion of 12 diabetics out of a total of 97 cases of acromegalia, while Hinsdale's statistics show a proportion of 14 diabetics out of a total of 130 cases of acromegalia. But these figures are too low, because, as glycosuria has not always been searched for in cases of acromegalia, many instances of diabetes must have been unrecognized. More recently, Borchardt has put the proportion at 35 per cent., while Pierre Marie seems to be nearer to the truth when he states that glycosuria exists in about 50 per cent. of the cases of acromegalia. Sometimes the cases recorded are purely clinical, while other writers, as in the 16 cases published by Launois and Roy, give the results of the autopsies, so that the constant lesion of the hypophysis has been recognized.

Diabetes is not less frequent in acromegalic giants, some typical observations having been published by Caselli, Buday and Jancso, Dallemagne, Alibert, and Launois and Roy.

Acromegalia and gigantism being due to lesions of the pituitary body, it results that there is a form of diabetes which offers close pathogenic relations with the hypophysis. It remains to define the nature of these relations, to establish the physiological mechanism of the glycosuria and polyuria in these cases, and to state whether or not this clinical type merits the name of hypophysary diabetes.

Case.—The case that I observed with S. Langlois will serve to elucidate some of these problems:

The patient, a male, æt. 48 years, a miner without diabetic or acromegalic heredity in his antecedents, had three tall brothers living, and a fourth one who probably died of acromegalia. After a normal

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* *Paris Médicale*, May 3, 1919.

growth up to the age of 25 years, the patient perceived that his hands, feet, and head began to increase in size. At the age of 48 the diabetes seems to have first been noted. At this time the patient complained of greater thirst and hunger than usual, and examination of the urine revealed polyuria of 5 litres and a glycosuria of 300 grammes. Some months later a carbuncle developed on the buttock.

The patient was a characteristic example of acromegalia. The hands and feet were enormous; the medius measured 13 centimetres in length, while the circumference of the head of the first phalanx of the thumb measured 10 centimetres; that of the head of the first phalanx of the toe measured 13 centimetres. The patient wore a No. 47 (French) shoe. The face was strongly prognathic; the lower lip was very thick; the tongue enormous, measuring 8 centimetres in length—the patient moved it with difficulty, and speech was interfered with. The ears were large. The frontal sinuses, as was shown by radiography, were three or four times larger than normal. The back was arched, the thorax enlarged at its base, so that, taken together, the appearance was that of a double hump. The height was 1 metre 86 centimetres, the weight 94 kilogrammes 600 grammes. Radiography of the skull revealed an increase in size of the sella turcica, indicating an increase in size of the hypophysis.

At the time the patient entered hospital he voided 4,500 c.c. of urine in twenty-four hours; with a diet containing 138 grammes of carbohydrates, the amount fell to 3,000 c.c. with 150 grammes of glucose. There was no acidosis, no albuminuria. All the tendon reflexes were completely abolished. The pupil reflexes were normal. Patient had not had syphilis. Digestion was quite good, some constipation. Liver normal. Heart and blood-pressure normal. The respiratory apparatus presented stethoscopic and radiographic signs—slight dullness over the right apex with decreased vesicular murmur, opacity of the right costo-diaphragmatic cul-de-sac, and thick shadows around the hilum—which led to the suspicion of tuberculous lesions, but there were no bacilli in the sputum.

With a reduced carbohydrate diet the glycosuria progressively fell, so that within six weeks it had dropped to 5 and 10 grammes in twenty-four hours, while after a fast of three days it disappeared. The patient was discharged from hospital, but came back from time to time to report. The glycosuria never returned.

Symptomatology.—This case presents a characteristic type of acromegalia and diabetes. The diabetes was without denutrition or acidosis, as is usual in cases of this kind.

In going over the published cases it will be found that the glycosuria, in spite of its intensity due to the large amount of food taken, will give way to a reduced carbohydrate diet, or will spontaneously disappear towards the end of the disease, because, on account of the cachexia, the patient does

not eat sufficiently. Thus, in F. Widal's case, the patient voided an average of 800 to 900 grammes of glucose in twenty-four hours, but he ingested 1 kilogramme of meat, 1 kilogramme of bread, and 1 kilogramme of potatoes daily. During the first years of the disease, Finzi's patient presented glycosuria with polydipsia, polyphagia, polyuria, and albuminuria, but during the last phase of the process both the glycosuria and albuminuria had ceased to exist. In Buday and Jancso's case the glycosuria disappeared three months before death occurred. The glycosuria varied with the diet in Achard and Loeper's patient, while in Strumpell's case the glycosuria disappeared when a meat and fat diet was given.

In certain cases the disturbance of nutrition will attain a more marked degree, the diabetes being accompanied by denutrition and acidosis.

Ravaut's patient, who had acidosis, voided 20,000 c.c. of urine, with 94 grammes of urea and 1,200 grammes of glucose, in twenty-four hours. Acidosis was present in the cases reported by Praun and Prescher, and Carnot and Rathery; Stadelmann's patient died from acidosis ending in coma. Death in coma has been mentioned in a certain number of cases, but it is not at all certain that it was diabetic coma, because no reference is made to the reactions of acidosis, so that it is possible that the coma was caused by the development of the cerebral tumour.

The onset of the process is usually with acromegalia, the glycosuria developing later on. In my case the acromegalia appears to have begun twenty-five years before the diabetes made its appearance. In Widal's case the acromegalia began at the age of 22 years and the glycosuria at 32 years.

But such is not always the case. The skeletal disturbances and glycosuria may appear simultaneously, and the glycosuria even has been known to precede the acromegalia. Schlesinger has reported the case of diabetes which developed in childhood and disappeared completely, only to recur later on in life with the early symptoms of acromegalia. Finally, there are cases in which the acromegalia is quite rudimentary, and others in which it was completely wanting. In Loeb's case the pituitary tumour was accompanied by glycosuria without acromegalia, and Pineles and Caselli have recorded similar cases.

The relation between glycosuria and polyuria in hypophysary diabetes is interesting to precisely define. As a general rule, in ordinary diabetics the polyuria is related to the hyperglycemia and follows the evolution of the glycosuria: when this decreases the polyuria diminishes; when the glycosuria subsides the amount of urine voided also returns to normal. It is most uncommon to see a polyuria persist after the glycosuria has disappeared.

In the case I have reported matters were quite different. Although the glycosuria disappeared by diet, the polyuria continued. At the onset there was a polyuria of 3,000 to 3,500 c.c., with a glycosuria of 150 grammes; a little later the polyuria was still 3,500 c.c., with a glycosuria reduced to 25 grammes, and at the end it amounted to 3,000 c.c., when the glycosuria had disappeared. It is therefore clear that the polyuria in this case was independent of the hyperglycemia and the glycosuria. Each had a different pathogenesis.

There is a hypophysary polyuria just as there is a hypophysary glycosuria, an insipid diabetes, and a diabetes mellitus. These two syndromes may be associated, as in the case here reported, although they remain independent of each other, but usually the polyuria alone exists.

This is the conclusion arrived at by Camus and Roussy from their experimental work on hypophysectomy in dogs. While they rarely induced a slight transitory glycosuria, they frequently produced a prolonged abundant polyuria. Clinical observation, like experimental work, therefore proves the independence of the polyuria and glycosuria in lesions of the hypophysis.

Pathological Physiology.—Attempts to demonstrate the pathogenical mechanism of glycosuria and polyuria in tumours of the pituitary body have resulted in the development of various hypotheses. For some they are due to a concomitant lesion of the pancreas or other vascular glands; others attribute them to a functional disturbance of the hypophysis; while still others suppose that they depend upon a lesion of one or several nervous centres situated at the base of the brain in proximity to the pituitary body.

1. The hypothesis of Dallemagne, Hansemann, and Pineles, which relates the glycosuria in tumours of the hypophysis to

a *concomitant lesion of the pancreas*, does not bear examination. In point of fact, there are cases in which no pancreatic lesion exists, while in others the lesion is too trifling to be seriously taken into consideration. In the present state of our knowledge there are no valid reasons for invoking pancreatic pathogenesis as a cause of diabetes, excepting when there is a sufficiently advanced destruction of the pancreas giving rise to insufficiency of the digestive secretion of the gland. Now, such a condition has never been encountered in acromegalia with diabetes.

2. The observers who invoke a *disturbance of the internal secretion of the hypophysis* can be divided into two groups:

(*a*) The first group believe that the glycosuria is the outcome of an insufficiency of the gland, their opinion being founded on Caselli's one experiment, who, by destroying the pituitary body, was able to produce glycosuria.

This experiment is contradicted by those carried out by Handelsmann and Horsley, who performed almost complete hypophysectomy on fifty-four animals, and in only two was a mild glycosuria noted, while Ascoli and Legnani never found a single instance of glycosuria in seventy dogs upon whom they removed the hypophysis.

(*b*) On the other hand, the second group attribute the glycosuria to a *hyperactivity of the hypophysis*. They base their opinion on two categories of experiments—namely, (1) injections of the extract of the pituitary body, and (2) by irritative lesions and excision of the hypophysis. Borchardt produced glycosuria in rabbits by injections of pituitary extracts, and Rossi has obtained the same result, while Ott and Scott have induced hyperglycemia by this means. But Franchini was only able to produce glycosuria by giving massive doses of pituitary extract, while Giadovini and Ruggieri failed completely in their attempts in this direction.

In man, Claude and Baudoin have met with glycosuria following injections of pituitary extracts, and attributed this phenomenon to hepatic insufficiency. Harvey Cushing, Goetsch and Jacobson have induced glycosuria by pricking the infundibulum; the post-operative phenomena are divided into two phases, the first of which is an irritation of the hypophysis, characterized by glycosuria; the second phase is one

of insufficiency of the gland, and is, on the contrary, characterized by an intense tolerance for carbohydrates; at this time injections of pituitary extracts lower the carbohydrate tolerance and induce glycosuria.

Cushing's experiments were much discussed, and were taken up by Camus and Roussy. Of the forty-five dogs upon whom they either destroyed the hypophysis or produced lesions at the base of the brain, only six of the animals developed glycosuria, and this glycosuria was mild and temporary, lasting only from twenty-four to thirty-six hours at the most. It would seem that the lesions at the base of the brain are of greater import than those of the hypophysis, because, of the six dogs in whom glycosuria was induced, in four of them important lesions of the base of the brain had been produced. On the other hand, Camus and Roussy never found that injections of pituitary extract lowered the tolerance for carbohydrates or gave rise to glycosuria.

Personally I have never seen any notable action on the glycosuria one way or another from pituitary opotherapy. Placed on a progressively reduced carbohydrate diet, the glycosuria likewise progressively decreased, and at length completely disappeared following a three days' fast in my case of acromegalia, while the treatment with pituitary extracts had no influence whatsoever, as will be seen from the table on p. 201.

Hence in acromegalia with diabetes the glycoregulator disturbance does not appear to depend upon the internal secretion of the hypophysis.

The question is the same for polyuria in lesions of the hypophysis. Some observers suppose that it is due to glandular insufficiency, because they have been able to reduce it by pituitary opotherapy. Lereboullet, Faure-Beaulieu and Vaucher, Bergé and Schulmann, Roemer, and David Jewett have reported instances in favour of this theory. On the other hand, there are the negative results reported by Laignel-Lavastine and others. In my patient pituitary opotherapy was completely negative, and I am of the opinion that the glycosuria and polyuria in tumours of the hypophysis have no connection whatsoever with secretory insufficiency of this gland.

Date.	*Average Carbohydrate Diet.*	*Treatment with Hypophysis Extract.*	*Average Polyuria.*	*Average Glycosuria.*
	Grammes.		c.c.	Grammes.
Aug. 8 to Aug. 19	125	—	2,890	129
Aug. 19 to Sept. 8	155	Ext. hypophysis (total), 50 centigrammes	3,390	89
Sept. 8 to Sept. 20	206	—	3,558	50
Sept. 20 to Oct. 3	206	Ext. hypophysis (post. lobe), 5 centigrammes subcutaneously	3,584	23
Oct. 3 to Nov. 7	150	—	2,906	13
Nov. 7 to Nov. 18	92	Ext. hypophysis (total), 50 centigrammes	2,409	8
Nov. 18 to Nov. 22	92	—	3,725	6
Nov. 22 to Nov. 25	—	—	2,833	5
Nov. 25 to Nov. 28	92	—	3,275	—

3. Loeb's hypothesis seems to be nearer to the truth. He supposes that the tumour of the hypophysis exercises its action by the intermediary of a *glycogenous centre* situated in the brain near to the hypophysis, perhaps at the level of the tuber cinereum. We know, in fact, that the glycogenetic centre discovered by Claude Bernard on the floor of the fourth ventricle is not the only one; Schiff induced glycosuria by producing lesions of the optic stratum, cerebral peduncles, pons Varolii, and middle and lower cerebellar peduncles. A temporary glycosuria quite frequently occurs following cerebral hæmorrhage. Lépine has reported a case of diabetes from softening of the corpus striatum with a lesion of the internal capsule. Erdheim has referred to two cases of diabetes in cerebral growths which did not involve the hypophysis. The first was a cholesteatoma which, starting from the orbital aspect of the frontal lobe, extended in the direction of the mamillary tubercle; in the second case there was an adenocarcinoma starting at the base of the brain, penetrating the anterior horn of the lateral ventricle and the third ventricle. Eckhardt has induced polyuria and glycosuria in rabbits by producing lesions in the posterior lobe of the vermis.

It is consequently quite admissible that a tumour of the hypophysis may determine glycosuria by compression or irritation of the structures in proximity to the base of the brain. It is in those cases where the destructive lesions have extended beyond the hypophysis that Camus and Roussy most usually succeeded in inducing glycosuria in their experiments on dogs. The disappearance of glycosuria following a retrogression of a tumour of the hypophysis, the variations of the glycosuria during the affection in man, are also in favour of the hypothesis that glycosuria is produced by excitation of a glycogenetic centre in proximity to the hypophysis.

In this conception diabetes mellitus, quite as well as diabetes insipidus, when induced by a tumour of the pituitary body, does not merit the name of pituitary diabetes, but represents a true nervous type of diabetes.

To sum up, it may be said that a study of the association of diabetes and acromegalia shows that a nervous type of diabetes exists in which the glycoregulator disturbance of variable intensity behaves in the same way as in pancreatic or hepatic diabetes—a fact that gives a distinct individuality to the diabetic syndrome. It would certainly seem as if glycoregulation depends upon a complex physiological apparatus in which the liver, pancreas, nervous system, and vascular glands participate, and that a lesion of any portion of this apparatus is sufficient to induce diabetes.

CHAPTER XX

DIABETES AND EXOPHTHALMIC GOITRE (THYROID DIABETES)*

The coincidence of diabetes and Basedow's disease, already referred to in 1867 by Dumontpallier, has since been noted by numerous writers. Gastaud, in his thesis inspired by Sainton in 1913, reports fifty cases. For my part, I have had at least five cases, while during the lapse of time that these came under observation I only met with a single case of diabetes associated with myxœdema. Although not frequent, this coincidence is not simply fortuitous; certain cases in which Basedowian attacks are seen to evolve simultaneously with diabetes lead to the impression that a true morbid association exists between the two affections.

The physiopathological relations admitted to exist between the diabetes and the exophthalmic goitre have given rise to numerous theories. It has been supposed that the thyroid gland, along with the liver, pancreas, and nervous system, plays a part in the mechanism of glycoregulation. And what is more, A. Lorand has gone so far as to pretend that every case of diabetes depends upon an abnormal functioning of the thyroid gland. This is going too far; neither the physiological nor the pathological data we possess allow such an opinion to be upheld. We can remain within the limits of reason by merely bringing forward the subject of thyroid diabetes, and attempting to characterize this form of diabetes from the clinical and physio-pathological view-points. This I shall attempt to do, relying upon my case histories and comparing them with those already published.

Case I.—Mrs. Chiffl, æt. 42 years, daughter of a diabetic father, has been herself a diabetic at least since the age of 27 years. Her glycosuria was discovered at the time a carbuncle developed on the neck; since this time the diabetes has remained moderate, because the

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* *Annales de Médecine*, 1920.

patient has never offered symptoms of hyperglycemia, while the glycosuria has hardly ever exceeded 20 grammes.

She also has Basedow's disease. At the age of 22 years a goitre appeared, and progressively increased in size; the tumour did not pulsate, and no vascular souffle could be heard. It would appear that this goitre assumed the Basedowian type at about the age of 40 years, at which time palpitations, exophthalmia, and a slight tremor of the upper limbs appeared. The patient entered hospital for a pericarditis with effusion, from which she recovered, although with a cardiac symphysis.

In my second case the Basedow's disease had a sudden onset and serious evolution; the glycoregulator disturbance remained moderate, only revealing itself in a mild, temporary glycosuria.

Case II.—Rue only gives in her antecedents some œdema occurring four and two years previously, the first time in the left foot, the second time in the right arm, which lasted three or four weeks and then subsided spontaneously.

In April, 1909, there was a sudden attack of chills, vomiting, diarrhœa, and sweating—symptoms which appeared to have been the consequence of an intoxication from spoiled meat. Progressively all the elements of Basedow's disease developed: disturbances of the sight, diplopia, palpitations, breathlessness, tachycardia, tremor of the upper limbs, and finally exophthalmia.

The diarrhœa persisted freely. Emaciation was excessive and rapid, so much so that in four months the patient had lost 12 kilogrammes (24 pounds).

In December, 1909, at the time she entered hospital, Rue presented a very characteristic exophthalmic goitre, frequent diarrhœa (ten to twelve fluid stools a day), and a mild glycosuria (4 grammes), without any other symptom of hyperglycemia. Examination of the fæces revealed the presence of bile, a deficient digestion and absorption of proteins and fats, and an incomplete digestion of fruit-stones. The glycosuria soon disappeared. The emaciation progressed, and was accompanied by nitrogenous waste.

My third case was a true diabetes of severe grade, with denutrition and acidosis, evolving in successive outbursts up to the time of death. The onset of the diabetes appears to have been sudden, following an emotion, and to have coincided with the goitre. In the symptomatology the diabetes constantly outdid the goitre, which was hardly Basedowian in type.

Case III.—Mrs. Lel developed a moderate goitre and diabetes at 45. She had been obese, and gave the history of an attack of jaundice

at the age of 20. The patient attributed the goitre and diabetes to a violent emotion due to the explosion of a locomotive. She was not injured in any way, but a persistent occipital headache developed and she passed much urine. When the urine was examined a few months later it was found to contain sugar.

It is impossible to say whether or not the emotion caused the diabetes. However that may be, this diabetes was badly treated and only by homeopathy.

At the age of 49 the patient consulted me because she was becoming very emaciated. The gums were very swollen and the teeth loose; the inside of the mouth was ulcerated; she complained of rheumatoid pains; the aorta was enlarged, with a systolic souffle; the patellar reflexes were normal. She voided 1,600 c.c. of urine containing 54 grammes of glucose, and there was a slight diaceturia as well.

Diet did not have any marked influence on the glycosuria, which at first increased and then fell to 40 grammes. She ate insufficiently and continued to emaciate; in three months she lost 3 kilogrammes (6 pounds).

During the following years her condition remained sensibly the same; she also had an attack of appendicitis and a pulmonary congestion.

At the age of 55 she was still more emaciated and the diabetes had become aggravated. In February, 1914, she passed 2,600 c.c. of urine, containing 13·7 grammes of glucose, with a diet containing only about 60 grammes of carbohydrates. There was also a slight diaceturia. A proper diet caused the diaceturia to cease and the body weight slightly increased, but the glycosuria remained abundant. With a strict diet it remained at 142 grammes.

In June, 1914, the diabetes became aggravated; in spite of a rather severe diet the polyuria was 3 litres, the glycosuria 208 grammes, while the acetonuria persisted without diaceturia; thirst was intense, with fatigue and insomnia. The heart-beats were violent, those of the carotids were very apparent. The pulse was 90. The patient complained of flushes of heat, although the goitre had not increased; there was no tremor or exophthalmos. The exhibition of five iodomaisine pills daily produced a remarkable result, and without any change in the diet the glycosuria progressively fell from 208 to 155 grammes, 137 and 116 grammes, and in one month had reached 51 grammes, while at the same time the patient's general health improved.

In my fourth and most interesting patient, the diabetes and exophthalmic goitre were both perfectly characteristic. The case was a severe diabetes with nitrogenous denutrition and outbursts of acidosis; the goitre, which at first was simple, became Basedowian at the age of 54 years. What was remarkable was the simultaneous combined evolution of both diseases. A simple goitre developed, then a diabetes became

installed; next the goitre became exophthalmic, while at the same time the diabetes became worse, and afterwards, each time that a Basedowian attack took place with palpitations and tachycardia, there was at the same time a marked attack of glycosuria with hyperazoturia, although this could not be attributed to any change of diet. As in Case III., treatment by diet appeared to have less influence than usual on the glycosuria.

Case IV.—Mrs. Fert had jaundice in her childhood. At the age of 20 years, following a pregnancy, a goitre developed. There were two later pregnancies without any accidents.

At the age of 50 years a glycosuria of 5 grammes was discovered, which spontaneously disappeared, and then reappeared, becoming permanent.

At the age of 54 the patient had violent paroxysms of palpitation, accompanied by a polyuria of 4 litres and a glycosuria of 320 grammes. After a few days, and without any diet, the polyuria fell to 2 litres and the sugar to 166 grammes.

During the summer of 1913 she was under the care of Dr. Porges. At this time there was a glycosuria of 42 grammes and a ureic excretion of 19 grammes. Then an attack of poroxystical tachycardia occurred, with 140 beats, followed by a glycosuria of 102 grammes, with a urea excretion of 48 grammes a day.

In November, 1913, I detected a small goitre animated by pulsations; a moderate tachycardia (88 beats); arterial hypertension, 20 to 10 by a Pachon instrument. The patient complained of hot flushes; there was neither exophthalmos nor tremor. The patellar reflexes were normal. Liver hypertrophied and painless; digestion good, with paroxysms of hunger. The glycosuria was 60 grammes with a diet poor in carbohydrates. No acidosis reaction.

A mixed diet with 40 grammes of carbohydrates and a series of medical treatments were commenced.

November 19.—After treatment with valerian, glycosuria = 47 grammes.

November 29.—After treatment with iodomaisine, glycosuria = 29 grammes.

December 9.—After treatment with KBr and spartein, diarrhœa developed, with profound fatigue and an increase of the glycosuria to 102 grammes. The urine contained acetone and diacetic acid. The goitre was animated by strong pulsations, and the pulse reached 104 and 128.

December 12.—After treatment with valerian the glycosuria fell to 70 grammes.

December 26.—After treatment with hemato-ethyroidine (2 to 4 spoonfuls daily) the glycosuria fell to 60 grammes.

December 30.—After treatment with iodomaisine, glycosuria = 45 grammes.

January 21.—After treatment with hemato-ethyroidine, glycosuria = 81 grammes.

February 5.—After treatment with valerian, glycosuria = 54 grammes.

February 28.—After treatment with iodomaisine, glycosuria = 37 grammes.

March 28.—General condition a little better. In a general way the glycosuria had somewhat decreased. Essays with vegetable and oat-meal diet temporarily increased it (110 and 122 grammes). The urine gave a strong Gerhardt reaction; the same was true of Legal's reaction; perhaps an attack of diarrhœa which had just taken place was the cause. The tachycardia persisted at 110.

Between times two attacks of tachycardia with 150 beats occurred accompanied by a polyuria of 2 litres, a glycosuria reaching 100 grammes, and an excretion of urea of 44 grammes. These attacks, which occurred without any cause, lasted two to three days.

April 13.—After treatment with sodium salicylate the glycosuria was 30 grammes.

April 19.—After three days of slight temperature the glycosuria slowly reached 92 grammes.

May 1.—After treatment with iodomaisine the glycosuria was 25 grammes. The palpitations had diminished and the patient felt stronger. The acidosis had decreased and there were only traces of diaceturia.

May 22.—After treatment with quinine (25 centigrammes to 1 gramme) the glycosuria reached 39 grammes.

June 18.—After treatment with iodomaisine the glycosuria reached 48 grammes.

There have not been any attacks of palpitation for some time.

The fifth case is one of exophthalmic goitre with an acute evolution ending in death. The diabetes set in soon after the goitre; the glycoregulator disturbance remained moderate, but there was at the same time denutrition accompanied by severe acidosis.

Case V.—Female, æt. 20 years. Without any notable hereditary or personal antecedent, this girl was taken ill in January, 1912. She rapidly lost her appetite, to such an extent that three months after the onset of her illness she had lost 13 kilogrammes; she was seized by tremor of the fingers, palpitations, and profuse sweating. Her parents were startled by the exaggerated bulging of the eyes. At the end of March she consulted a physician, who found a goitre and made a diagnosis of Basedow's disease. At this time there was neither sugar nor albumin in the urine.

Eleven days later she was seized with intense thirst and polyuria, and glucose was found in the urine.

She entered hospital on May 10, 1912. Examination revealed a slight hypertrophy of the thyroid gland, strong pulsations of the carotids, a rather pronounced exophthalmia with brilliant eyes and von Graefe's sign, very marked tremor of both upper and lower limbs, an intense tachycardia (pulse 166, small and regular), violent heart-beats without any souffle, a continuous feeling of heat without any fever, night sweats, normal digestive functions, hypertrophied liver, insufficient menses, and weak patellar reflexes.

The patient was put upon a mixed diet which furnished her with 119 grammes of albumin and 88 grammes of carbohydrates per day. She voided 2,550 c.c. of urine, with 31 grammes of urea and 15·77 grammes total nitrogen. The azoturic coefficient was 86 per 100; there were 49 grammes of glucose, and both Gerhardt's and Legal's reactions were strong. The fæcal nitrogenous excretion was 2·33 grammes, which makes the coefficient of nitrogenous intestinal absorption 87·8 per 100. The nitrogen balance was positive.

In spite of treatment the patient's condition became rapidly aggravated; she complained of headache and pain at the base of the thorax. She vomited almost all food taken. The reactions of acidosis persisted with the same intensity. The tachycardia remained at 130.

The patient left hospital on May 28, and died a few days later in complete consciousness, probably from asystolia.

These case histories show that in the association of diabetes and Basedow's disease the diabetes may assume any form. Sometimes it is a serious diabetes with denutrition and acidosis, as in Cases III. and V. and those reported by Lépine, Murray, Drury, and others. In several cases death even took place in diabetic coma (Pitres, Murray, Hausmann, Budd).

Occasionally the acidosis is intermittent, and only manifests itself by outbursts, as in the case recorded by Lannois. It is, for that matter, possible that the acidosis at first occurs intermittently, and later on becomes permanent, as is often observed in diabetes with denutrition whose evolution is progressive.

In the somewhat less serious forms the absence of acidosis is expressly noted. Such was the case in the observation recorded by Grawitz. On the other hand, an early intense acidosis, with a relatively less considerable glycoregulator disturbance, may be observed. Such was Case V., in which there was still tolerance for carbohydrates (glycosuria of 49 grammes for a daily intake of 88 grammes of carbohydrates), and which nevertheless presented an abundant diaceturia.

In descending the scale of gravity we come to moderate

diabetes in which the glycosuria is slight, transitory, and intermittent, and is the only indication of hyperglycemia. Such was the condition in the first two cases here reported, although in one of them the exophthalmic goitre appeared to be of extreme gravity. The same remarks apply to Ballet's case and the two observations reported by Gastaud. Out of a total of fifty-nine cases of Basedow's disease, Kocher met with spontaneous glycosuria in two.

Finally, the glycoregulator disturbance, still more moderate, may only be detected by the alimentary glycosuria test. A certain number of observers have obtained positive results by submitting Basedowians to this test, among them being Konrad Alt, Ludwig, and Kraus. Chvosteck provoked an alimentary glycosuria in five cases out of eight, and Strauss three times out of seventeen, but other writers have obtained it less frequently (Zulzer, Friedheim, Naunyn, M. Levy, Kocher). Diénot produced it in one out of sixteen and Parisot in one out of eight patients.

In its evolution, the diabetes of Basedowians offers some peculiar aspects. The glycosuria has seemed to me to be more resistant and more independent of diet than in ordinary diabetes. Thus, in Case III. a reduced diet did not do away with the glycosuria, as might have been expected, and merely decreased it. Glycosuria often appears and disappears without any known cause. Occasionally the outbursts of the diabetes are distinctly related to the outbursts arising in the evolution of exophthalmic goitre. At the same time that the goitre appears the glycosuria develops; if the goitre becomes Basedowian or if it becomes aggravated, the diabetes likewise becomes aggravated. The pathologic symbiosis could never be more evident than in my fourth case; upon several occasions we witnessed attacks of tachycardia with exaggeration of the pulsations in the goitre, diarrhœa, and profound fatigue lasting two to three days. These attacks were accompanied by a marked polyuria; an increase of the glycosuria, which went from 40 to 100 grammes; a high hyperazoturia, with the elimination of from 44 to 48 grammes of urea and an increase of the reaction of urinary acidosis. At the same time that the Basedowian paroxysm ceased the diabetic attack likewise disappeared.

Besides those instances in which the diabetes is combined with exophthalmic goitre, it is essential to refer to some very interesting remarks made by certain observers who have met with the development of diabetes and goitre in several members of the same family. Manby has published three examples of this morbid association. In the first a diabetic father engendered a diabetic son and a Basedowian daughter. In the second a female Basedowian had a diabetic sister and a father who lost two children from acute diabetes. Lastly, in the third there were three sisters, two of whom died of acute diabetes in childhood, while the third has an exophthalmic goitre. Lancereaux, Winter, Pribram, Schmey, Diénot, and Gastaud have each published similar cases which show the existence of a morbid connection between diabetes and exophthalmic goitre.

What also strikes one in the diabetes of Basedow's disease is the ease with which it becomes complicated by acidosis; only the very serious types complicated by acidosis are met with, or else they are the very mild types amounting only to a simple glycosuria without any other symptoms of hyperglycemia. This tendency to acidosis perhaps results from the disturbed nitrogenous metabolism which belongs to exophthalmic goitre. It is known that hyperthyroidization destroys the cellular albumins and provokes nitrogenous loss. There is here an exaggeration of the nitrogenous metabolism similar to that observed in the serious forms of diabetes, so that it is not astonishing that this exaggerated metabolism becomes complicated by a condition of affairs ending in acidosis.

The action of drugs also contributes to impart a peculiar physiognomy to Basedowian diabetes. In two of my cases I tried various medications. Hemato-ethyroidine had no effect; valerian and the bromides gave rise to only moderate action; quinine and sodium salicylate gave better results; but several times in Case IV. the iodine treatment with iodomaisine proved to be the most efficacious, because it not only decreased the palpitations and tachycardia, but lowered the glycosuria in notable proportions. In Case III. the action of iodine was still more remarkable, because in one month it progressively lowered the glycosuria from 208 to 71 grammes, and at the same time improved the general health of the patient. It would

consequently seem that in diabetes a treatment directed to the thyroid gland possesses real efficaciousness, while in ordinary diabetes the uselessness of all drug treatment is generally recognized.

When diabetes of exophthalmic goitre is studied from the clinical standpoint it is difficult not to suppose that it is due to a functional disturbance of the thyroid, and in this respect a certain number of clinical and experimental reasons incline us to believe that the thyroid gland plays a part in the metabolism of carbohydrates.

Many observers have noted glycosuria arising in subjects submitted to intensive thyroid opotherapy. Béclère has published the case of a patient with myxœdema who, after having ingested ninety-two sheep's thyroids in the space of eleven days, developed palpitations, paroxysms of suffocation, tremor, polyuria, and glycosuria. Notthaft, in a corpulent patient undergoing an intensive thyroid treatment, found that it produced the Basedowian syndrome with glycosuria; these accidents subsided when treatment was discontinued. Senator has also noted that glycosuria develops from thyroid opotherapy in exophthalmic goitre. Muller has seen a serious diabetes ending in coma and death develop in a patient undergoing thyroid opotherapy, while, in a myxœdematous subject, Ewald noted that thyroidine provoked the development of diabetes; the glycosuria improved when the drug was given up, but again appeared when treatment was resumed. It disappeared when opotherapy was definitely discontinued, but returned later, and this time was permanent. We here have a series of examples showing the diabetogenous action of hyperthyroidization.

To obtain such results, thyroid gland must be exhibited in very large doses. When this substance is taken in moderate amount glycosuria is exceptional, as is made evident from the cases reported by von Bruns, Stabel, and Leichtenstein. Bettmann has not seen spontaneous diabetes develop, but he did obtain an induced alimentary glycosuria in 50 per cent. of patients undergoing thyroid treatment, while this occurred with greater infrequency in cases treated by Strauss and Marwin.

Animal experimentation has given contradictory results.

Kulz, Medinger, Georgicowky, and Porges obtained tachycardia, excitement, polydipsia, polyphagia, and polyuria, and glycosuria several times, in animals fed with thyroid preparations.

Parhon found that in rabbits the hepatic glycogen decreased after absorption of thyroid glands, although no glycosuria developed, and is of the opinion that there is an excess of sugar utilization on account of the exaggeration of muscular activity resulting from the influence of the thyroid.

In a series of experiments in rabbits that I carried out with Dr. Vitry, some of the animals being normal, others ethyroid or hyperthyroid, I was unable to observe any notable difference in the manner of utilizing the glucose given intravenously; it even seemed that removal of the thyroid gland slightly decreased the combustion of glucose and aided glycosuria.

The results obtained by Blachstein, Claisse, Jordon, Branthomme, and Lépine in diabetics undergoing thyroid treatment are absolutely paradoxical, because these observers state that they produced a manifest amelioration in their patients. Inversely, Grawitz has seen the glycosuria increase in a diabetic from the exhibition of thyroid gland. For my part, I have tried thyroid treatment in some cases of diabetes without results.

From this long list of therapeutical and experimental essays no positive results can be reached. They are variable. Sometimes hyperthyroidization diminishes the capacity for sugar combustion, or, on the contrary, appears to increase it; it likewise exercises its action on sugar combustion at times in one way, at others another. Perhaps it is only upon the condition of producing a true intoxication or in particularly sensitive subjects that the thyroid gland provokes a glycoregulator disturbance comparable to that of diabetes. Some writers believe that thyroidine only reveals a latent diabetes. It is possible that the healthy thyroid gland does not take any part in the mechanism of glycoregulation, and that only a pathologically changed thyroid intervenes in the genesis of glycoregulator disturbances.

The mechanism of the action of the thyroid gland in the combustion of sugar is probably much more complex than we imagine; perhaps this mechanism has no direct action on the

tissues, but indirectly by the intermediary of the principal organs of glycoregulation—the liver, pancreas, nervous system, or even the kidneys. Eppinger, Falta, and Rudinger have admitted the intimate physiological relations existing between the thyroid, pancreas, and suprarenals, and they maintain that the thyroid and pancreas mutually inhibit themselves. Consequently, hyperthyroidization would be tantamount to the suppression of the internal pancreatic function. Whatever may be thought of this theory, which is open to many objections, it is probable that the action of the thyroid gland in glycoregulation is far from being a simple matter, so that an act in appearance identical like hyperthyroidization need not invariably produce the same reaction.

Although we are yet unable to define its physiopathological mechanism, it is nevertheless true that in Basedowian patients there exists a peculiar form of diabetes distinctly evolving at the same time as an exophthalmic goitre, so that we may logically look upon it as a thyroid diabetes.

CHAPTER XXI

THE FOOD RATION AND THE NITROGEN RATION IN DIABETES*

Not long ago the rule was to gorge diabetics. The regimens prescribed testified to the general belief that diabetics had need of much more food than other people.

Unquestionably Bouchardat, to whom one must always turn for all that concerns the diet in diabetes, never recommended overfeeding or gavage; he even showed the necessity for moderating the amount of meat and other nitrogenous foods taken, and to increase the intake of vegetables and fats. But as he never indicated the quantity of necessary foods, he left the field open to all kinds of excess.

On the contrary, Potain, although believing that patients do not need to eat all they wish for, preconized a fearful meat diet consisting of an average of 600 grammes of meat with from 60 to 300 grammes of fat. Jaccoud believed that polyphagia was necessary for maintaining the organic equilibrium of diabetics; Lecorché advised a very large nitrogen ration; while Demange summed up the classical opinion of twenty years ago when he wrote that it was essential to give all necessary food to diabetics from the fear that they might consume themselves.

Although not expressly advising overfeeding, Bouchard, Dreyfus-Brisac, Le Gendre, and Robin did not protest against its use, so that, in his work on food and diet published in 1904, Professor A. Gautier advised a diet comprising 273 grammes of albuminoids, 90 grammes of which should be butcher's meat, and 150 grammes of fish for a patient weighing 70 kilogrammes!

The dogma of overfeeding diabetics rested on the idea that their organic needs were much greater than in other subjects. As proof of this the excessive appetite and azoturia—that is to

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say, the excessive amount of nitrogen rejected in the urine—was brought forward. It was thought indispensable to compensate this nitrogenous disassimilation by a suitable diet, for otherwise the subject would slowly consume all his tissues.

All this was, of course, an erroneous interpretation of facts. It is not an exaggerated nitrogenous disassimilation that is the cause of an excessive nitrogenous excretion. If much urea is present in the urine of diabetics it is because they are frequently large eaters, either by nature or because they are ordered to overeat; but they have no more urea than is produced by their diet, they do not have a supplementary excretion, and they do not offer hyperazoturia. Besides, as I have shown with H. Labbé, the high amounts of urea given by some writers—110 grammes in one of Lecorché's cases—are often due to mistakes in dosage, because Regnard's ureometer or the hypobromite method are used for estimating the urea, and usually give too high figures in diabetics.

Naunyn and von Noorden have rightly protested against the notion of azoturia, which they do not think necessarily exists in diabetic subjects. With H. Labbé I have endeavoured to show by precise dosages that the majority of diabetics do not have a nitrogenous waste, and have no need for more albuminous food than the average person; only thin diabetics offer nitrogenous denutrition, and therefore require larger amounts of albumin. Hence we shall separately envisage these two categories of diabetics in the evaluation of the diet.

For some time past a reaction against gavage of diabetics has become manifest. Naunyn was one of the first to protest against an excess of albumin in the diet. He estimates the needs of diabetics at the same rate as in healthy subjects, and even cites a patient, followed for several months by Weintraud, who increased in weight with a diet which gave an average of 25 calories per kilogramme of body weight, instead of the 30 to 35 calories necessary in normal subjects. Von Mering, Minkowski, and Ebstein have insisted on the necessity of reducing the proteins, and this is also von Noorden's opinion, and he has observed diabetics maintain their nitrogenous equilibrium and take on weight and strength with a diet only containing 50 to 60 grammes of vegetable albumin.

Allen and Joslin are convinced of the necessity of reducing

the diet and the advantages of fast cures. Benedict and Joslin have carried out researches on the alimentary needs of diabetics; they admit that these needs are very variable, that they are greater in hyperglycemia and acidosis, and decrease after a cure of fasting.

Maurel considers that diabetes is often the result of overfeeding, and advises treating the morbid process by a reduced milk diet.

Upon several occasions Linossier has pointed out the danger of an excess of meat in the regimen of diabetics; he is of the opinion that meat may aggravate the disease, and may even increase the glycosuria. In a reply to a paper by Linossier and Lemoine on this subject, we made a distinction between the effects of a meat diet in the two types of diabetes: in diabetes with denutrition meat increases both the glycosuria and acidosis; but in diabetes without denutrition—providing that the diet is kept within reasonable bounds—the intake of meat has no very great influence on the glycosuria, whose percentage varies with the quantity of carbohydrates in the diet.

Guelpa's inanition cure will be discussed elsewhere, while many prescribe Cantani's old practice of a "vegetable day," which is a day of relative fast in the midst of an ordinary diet.

In my book on "Les Régimes Alimentaires," I have laid stress upon the inadvisability of overfeeding in diabetes, and the necessity of not only prescribing the quality, but also the quantity of food that should be taken daily.

The Measure of Alimentary Needs.

Using the numerous case records from my practice, I have attempted to measure with all due precision the alimentary needs of diabetic subjects.

Strauss (Thesis, Paris, 1911) has calculated the food rations that maintain the equilibrium of the body weight and the nitrogenous balance of diabetics.

1. **Diabetes without Denutrition.**—The following case may serve as an example: A male, æt. 24 years, had been a diabetic for two years. Height, 1 metre 73 centimetres; weight, 75 kilogrammes. He could tolerate at least 60 grammes of

carbohydrates without developing glycosuria. He was placed upon a mixed diet comprising 115 grammes of albuminoids, 152 grammes of fat, and 60 grammes of carbohydrates, this being the equivalent of 2,020 calories. During the two days' test the body weight remained unchanged, and he made an appreciable gain in nitrogen—3·35 grammes a day. If the body weight be considered, it will be seen that this diet gave 27 calories and 1·53 of albumin per kilogramme of body weight.

DIABETES WITHOUT DENUTRITION

Name and Age.	*Weight.*	*Height.*	*Equilibrium of Weight.*	*Nitrogenous Equilibrium.*	*Ingested Albumin.*	*Ingested Calories.*	*Albumin per Kilogramme of Weight.*		*Calories per Kilogramme of Weight.*	
							Gross.	*Ideal.*	*Gross.*	*Ideal.*
M. D., 66 years	74·0	1·41	=	= +	10·46	1,475	1·41	2·07	19·9	29·5
G., 34 ,,	74·0	1·56	-	= -	80·0	1,360	1·08	1·33	18·3	22·6
Mal., 24 ,,	80·0	1·73	=	= +	106·0	2,010	1·32	1·45	25·0	27·0
	75·0		-	+	115·0	2,020	1·53		27·0	
Henr., 11 ,,	31·0		= +	= -	129·0	2,630	4·0		73·0	
Tor., 16 ,,	52·0		=	=	126·0	1,720	2·42		33·0	
B., 41 years;	54·0	1·73	=	+	96·5	1,790	1·7	1·3	32·0	23·0
Pulm. T.B.	58·0		=	. . -	118·0	2,910	2·2	1·6	42·0	34·0
M. B., 15 years	44·0		+	+	131·0	2,100	2·96		47·46	
R., 45 ,,	85·0		=		152–175	2,419-3,139	1·92		32·6	
P., 62 ,,	50·0		=		91·0	2,019	1·83		40·3	
			=		88·8	1,757	1·75		34·7	
Or., 59 ,,	63·0		= -		72·0	1,162	1·15		18·4	
			-		63·0	1,055	1·0		16·7	
N., 70 ,,			=		103·0	1,785	1·49		23·48	
					81·4	1,443	1·07		18·98	
L., 68 ,,	70·0		=		75·0	1,415	1·07		20·0	
G., 53 ,,	55·0		= +		79·0	1,360	1·43		24·7	
C., 54 ,,	81·5		=		149·0	2,465	1·81		30·0	
B., 50 ,,	51·0	1·67	=		82·0	1,395	1·65	1·29	27·9	21·0
			+		108·0	1,821	2·16	1·6	36·4	27·0
D., 50 ,,	64·0		-			1,514				
			+		118·0	2,127				
			+			2,400	1·84	1·7	37·0	

This regimen of 27 calories per kilogramme of weight for an adult male leading a moderately active life with a normal corpulence was hardly adequate. In reality, some little time before, this young man, in the same conditions of life and with an almost equivalent diet, lost weight to the extent of 80 and then 75 kilogrammes.

The results obtained in sixteen cases of diabetes without denutrition permit one to establish an average of the needs required by energy and the nitrogenous requirements of these patients. Certain cases merit to be considered by themselves, because they were instances of diabetes complicated by tuberculosis, or else were diabetes arising in adolescents in the period of growth whose needs were unquestionably much greater.

From the reading of these cases it becomes evident that the equilibrium of the body weight was maintained with diets giving from 20 to 40 calories, an average of 28·2 calories per kilogramme of body weight. On the other hand, diets containing 16 to 24 calories, an average of 19·7 calories per kilogramme of body weight, resulted in emaciation. Diets containing 25 to 47 calories, an average of 36·2 calories, produced an increase of body weight. If, instead of considering the real weight, the ideal body weight be examined—that is to say, the weight that the subject should have given his height and a normal corpulence—we come to the following averages:

Equilibrium of body weight,	diet containing			26·8	cal.	per kilogramme.
Emaciation	,,	,,	,,	22·6	,,	,,
Increase	,,	,,	,,	30·0	,,	,,

A diet of 28 calories per kilogramme of actual body weight, or of 26·8 calories per kilogramme of ideal body weight, is lower than the estimates regarded by physiologists as requisite for healthy individuals living in the same conditions of life as my patients. According to Rubner and Atwater, an average of 35 calories is necessary, while Chittendon maintains that about 30 calories per kilogramme of body weight are sufficient. At all events, these figures are higher than those I have found in my diabetic cases. It must also be recalled that I did not try to ascertain the minimum diet necessary for maintaining the weight equilibrium in my diabetic patients, and that undoubtedly the figure expressing the minimum need of energy may be still lower. Finally, it is very exceptional that patients fatten on a diet of 25 calories per kilogramme, as did occur in one of the cases.

One is therefore entitled to conclude that, contrary to what the older writers supposed, *the needs of diabetics without de-*

nutrition are in no way superior to those of healthy subjects, and that in reality they are lower.

There is here something comparable to what one observes in certain obese subjects, and this is not to be wondered at, since diabetics belonging to this category are often excessively corpulent. I would nevertheless point out that this reduction of the alimentary needs is not only met with in obese diabetics, but also in diabetics having a normal corpulency.

Some observers have also referred to analogous facts. Naunyn thought that a diabetic could fatten with a diet of 35 calories per kilogramme. Weintraud noted that one of his patients fattened on a diet of 25 calories, while Linossier and Lemoine have mentioned the case of a patient who did well with 20 calories per kilogramme. De Renzi states that he has seen diabetics fatten on a diet furnishing only 10 to 12 calories per kilogramme, but perhaps this statement may be a little exaggerated. Borchart and Finkelstein submitted diabetics and healthy subjects to a like restricted diet, and found that only the diabetics retained their weight equilibrium.

The minimum need of albumin is very difficult to estimate in diabetics; in point of fact, one cannot greatly reduce the nitrogen in the diet without rendering the total food ration insufficient in those patients who do not utilize carbohydrates. However, without indicating the minimum limit of the nitrogenous need, my observation shows that albumin overfeeding is not indispensable for maintaining the nitrogen equilibrium. In four of my cases this equilibrium was preserved with diets containing 1·32 to 2·96 grammes of albumin, an average of 1·84 grammes per kilogramme of body weight.

In calculating the amount of albumin sufficient to preserve the nitrogenous equilibrium in ratio to the ideal weight, it will be found that it represents an average of 1·60 grammes per kilogramme.

This certainly shows that the excessive overfeeding with meat that was formerly imposed upon diabetics is abolutely unnecessary.

2. **Diabetes with Denutrition.**—It is very much more difficult to estimate the alimentary needs of diabetics belonging to this class. It can even be said the problem is insoluble, since nitrogenous waste properly belongs to these patients, no

matter what may be the diet upon which they are placed. On the other hand, the variations in the hydration of the tissues are so considerable in them that one could not interpret the oscillations of the body weight as fattening or emaciation; the œdema present at an advanced phase of the disease usually conceals the actual loss of weight.

Thus, one of my patients, with sclerous pancreatitis and pancreatic lithiasis and diabetes with denutrition, who was under my care for many months, presented variations in weight to the extent of several kilogrammes, which were in no way related to the diet. With a regimen of more than 4,000 calories—95 calories per kilogramme of body weight—this patient, a female, lost weight, while a few months later with a diet rendering 2,200 calories her weight increased; later, at a time when cachexia was making rapid headway, her weight increased several kilogrammes with a diet rendering 2,700 calories.

This patient presented variable nitrogenous losses, and it would certainly seem that the quantity of the albumin in the diet exercised an influence over the nitrogenous equilibrium; a diet very rich in albumin diminished or prevented nitrogenous waste, as is shown by the three following experiments:

Albumin Ingested.	*Excretion of Nitrogen.*		*Nitrogenous Balance.*
	Urine.	*Fæces.*	
(1) 141 grammes (N 22·5 grammes)	16·05	9·8	− 3·35
(2) 170 ,, (N 27·2 ,,)	14·19	13·09	− 0·08
(3) 228 ,, (N 36·4 ,,)	15·3	21·0	+ 0·10

With 3·2 grammes of albumin per kilogramme of body weight the nitrogenous equilibrium was broken, but with 5·4 grammes of albumin per kilogramme of weight the N equilibrium was obtained.

Another diabetic, æt. 27 years, height 1 metre 71 centimetres, weight 56 kilogrammes, was given a mixed diet corresponding to 2,663 calories and comprising 139 grammes of albumin. The patient put on a little flesh.

Now this diet represented:

Per kilogramme of body weight	..	2·4 grammes albumin	and	46 cal.
,, ,, ideal ,,	..	1·9 ,,	,,	37 ,,

A woman, æt. 20 years, with diabetes and acidosis, weighing 42 kilogrammes, was put on a mixed diet which furnished 131 grammes of albumin and 2,326 calories, hence representing 3·3 grammes of albumin and 55 calories per kilogramme of weight. The daily N waste was constant; however, it was influenced by the amount of albumin in the diet, as the following two experiments show:

Albumin Ingested.	*Excretion of Nitrogen.*		*Nitrogenous Balance.*
	Urine.	*Fæces.*	
(1) 184 grammes (N 29·4 grammes)	28·59	4·68	− 3·7
(2) 284 ,, (N 45·4 ,,)	43·72	2·27	− 0·9

The first diet represents 4·1 grammes of albumin and the second 6·5 grammes of albumin per kilogramme of body weight.

In my patients the weight equilibrium was maintained by very large food rations; this does not imply that such large rations are indispensable, because I did not attempt to estimate the minimum ration capable of preventing emaciation.

On the other hand, the influence of large amounts of albumin on the maintenance of the nitrogenous equilibrium is very evident; the greater the amount of N in the ration, the less was the nitrogenous waste. From this view-point it is consequently advantageous to give a diet rich in albumin to these patients.

Conclusions.—From what has been said one may deduce a certain number of practical consequences.

We have seen, contrary to what was formerly thought, that *diabetics without denutrition* have relatively smaller organic needs than those of healthy subjects. Overfeeding is useless, not to say dangerous. These patients must not be ordered excessive diets, and since they are oftentimes large eaters

naturally, a reduced diet should in the first place be ordered. To precisely state my ideas, I would say that a diet representing an energy value of from 28 to 30 calories per kilogramme of body weight, deduction being made of the calories lost by combustion of the carbohydrates, is the one which appears to me the most suitable in the majority of cases.

If the patient emaciates on this diet, I see no reason to change it. It is a mistake to suppose that a diabetic should not lose weight, this error being based upon an inexact assimilation made between diabetes with denutrition—usually a serious affection—and diabetes with corpulency, which is generally a benign process. When diabetes is accompanied by obesity, it is advantageous to order a reduced diet and simultaneously to treat both affections.

The organic needs of N are not very great; hyperazoturia is absent in diabetes without denutrition. For this reason the excessive meat regimens, such as were advised by Cantani and others, should be absolutely proscribed. They can only be detrimental from their injurious action on the liver.

However, the albumin in the diet cannot be reduced to an extreme degree; these patients are deprived of the carbohydrates, which for them represent the most prejudicial article of diet; they cannot be fed exclusively on fats; hence a sufficient quantity of albumin should be allowed. From 1·5 to 2·5 grammes of albumin per kilogramme of body weight seems to me adequate.

Diabetics with denutrition have greater organic needs than those without denutrition. They are thin, and their emaciation may even be excessive. Their tissues and muscles are progressively destroyed, while their nitrogenous waste is increasing.

Therefore they should be more abundantly fed in order to arrest their general denutrition as far as is possible, and, above all, to furnish them with a rather large amount of albumin, because it is only with 5 to 6 grammes per kilogramme of body weight that one will be able to compensate, or at least limit, the nitrogenous waste.

In one way a highly nitrogenous diet is consequently indicated in these cases. Unfortunately meat diets have, in the circumstances, two disadvantages: (1) They increase the

hyperglycemia, because these patients do not utilize the glucose derived from the transformation of the albuminoids in the diet; (2) they lead to acid intoxication and diabetic coma. Hence it is sometimes better practice to allow denutrition and emaciation to continue rather than to prevent them by a meat diet.

Nevertheless, since the albumins of milk and vegetables do not expose the subject to acid intoxication to the same extent as those of meat, the former may be introduced into the diet to as high a degree as is possible in diabetes with denutrition. Milk, which represents a food relatively rich in albumin, often gives good results in these cases, while a vegetable diet has seemed to me to act still more favourably. Finally, it is good practice to use certain pure albumins derived from the vegetable kingdom in order to increase the nitrogen in the vegetable diet; by so doing one combines the two principal dietetic indications —namely, to prevent nitrogenous denutrition as well as acid intoxication. More research work in this direction is needed, and more practical applications are still forthcoming.

CHAPTER XXII

THE USE OF POTATOES IN THE DIET OF DIABETICS

Par excellence a starchy food, potatoes have been strictly proscribed in the diet of diabetics promulgated by Bouchardat and Cantani. Still more recently Dreyfus-Brisac, Arnozan, Ebstein, Munk, and Ewald have interdicted their use.

However, as far back as 1886 Coignard showed that this tuber presented many and considerable advantages when a reduction of the carbohydrates in a diet was desired on account of its relatively low tenor of starch.

In 1902, Mossé attempted to establish the superiority of a potato diet over a bread diet in diabetics by publishing some very suggestive cases. He showed that, in equal weight, the carbohydrates of the potato are better supported than those contained in bread, and give rise to a less abundant glycosuria; hence he concluded that the "parmentière cure" was a truly curative treatment.

Before accepting Mossé's conclusions it is advisable to examine his case reports in detail, because nothing is more difficult than to judge the effect of treatments and diets in diabetic subjects.

Mossé's first case was a female, æt. 55 years, who was successively given a bread diet and a potato regimen. During the bread diet the glycosuria reached an average of 115 grammes daily; during the potato diet the glycosuria progressively fell to 35 grammes, and reached a daily average of 67 grammes. A bread diet was then again given, and the glycosuria increased slightly and progressively, reaching an average of 62 grammes per day. Finally, a second potato diet was given, the glycosuria remaining practically stationary with an average of 53 grammes in twenty-four hours.

From this it would appear that the potato diet had been very favourable, but if the case be closely examined it will be seen that the results obtained are in no way due to the sub-

stitution of potatoes for bread, and are simply caused by a variation in the quantity of the carbohydrates. The hospital diet with 400 grammes of bread furnishes about 278 grammes of carbohydrates, while the same diet with from 700 to 900 grammes of potato only furnishes 226 grammes of carbohydrates; otherwise, 52 grammes less. The apparent tolerance of the patient for carbohydrates—that is to say, the difference between the total amount of carbohydrates ingested and the total amount of the glycosuria—was not higher during the potato diet than during the bread regimen; it was:

163	grammes	during the	first bread diet.
159	,,	,,	,, potato ,,
216	,,	,,	second bread diet.
173	,,	,,	,, potato ,,

Therefore, the potatoes were not tolerated any better than the bread, and although the glycosuria progressively fell during the first potato diet, it was because the carbohydrate intake had been quite markedly reduced.

Mossé's fourth case is still more characteristic. A male, æt. 54 years, was on an ordinary diet with 500 grammes of bread—that is to say, he was ingesting about 330 grammes of carbohydrates—and excreted from 170 to 250 grammes of glucose in twenty-four hours. When the bread was replaced by 1,500 grammes of potato—this representing a daily intake of 370 grammes of carbohydrates—the glycosuria fell, varying between 110 and 40 grammes. Therefore, the tolerance was 120 grammes with the bread diet and about 300 grammes with the potato regimen. Otherwise put, the patient supported the potatoes far better than the bread.

Hence it results from Mossé's cases that although the advantages of the "parmentière cure" are not constant, at least the potatoes were invariably well supported by diabetics, and in some cases they were better tolerated than bread.

Mossé's writings resulted in numerous other researches. Friedenwald and Ruhrah experimented with partial substitution of potatoes for bread in the diet of diabetics, and came to the conclusion that potatoes are, with an equal weight of starch, better tolerated than bread.

Nearly all observers have recognized the advantages of

potatoes in diabetic subjects, but they generally conclude that the results are due to the low tenor of carbohydrates in the potato, which permits reducing the carbohydrate diet, and not to a specific action of the tuber itself, as Mossé maintained.

Thus, von Noorden replaces bread by an equivalent quantity of potatoes, taking into consideration the different proportion of carbohydrates contained in the two foods, 100 grammes of bread furnishing about the same amount of starch as 300 grammes of potato; but he believes that the latter are no better tolerated than bread, and does not recommend an exclusive " parmentière " diet.

In order to settle this controversial question of potato diet, I undertook some feeding experiments in diabetic subjects, at the same time attempting to eliminate all possible cause of error.

Experiment I.—Female diabetic, who at the beginning of the treatment presented a glycosuria of 147 grammes, was placed upon a restricted diet containing between 121 and 135 grammes of carbohydrates.

Diets of bread, milk, peas, and potatoes were successively essayed for at least one week each. With the bread diet, as well as that of milk, the apparent tolerance was 52 grammes of carbohydrates; with a dry pea diet the tolerance was 79 grammes; finally, with potatoes it rose to 106 grammes. Hence the tuber was much better tolerated than the other carbohydrates by this patient.

During a second phase of observation, the apparent tolerance for potatoes varied between 74 and 54 grammes, while the tolerance for macaroni was 61 grammes, for oatmeal 58 grammes, for rice 47 grammes, while for dried vegetables it was only 41 grammes.

Upon different occasions when I attempted to put this patient back on bread without changing the amount of carbohydrates ingested, the glycosuria, which was tending to disappear, returned.

Experiment II.—Female diabetic, having an abundant glycosuria, was placed successively upon a bread, potato, and oat-flour-diet, each diet comprising 2 litres of milk.

During the four days of bread diet the patient ingested a daily average of 202 grammes of carbohydrates, and excreted an average of 147 grammes of sugar; therefore, her average tolerance was 202 – 147 = 55 grammes.

During the five days of potato regimen she ingested daily 217 grammes of carbohydrates, and excreted 135 grammes of sugar; hence a tolerance of 82 grammes.

During the five days of oatmeal diet the daily intake of carbo-

hydrates was 208 grammes, and 140 grammes of sugar were excreted; therefore a tolerance of 68 grammes. In other words, in this diabetic:

100	grammes	of potato starch	gave a	glycosuria	of	62	grammes.
100	,,	oat-flour	,,	,,	,,	67	,,
100	,,	bread	,,	,,	,,	72	,,

Hence, one may suppose that the potatoes were better tolerated than the oatmeal, and especially the bread.

EXPERIMENT III.—A male diabetic supported potatoes better than milk or bread, but nevertheless less well than a pea diet. From an observation of several weeks, during which he was submitted to a bread, milk, potato, and pea diet, it resulted that his average tolerance was:

For peas ..	..	..	128 grammes of carbohydrates.
For potatoes	..	..	79 ,, ,,
For milk ..	..	..	77·7 ,, ,,

By comparing the excretion of sugar with the intake of various carbohydrates, I was able to establish that, when ingested by this patient—

100	grammes	of pea starch	resulted in a	glycosuria	of	25	grammes.
100	,,	potato ,,	,,	,,	,,	41	,,
100	,,	milk sugar	,,	,,	,,	42	,,
100	,,	bread starch	,,	,,	,,	47	,,

It is needless to give other cases; I have chosen the most typical and which better escape criticism. In point of fact, it is not enough to show that the substitution of potatoes for bread in the diet reduces the glycosuria in order to prove the superiority of potatoes over bread; it is also necessary that the experiment should be carried out at the time when the patient is in glycemic equilibrium. If the tests are undertaken at a time when the patient, on a reduced diet, is eliminating the excess of sugar previously accumulated and is slowly returning to a normal glycemia, the results obtained would be open to criticism.

In 1911 Rathery carried out further experiments on diet in diabetics, and came to similar conclusions. He does not believe that the "parmentière" cure is in any way specific; the good results obtained in certain cases of diabetes are to be explained by the unconscious reduction of the carbohydrate diet that ensues.

Various theories have been put forward to explain the effects of the potato cure in diabetes. Mossé, in the first

place, endeavoured to show that they were not due to a defective absorption of potato starch by the intestine; he noted that in the same patient the amount of carbohydrates escaping the digestive juices and passing directly into the fæces is greater during the bread diet period—1·22 grammes on an average—than during the period of potato diet—0·46 gramme.

According to Mossé, potatoes exercise a curative action on diabetes. From their high content of organic salts, principally those of potassium—1 kilogramme of potatoes can by organic combustion furnish about 5 grammes of potassium carbonate—potatoes alkalize the liquids of the organism and awaken glycolytic activity; hence a "parmentière" cure is equivalent to an alkaline treatment.

I do not feel that this interpretation is acceptable, because potatoes do not in reality increase the tolerance of the patient for other carbohydrate substances. They are better tolerated, which is due to the nature of their starch or of the sugar derived from it, although at present no satisfactory explanation for this tolerance can be offered.

And still more, it is dangerous to accord a specific action on diabetes from potatoes. By regarding this tuber as a useful food, one has been led to feed diabetics as much as possible on it, and the result has been a therapeutical fiasco. Each day we meet with instances of the disadvantages of this conception. I once cited the case of a woman with diabetes complicated by an insupportable vulvar erythema who was referred to me by her physician. The patient supposed that she had done everything possible for her disease simply because she had given up bread and was gorging herself with potatoes; her glycosuria, which had been present for ten years and was supposed to be irreducible, reached from 150 to 200 grammes a day. A reduced carbohydrate diet was all that was necessary to cause the glycosuria to disappear in ten days, and the erythema as well.

Briefly put, the specific action of a potato regimen on diabetes does not exist. Cases like my own and those of Rathery show that the happy results obtained in certain instances are simply due to the reduction of carbohydrates resulting from the substitution of bread by potatoes.

It has also appeared to me that potato starch is relatively better utilized than other starches by most diabetics. Out of seven cases in which equal amounts of starch were given, that of potato was tolerated better than bread in six; compared with other carbohydrates, potatoes were much better tolerated than milk and sugars; even as compared with oatmeal and vegetables they are more advantageous. Rathery believes that this superiority only exists in exceptional cases, while Linossier admits it in a general way, and attributes it to the average total reduction of the diet resulting from the use of potatoes, a food very poor in albumin and fat.

From what has been said it may be concluded that potatoes are the best carbohydrate food, or rather the least obnoxious for diabetic subjects, and that they can render real service in the diet of these patients on the condition that they are properly used.

In order to know the amount of potatoes to be permitted in a given case of diabetes, the patient's tolerance in respect to carbohydrates must first of all be ascertained. When this has been done it is easy to calculate the quantity of potato to be ordered, knowing the proportion of carbohydrates contained in this tuber.

It should be recalled that an adult potato, that of the autumn or winter, contains from 20 to 22 per cent. of carbohydrates, while new potatoes, those of the spring, only contain 16 to 18 per cent.

Balland gives 20 per cent. of carbohydrates as an average for all potatoes; Atwater puts it at 18·4 per cent. These carbohydrate substances are almost entirely composed of starch, and, according to Atwater, there is only 0·4 per cent. of unassimilable cellulose; therefore, practically almost all of the carbohydrates of potatoes is absorbed by the intestine and contributes to the formation of glucose.

The potatoes for a day's diet should be weighed in the raw state. However, if this is not done, they can be weighed after they have been cooked, taking into consideration the concentration resulting from evaporation of their water caused by the cooking. Potatoes boiled in water hardly change in weight; they undergo the very slightest concentration, which brings the carbohydrates up to 20·9 per cent.

(Atwater). Steamed potatoes lose more water and contain 25 per cent. of carbohydrates, while baked potatoes present about a like concentration. Fried potatoes also concentrate, so that 300 grammes of raw potatoes will only give 120 grammes when fried, hence the latter will contain about 50 per cent. of carbohydrates. On the contrary, washed potatoes absorb water and about double their original weight, so that they only contain 10 per cent. of starch.

Potatoes make an excellent food for a reduced diet in diabetes. Since in equal weight they contain two and a half to three times less carbohydrates than bread, the latter may be replaced by a portion of potatoes weighing two and a half to three times more than the ration of bread allowed. Diabetics can often be persuaded to eat one potato at each meal, which, according to the size of the potato, equals from 100 to 200 grammes a day—that is to say, only 20 to 40 grammes of carbohydrates.

Potatoes satisfy the diabetic for two reasons. In the first place, the patient estimates his feeding by weight, and three large potatoes weighing 100 grammes each represent more to the eye than 100 grammes of bread. Secondly, diabetics usually are large bread eaters, and it is easier to get them to give up bread completely rather than to accept a reduced ration.

Potatoes are usually liked by everybody, and can be supported in large quantities for a long time; one can arrive at a daily ration of 1,000 to 1,500 grammes. Mossé even went as far as 3,000 grammes. Usually, however, when more than 1 kilogramme is given the patient will complain of fullness and will refuse to eat more than this weight, which is another advantage, because there is usually no good reason to reach the limit of tolerance for carbohydrates in diabetic subjects.

Potatoes have yet another advantage in that they permit the ingestion of large quantities of fat. Whether they are eaten in purée, mashed with butter, fried or stewed, they can incorporate a great amount of fat without becoming nauseous to the patient. Fried potatoes retain about 7 to 9 per cent. of fat; potato purée a much higher percentage. Now, fat is very useful in the diet of diabetics, because it is very nourishing, hence the potato, besides its own peculiar qualities, is a useful adjuvant to the diet.

Finally, from the culinary view-point potatoes have a great advantage over bread, in that they can be cooked in so many different ways, thus giving more variety to the diet.

For all these reasons this tuber should enter into the diet of diabetics, but when ordering it the physician must not imagine that he is prescribing a specific curative regimen; he must not allow an unlimited quantity or give it as a supplementary food without reducing other carbohydrates; he should merely permit a quantity of potatoes not exceeding the patient's tolerance for carbohydrates.

Whatever may be the advantages of potatoes over bread, the principle should never be lost sight of that in the prescription of a diet for diabetics the quantity of carbohydrates is far more important than the quality.

CHAPTER XXIII

THE TREATMENT OF DIABETES WITHOUT DENUTRITION

In diabetes without denutrition in which only the syndrome of hyperglycemia exists without complications, the treatment is quite simple. It essentially consists of a diet of reduced amounts of the carbohydrates.

Evolution of the Treatment.

This offers two successive phases: (1) The cure of the hyperglycemia; and (2) a diet of CH tolerance.

It is usually on account of an attack of hyperglycemia that treatment will be called for, the principle of which is to oblige the patient to eliminate the glucose accumulated in the tissues and fluids of the body by imposing a diet lower in carbohydrates than is his tolerance for them. As the degree of this tolerance is unknown, the carbohydrate diet should be as reduced as possible. Under the influence of this *reduction diet* the glycosuria progressively decreases, and then subsides altogether. This result is obtained more or less quickly, sometimes in a few days, sometimes only after the lapse of several weeks or even several months, the time depending upon the gravity of the case and the severity of the diet imposed. When the object has been accomplished it is well to continue the diet for several days, in order to more completely rid the organism of the accumulated glucose. Then the carbohydrate intake is increased in known amounts and the urine is watched. If after one week the glycosuria reappears, it means that the patient's tolerance for CH has been exceeded, so that the amount ingested must be reduced. If the glycosuria ceases, it is to be supposed that the tolerance is comprised between the amount of CH which produced the glycosuria and that causing it to subside.

Then the *tolerance diet* can be given—that is to say, a diet containing an amount of CH inferior to the patient's tolerance for them. Thanks to the stability of the tolerance, this diet may be continued for a very long time without causing the glycosuria to return.

Prescription of the Diet.

The diet is composed of four parts:

1. The fundamental carbohydrate food.
2. The accessory carbohydrates.
3. Albuminous, fatty, and alcoholic foods.
4. The proscriptions.

The Fundamental Carbohydrate Food is usually potato. The quantity should be *exactly prescribed in weight*, and never left to the fancy of the patient. In the tolerance diet one should calculate in such a way that the CH contained in the given quantity of potato is 10 to 20 grammes less than the patient's tolerance. This calculation is readily made by referring to the food tables worked out by Koenig, Gautier, Atwater, or Alquier. Thus, a diabetic with a tolerance for 100 grammes may be allowed 80 to 90 grammes of potato starch. Now, since the potato contains an average of 20 per cent. starch, he may be allowed 400 to 450 grammes of potato a day. The potatoes are weighed raw, and afterwards prepared according to the patient's taste.

This fundamental carbohydrate is used in conjunction with other dishes. It replaces bread, which I generally prohibit on account of the low utilization of its starch, as well as the difficulty of measuring the proper allowance.

The fundamental carbohydrate can be varied. When potatoes have been prescribed for one or several weeks it is advantageous to replace them by some similar foodstuff, as it breaks the monotony of the diet and pleases the patient. The new food will be given in an amount such that the authorized quantity of carbohydrate will remain the same. If one wishes to replace the 450 grammes of potato by an isoglucosic quantity of rice, which contains 79 per cent. of carbohydrates, one should order 112 grammes of rice *pro die*.

A table indicating the various foods capable of supplying 100 grammes of carbohydrates, like the one computed by Chavois, will make the changes in diet an easy matter.

100 grammes of carbohydrates are supplied in:

Potatoes	500 grammes.
Bread..	190 „
Rice	112 „
Dry peas, etc.	170 „

In the choice of the fundamental carbohydrate one is to be guided by the patient's taste, by the ease with which it can be cooked, and especially by the degree of tolerance that the particular patient possesses in respect to the particular foodstuff in question.

In point of fact, the various carbohydrates are not consumed in the same way by diabetic patients; some are better utilized than others, and in equal quantities set up a lesser degree of glycosuria. A large number of comparative experiments that I have carried out in diabetics have allowed me to establish a scale of tolerance for the ordinary carbohydrate foods. They are classified in the following order: Potatoes, oat-meal, macaroni, chestnuts, rice, kidney beans, lentils, peas, milk, bread, and sugars.

Practically the most advantageous are: (1) Potatoes; (2) dried vegetables, which contain a large proportion of albumin, and take the place of bread especially well; (3) rice; and (4) macaroni and similar articles. Milk does not offer the qualities that many have maintained; its lactose is poorly utilized. Therefore, there is no advantage in giving an exclusive milk diet, excepting when a diabetic presents serious digestive disturbances or chloride retention. A milk diet may even be dangerous for diabetics with a low tolerance, because it necessarily introduces a rather high proportion of sugar.

The Accessory Carbohydrates are necessary to supply the deficiency of bread in the diet, as well as to season meats.

They are supplied by green vegetables and salads; endives, sorrel, cabbage, cauliflower, Brussels sprouts, asparagus, celery, cucumbers, egg-plant, leeks, tomatoes, and sauerkraut only contain a small proportion of carbohydrates, and

can therefore be allowed to the extent of 400 grammes a day or even *ad libitum*.

They hardly furnish more than 12 grammes of carbohydrates a day; cooked green vegetables are even more advantageous than salads, because cooking in water extracts an appreciable quantity of their carbohydrates.

Albuminous, Fatty, and Alcoholic Foods are to be ordered in moderate amounts. They should complete the number of necessary calories for the maintenance of the individual, and supply the nitrogenous substances indispensable for the organism. It is good practice to exactly indicate the quantity to be taken, because some diabetics do not take enough food, and emaciate because they suffer from anorexia. This is more prone to occur in diabetics who have only a low tolerance, and consequently can only rely upon nitrogenous, fatty, or alcoholic foods for their nourishment.

More frequently, diabetics who are large eaters will tend to indulge excessively in these foods, which, of course, is bad for them. The danger of an excessive meat diet is due to the fact that the albumins acidify the organism, thus leading to the development of acidosis and coma; meat may also induce hepatic disturbances, and an aggravation of the diabetes may ensue. But meat does not act directly upon the hyperglycemia, because in diabetics without denutrition the glycosuria does not appear to take its origin in the transformation of either albumins or fats.

The Proscribed Foods include all carbohydrate foods with exception of those already mentioned. They are: Ordinary bread and the so-called diabetic breads, biscuits, pastry, dried vegetables, macaroni and similar products, rice, chestnuts, all kinds of flour, chocolate, sugar, sweets, preserves, fruits, milk, sweet wines, cider, beer, and syrups.

This diet, which in its indications resembles Bouchardat's classical diet, essentially differs from it by the way it is ordered. Its principle is to control not only the quality of the food, but the quantity as well.

Bouchardat's diet is a regimen of *proscriptions;* he formally prohibited a certain number of indispensable foods, and with reserve permitted certain substances less rich in carbohydrates,

but without specifying the amount to be taken, so that the patient exceeded the proper quantity when a given food was to his liking. My regimen is a regimen of *prescriptions ;* the patient is ordered a quantity of albuminous, fatty, and carbohydrate foods in relation to his tolerance and organic needs, and he is allowed nothing excepting the foods prescribed.

When no choice is left to the patient, a better result is obtained than when he is allowed to follow his own selections. Diabetics are frequently undisciplined persons, so that it is easier for them to blindly obey than for them to become reasonable. For that matter, one should invariably question the patient as to his likes and dislikes, so that he shall not be given a diet intolerable to him, while at the same time he is made to understand the necessity for rigorously submitting to the régime. My experience has proved to me that a good result may be obtained in the vast majority of cases.

Formula of the Diet.

Here is an example of a diet for a diabetic of medium height and weight, having a tolerance for 100 grammes of carbohydrates:

1. **Principal Carbohydrate.**—Potatoes, 400 grammes; these may be replaced by the following:

Rice	100 grammes.
Dried vegetables	136 „
Macaroni or similar products ..	112 „
Or bread	150 „

2. **Accessory Carbohydrates.**—Green vegetables or salad, 400 grammes. A choice can be made among the following: Endives, sorrel, spinach, cabbage, cauliflower, brussels sprouts, sauer-kraut, asparagus, celery, egg-plant, cucumber, leeks, tomatoes.

3. **Albuminous, Fatty, and Alcoholic Foods.**—Red meats, fowl, fish, or pork-butcher's meat, 300 grammes. Three eggs. Dry cheese (Gruyère, Dutch), 50 grammes; or fresh cheese (Petit-Suisse, Gervais), 100 grammes. Butter, 60 to 80 grammes. Fresh cream, 100 grammes. Wine, 250 to 500 c.c.

4. **Proscribed Foods.**—Ordinary and special breads, biscuits, pastry, dried vegetables, macaroni, rice, chestnuts, flours, chocolate, sugar, sweets, preserves, fruit, milk, sweet wines, cider, beer, syrups.

Special Cures.

Various methods of treatment have been proposed, such as Maurel's *milk cure*, Mossé's *potato cure*, etc. These cures favourably act only to the extent that they reduce the intake of carbohydrates or reduce the total daily intake of food. They are somewhat blind procedures, and in their stead I much prefer the diet of carbohydrate reduction that I have already outlined. As to the fast cures (inanition cures), the reader is referred to Chapter XXV., which is devoted to a discussion of the subject.

Adjuvant Medication.

I have insisted on treatment by diet because it is the basis of the treatment of diabetes. Drugs only play an accessory part in the therapeutics of the disease. None of them exercises any influence over the glycoregulator disturbance. Antipyrine, which has been so greatly extolled, has never been known to ameliorate a case of diabetes; it merely delays the cure of the hyperglycemia by decreasing diuresis. Neither the salicylates, opium, belladonna, the bromides, santonin, semen contra, nor permanganate influence the morbid process; the reduction of the glycosuria that may have been observed by their use is due to the action of the diet instituted at the same time, or else to the dyspepsia caused by the exhibition of these drugs, which prevents the patient from feeding properly.

Some adjuvant medications are, however, useful. Some are directed to the digestive tract, and especially the liver, which is frequently congested in diabetics who are large eaters. Such are the alkaline cures at Vichy, Vals, Brides, Capvern, etc. They should be repeated for several summers at these spas, and the effect there obtained should be continued during the year by cures carried out at the patient's home. Other treatments are directed against the psychical and physical depression or emaciation of the subject. Arsenic, the glycerophosphates, phytin, and strychnine are indicated, while cures at La Bourboule or Royat render considerable service.

Above all, the diabetic should lead a rigorously hygienical

life. He should avoid sedentariness, taking each day sufficient exercise, although avoiding fatigue as well as excesses of any kind. Hydrotherapy, dry or alcohol frictions are excellent. Finally, as diabetics present a lessened resistance, they should take every possible precaution to avoid disease or accident, especially contagion of tuberculosis, and they should be taught that the only way to increase their resistance is to maintain a normal glycemia by means of proper diet.

CHAPTER XXIV

THE TREATMENT OF DIABETES WITH DENUTRITION

Although the treatment of diabetes without denutrition is relatively simple, that of diabetes with denutrition is much more difficult. The physician is often placed face to face with formidable accidents against which he must act promptly and forcibly.

Patients with diabetes with denutrition are not only exposed, like those with ordinary diabetes, to the danger of hyperglycemia with all its unfortunate consequences, but are also liable to nitrogenous denutrition, which will end in a progressive destruction of their tissues, and acidosis, which leads more or less quickly, but with certainty, to coma.

These three dangers of diabetides with denutrition require three particular therapeutical measures belonging to diet, hygiene, pharmacotherapy, and crenotherapy. The lion's share must be given to diet, because it is by far the most important.

Dietetics.

Dietetic Indications.

These are derived from the three dangers to which diabetics with denutrition are exposed—namely, hyperglycemia, nitrogenous waste, and acidosis.

1. **Hyperglycemia.**—Its treatment requires a reduction of the carbohydrates similar to that carried out in diabetes without denutrition. Contrary to what is too often maintained, diabetics with denutrition are quite as sensitive to reduction of the carbohydrates as are other diabetics; their glycosuria proportionally varies with the amount ingested, only it does not disappear when the carbohydrates are completely eliminated from the diet. These patients have no carbohydrate tolerance whatsoever.

Since the glycosuria is partly due to the metabolism of

albuminoids, there is reason to reduce these aliments. Occasionally it happens that the glycosuria, which has not subsided by the elimination of carbohydrates in the diet, will disappear when the amount of meat is reduced. Cantani and Naunyn have published examples of this fact, and I have observed a similar result in a woman with pancreatic diabetes:

With a mixed diet comprising only 37 grammes of carbohydrates and 264 grammes of albumin, the glycosuria remained at 26 grammes per day; 200 grammes of meat were removed from the diet, and the glycosuria dropped to 6 grammes; finally, two eggs were eliminated, which only left the patient 150 grammes of albumin per day, and the glycosuria fell to 1 gramme, and finally completely disappeared.

But disappearance of the glycosuria is not always obtained by a reduction of meat, and there are cases in which it continues even when a fast is taken.

As to fats, which appear to play a much less important part in the production of glucose, their consumption need not be restricted in the same degree.

Is there any advantage to be gained by combating the hyperglycemia of these diabetics? Some writers have maintained that there is none, and believe that only disadvantages result from a too strict diet. Naunyn and Magnus Lévy believe that, on the contrary, it is better to do so, and that by perseverance and caution one can sometimes cause a glycosuria to subside which at first sight appeared to be irreducible. Personally I have become convinced of the necessity of reducing the hyperglycemia; the patients are bettered and may lead a nearly normal life for a long time, since they are no longer tormented by the distressing symptoms and accidents to which hyperglycemia gives rise.

2. **Nitrogenous Denutrition.**—An abundant diet, rich in albumin, is necessary to combat nitrogenous waste.

Ration of Albumin.—I have shown experimentally that nitrogenous overfeeding impedes denutrition, and may even prevent it. Consequently, from this view-point there is reason to order a diet rich in albumin.

To compose this diet one must resort to meat and eggs, which furnish nitrogenous substances without, at the same time, containing carbohydrates that would increase the

hyperglycemia. But for other reasons, as I shall show, meat is deleterious.

Total Ration.—To the question of nitrogenous denutrition, that of the total quantity of food to be given in serious diabetes is closely allied. It is known that the carbohydrates and fats exercise a saving action in respect of albuminoids. Therefore, it is indicated to increase the amount of these aliments in diabetics in order to limit nitrogenous denutrition. But since the carbohydrates are not burned by the organism, fats only can play a saving part, so that it is advantageous to give them in large quantities.

In a general way the alimentary needs are large in diabetics with denutrition. The patients that I have observed have maintained their weight equilibrium with rations equivalent to 46 to 55 calories per kilogramme of body weight. For that matter, their weight is an imperfect indication of the value of the food ration; they may present nitrogenous waste although the equilibrium of the body weight is maintained, the tissue waste being concealed by hydration.

3. **Acidosis.**—Acid intoxication is characterized by the entrance into the body fluids and excretion by the urine of the acetone compounds—acetone, diacetic acid, β-oxybutyric acid—as well as an excess of ammonia and amino-acids.

The acetone compounds may be derived from fats and albuminoids.

Fats were the first to be incriminated by Geelmuyden and Rumpf. Unquestionably they may furnish acetone compounds by their transformation. But this theoretical notion has never been verified in diabetics; even when these subjects present acidosis, the excretion of the acetone compounds does not increase in proportion to the amount of fat ingested; if there is any increase it is quite insignificant. Maignon's experiments, carried out on a diabetic dog, on the contrary, have shown that an exclusive olive-oil diet lowered the amount of acetone excreted from 1·25 grammes to 50 centigrammes. I therefore think that Magnus Lévy is correct when he affirms that the danger of fats in serious diabetes is illusory.

From the view-point of the production of acidosis, should a distinction be made between fatty substances ?

These substances are composed of a mixture of the glycerides of the fatty acids, among which are to be found the cetogenous bodies, such as butyric, caproic, caprylic, caprinic, palmitic, oleic, and stearic acids; and the anti-cetogenous bodies, such as proprionic, normal valerianic, heptylic, nonylic acids, etc. The composition of edible fats does not permit one to make a distinction between the cetogenous and anticetogenous fats; vegetable fats, such as cocose, vegetaline, and olive oil, are not less cetogenous than animal fats, such as grease from butcher's meat and butter. The latter is perhaps the most redoubtable on account of the free butyric acid it contains when not absolutely fresh. Certain cheeses containing proprionic and valeric acids may be regarded as anticetogenous.

All things considered, fats should not be regarded as dangerous in acidosis, and can be freely given in the diet of serious diabetides.

Embden, Baer and Blum, Knoop, Friedmann, Flatow, Dakin, Neubauer, not to mention others, have shown that the principal source of the acetone compounds in diabetics is represented by *albuminoid substances*. Hence the danger resides in albuminous foods, and therefore they are to be restricted in diabetic subjects threatened with acidosis.

However, all albumins are not equally deleterious. Among the amino-acids which enter into their composition there are those which are cetogenous, like leucin, tyrosin, and plenyl-alanin; and others, on the contrary, that are anticetogenous, like glycocoll, alanin, aspartic acid, and phenylacetic acid (Schwartz, Embden, Baer and Blum, Borchardt and Lang, Satta). Hence one may foresee, according to the constitution of a given protein substance, what will be its influence in the production of acetone compounds. At my request, H. Labbé has drafted the following table:

Cetogenous Albumins.	*Anticetogenous Albumins.*
Serum albumin.	Egg albumin.
Cow's milk albumin.	Legumin of dried vegetables.
Serum globulin.	Soja globulin.
Globin of oxyhemoglobin.	Gliadin and gluten from wheat, zein from corn, hordein from barley, avenin from oats.
	Fibrin.

In a general way this table shows that the albumins of meat and milk are especially cetogenous, while those of eggs, cereals, and vegetables are anticetogenous. Therefore it is particularly advantageous to use egg and vegetable albumins rather than those derived from meat in diabetics with acidosis.

The acetone compounds are not derived from carbohydrates. The latter even appear to prevent their formation. This anticetogenous action, which is clearly demonstrated in healthy subjects during fast, is less evident in diabetics, especially those with denutrition. In order that the carbohydrates shall be anticetogenous, they must be carburetted in the organism. Now, diabetics with denutrition do not possess this faculty, so that the addition of carbohydrates to their diet is of questionable value. At all events, experience has shown that in order to play their anticetogenous part carbohydrates need not be given in large amount; 50 grammes seems to be quite sufficient.

It was formerly held that patients who refused to submit to an antidiabetic regimen and whose intake of carbohydrates was large were less liable to coma than those who did. It is certain that severe diets have been more than once responsible for the advent of coma. But this fact has not the signification that some have been inclined to give it. If a strict diet is dangerous in diabetics with acidosis, it is not because of its paucity in carbohydrates, but on account of the excessive amount of meat that entered into it. When a meat diet is given in moderate amount it no longer offers the same danger. On the other hand, it really does not seem as if indocile diabetic patients who gorge themselves with all kinds of food survive longer than the others. I have even seen excessive eating result in coma in diabetics without denutrition who, from the nature of their diabetes, were not fatally exposed to this complication.

According to the experiments of Neubauer, and Benedikt and Torök, it would seem that *alcohol* prevented the formation of acetone compounds. The researches that I carried out with Violle show that the acids with an alcohol function are less comatigenous than those not possessing this function. It is therefore legitimate to attempt the etherification of the acids in the organism by the ingestion of alcohol. Magnus

Lévy prescribes a pint of wine or two to three small glasses of cognac to patients threatened with coma. One must, however, be cautious in the use of alcohol, because in large doses it is deleterious, and alcoholic excesses have been known to induce coma.

Conclusions.—If we sum up the dietetic indications derived from the data given above, it will be seen that hyperglycemia requires a reduction of the carbohydrates and albumins; nitrogenous denutrition demands an increase of the ration of albumins and fats, while in acidosis the albumins must be reduced.

Unfortunately these indications are contradictory, and it is impossible with a single diet to fulfil all these desiderata.

Various Diets.

We will now examine the results obtained with different diets that have been recommended in the cases under consideration.

1. **Mixed Diet with Reduction of the Carbohydrates.**—This is the fundamental regimen of diabetics, and is composed of meat, whose quantity should never exceed 400 grammes per day, with eggs, cheese, and a large proportion of fat, green vegetables and a small quantity of potato, the total amount not to contain more than 40 to 50 grammes of carbohydrates per day.

This diet is well tolerated by all patients; it maintains their strength, and from the notable proportion of albumin it contains (120 to 140 grammes) it prevents nitrogenous denutrition. Its only drawback is the animal products entering into its composition, these predisposing to acidosis.

2. **Milk Diet.**—This has at times been lauded, at other times decried. At present it is generally admitted that it is no panacea. All depends upon the way it is given and upon the patient as well. When carried out according to Maurel's indications, a milk cure is nothing less than a reduction of the total daily amount of food. Applied to diabetics without denutrition, a milk diet is advantageous if the patient's tolerance for carbohydrates is sufficiently high, while it is very inferior

when compared with a mixed diet if the tolerance is low. As I have shown, lactose is one of the carbohydrates the least utilized by hyperglycemic subjects.

Its use should be reserved for certain particular cases, and above all for diabetes with denutrition and acidosis. Magnus Lévy does not refer to it in serious diabetes, but gives it in coma. Landouzy and Cottet caused the acidosis to disappear by a milk diet in a case of diabetes, as well as the glycosuria that was not influenced by Bouchardat's diet.

I have also had good results with milk diet in acidosic diabetics; the acetone compounds in the urine decreased, as well as the menace of coma.

A milk diet is therefore useful in acidosis, but it increases the hyperglycemia on account of the large proportion of lactose it contains. In order to make its use more advantageous, I am in the habit of increasing the proportion of albumin and fat, and of reducing that of the lactose, by prescribing it as follows:

Milk, from 1,500 to 2,000 c.c.; curdled milk, 500 c.c.
Fresh cheese, 100 to 200 grammes; or old cheese, 80 grammes.
Fresh cream, 100 to 200 c.c.
Coffee, rum.

3. **Cereal and Oat Diets.**—Von Noorden, as far back as 1902, recommended an oat diet in serious diabetes. The patient daily consumes 200 to 250 grammes of oatmeal or flaked oats in the form of pap, 300 grammes of butter and 100 grammes of some vegetable albumin such as tropon, which he sometimes replaces by the white of eggs.

In fortunate cases of diabetes with glycosuria and acidosis which did not yield to reduced carbohydrate diet the oat regimen will cause the glycosuria to subside, while at the same time the acetonuria, ammonuria, and Gerhardt's reaction disappear. In other cases the glycosuria persists, but the acidosis decreases, the emaciation ceases, and strength returns. In less fortunate cases the diet has no effect on the glycosuria or the acidosis, and even oatmeal may be less well tolerated than the other carbohydrates; especially is this true of mild cases of diabetes. But, in practice, von Noorden recommends this diet especially in serious diabetes with acidosis.

His statements have in general been confirmed. In certain cases Luthje has noted an amelioration in the tolerance for carbohydrates and a decrease of the acidosis. Friedenwald and Ruhrah found that the results varied in respect of the glycosuria, but that Gerhardt's reaction usually became negative. Although the oat diet was often without avail in so far as the glycosuria and acetonuria are concerned, Falta nevertheless recognizes the value of this regimen, especially when it is preceded by one day of fast, and that a return to a meat diet is not attempted too quickly. Croftan, Langstein, Hirschfeld, Lampe, Siegel, Nerrick, and Strauss have frequently obtained good results with a milk diet.

On the contrary, Lipetz criticizes oat diet; he mentions a case in which the result was bad, the oatmeal increasing the excretion of diacetic acid. He prefers the ordinary strict diet to an oatmeal regimen. Mohr discussed Lipetz's cases, and considers oat diet indicated in serious forms of diabetes in which the glycosuria cannot be controlled, when the acidosis is marked, and when digestive disturbances exist.

I have resorted to the oatmeal regimen in many cases of diabetes of different types. In diabetes without denutrition I have found that the starch of oatmeal was relatively better tolerated than most of the others, especially that of bread, but less, however, than potato starch.

In diabetes with denutrition I have obtained some good results. In one of my patients the acidosis disappeared on an oatmeal diet combined with sodium bicarbonate, while in another the diaceturia and acetonuria almost completely subsided by an oatmeal diet of eight days' duration. Upon different occasions in diabetics with acidosis and threatened coma I have given an oatmeal diet in place of a mixed regimen, and it has seemed to me that this diet was the means of warding off the imminent danger.

The study of amino-aciduria in diabetics subjected to various regimens has shown that oat albumin is better utilized than that of meat, and that it gives rise to a less strong excretion of amino-acids as well as the toxic substances derived from protein matter; on the contrary, oat albumin is not as well utilized as that of milk, and especially the albumin of dried vegetables.

Oatmeal diet has one great drawback—namely, the difficulty experienced by patients to submit to it. Many have diarrhœa, abdominal distension, and vomiting, and consequently refuse to continue the regimen. I have rarely been able to carry it out for more than three days in succession either in private or hospital practice. In order to have the patient accept it I have been obliged to give the oatmeal in the form of pudding or cake as well as pap. Finally, certain diabetics have been unable to exceed 100 to 150 grammes of oatmeal per day, which in reality is a relative inanition cure.

The Germans do not seem to have encountered the same difficulty, and their patients will continue the diet for weeks; Mohr even mentions a patient who, while travelling on business, continued the regimen for four months. Strauss, however, seems to have met with some opposition from patients, and von Noorden himself has admitted that in order to make the diet tolerable some wine, brandy, tea, and mineral waters must be allowed the patient.

The development of œdema has been mentioned as occurring after an oatmeal diet (Minkowski), and Strauss recommends the exhibition of theocin for its relief. The oatmeal diet being often combined with an alkaline treatment, it may be asked if the œdema may not be due to the sodium bicarbonate rather than the régime.

Although the good effects of oatmeal diet in serious diabetes complicated with acidosis are generally conceded, opinion is moot in respect to the action of the regimen. It, however, would appear that at the present time no specific action can be attributed to it, and that its principal advantage resides in the reduction of albumin and in the replacement of animal albumin by that of vegetable albumin. Von Noorden has changed his diet in this direction, since he precedes and follows it by a three days' cure of vegetables and eggs, while he no longer attempts to increase the amount of proteins by the addition of pure albumins, and at the same time he reduces the amount of meat in the strict diet to which the patients are afterwards subjected.

In my opinion, it is not so much to the properties of the starch as it is to those of the oat albumin that the good effects of the diet are due. As I have already said, the proteins of

oats and vegetables in general furnish by their degradation fewer cetogenous amino-acids than does meat; hence their metabolism gives rise to fewer toxic bodies, the factors of acidosis, and their use is therefore justified in diabetics threatened by coma.

4. **Dried Vegetable Diet.**—Dried vegetables—peas, beans, lentils, kidney beans, etc.—have not been employed systematically in diabetes. Siegel states that his results were not so satisfactory when pea flour was used instead of oatmeal.

In diabetics with denutrition and acidosis, I have attempted to replace the oatmeal diet by that of dried vegetables, and have been struck by the good results obtained.

Each day the patient is given 300 grammes of dried vegetables, 150 grammes of butter, 3 to 6 eggs, and 3 to 4 rolls of aleuron bread. Besides, 3 to 4 wineglasses of red wine and some green vegetables may be allowed, but no meat whatsoever. The vegetables must be well cooked, and, in order to be more certain that they shall be well digested, they should be thoroughly mashed and passed through a sieve. Intestinal absorption of dried vegetables is defective; it is not uncommon to find whole peas or beans in the fæces in patients who masticate insufficiently. On the other hand, dried vegetables that have been properly prepared and masticated will be very completely absorbed by the intestine.

To ordinary dried vegetables it is indicated to add soja beans (soy beans) to the diet, because of their rich albumin and fat content and paucity in starch. The soja bean contains in 100 grammes an average of 36 grammes of albumin; fats, 13·5 grammes; starch, 30 grammes; cellulose, 5 grammes; ashes, 5 grammes; and water, 10·5 grammes. Comparatively, the dried vegetables in most countries contain: Albumin, 21 grammes, fats, 1·5 grammes; starch, 59 grammes; cellulose, 3 grammes; ashes, 3 grammes; and water, 12·5 grammes.

Unfortunately, soja beans are very difficult to cook, and even when well prepared their peculiar taste is disagreeable to many patients. An attempt should nevertheless be made to induce them to take them, because the bean lends itself to many culinary devices such as bread, cake, and cheese, some of which are not disagreeable. Le Goff has used soja beans in the diet of diabetics with very good results.

The vegetable diet is usually well tolerated; patients generally prefer it to oatmeal pap and milk diet; it appeases the appetite better than milk, and it does not constipate; it does not give rise to diarrhœa, as is the case with oatmeal, and it is readily digested.

The diet should be given for three days at least; some patients continue it for one or two weeks, or even more.

The effects of this regimen are remarkable, especially in the more serious forms of diabetes. They are noticeable particularly as regards the glycosuria, nitrogenous denutrition, and acidosis.

In spite of the large proportion of starch contained in this diet, the glycosuria is often no greater than with a mixed diet poor in carbohydrates, while sometimes it is even less. In certain fortunate cases, the dried vegetable diet will cause the glycosuria to subside when it has not been influenced by other regimens.

The study of apparent tolerance places the advantages of this diet in relief. It is distinctly evident that the starch of dried vegetables is better utilized by the organism of diabetics than that contained in other foods. Thus, in one of my cases, the patient offered an apparent tolerance of 65 grammes with a vegetable diet; on an oatmeal diet the tolerance was 35 grammes, and 15 grammes with a milk diet. Finally, with a mixed meat diet the tolerance became negative (− 42 grammes), and the patient eliminated a greater quantity of glucose than the amount of starch ingested.

To prevent nitrogenous waste the advantage of dried vegetables is still more evident. Taking all my cases together, the nitrogenous balance was distinctly positive (+1·16 grammes per day) with a vegetable diet; with an oatmeal regimen it was in equilibrium (+5 centigrammes); negative (− 27 centigrammes) with a milk diet; and extremely negative (− 2·02 grammes) with a mixed diet. Hence vegetable albumin is better utilized than meat albumin, and also that of milk and cereals.

In acidosis the vegetable diet renders great service; clinical observation and the systematic search for the reactions of acidosis prove this. Upon several occasions I have succeeded with this diet in dissipating somnolence and anorexia and

removing the menace of coma. The dried vegetable diet decreases the acidity of the urine better than do milk or oatmeal regimens. Thus, in one of my patients 30 grammes of sodium bicarbonate was sufficient to alkalize the urine when a dried vegetable diet was being taken, while 40 grammes of bicarbonate was not enough when the patient was on a mixed diet. The average of the urinary acidity in my cases has been: 1·63 grammes with a vegetable diet; 2 grammes with oatmeal; 2·15 grammes with milk; and 4·04 grammes with a mixed regimen.

Of all the diets, that of dried vegetable gives the lowest acetonuria. The average has been: 2·11 grammes with vegetables; 2·73 grammes with oatmeal; 3·20 grammes with milk; and 3·20 grammes with a mixed diet. It decreases the diaceturia, and sometimes it will cause it to disappear in the intermediary forms of diabetes. Finally, it reduces the proportion of non-dialyzable colloidal nitrogen that is present in excess in the urine of serious diabetes. And nevertheless, if its effects on the ammonuria and amino-aciduria be studied, it would seem to increase the excretion of these substances, which would indicate a less complete degradation of the vegetable albumin. This is a paradox that I mention without attempting to explain it.

In diabetics without denutrition I have noted that dried vegetables are almost as well tolerated as potatoes or oatmeal, and much more so than milk, bread, or sugars. Rathery has come to similar conclusions.

Taking all these data together, it becomes evident that the starch and albumin of dried vegetables are better utilized than the others by the organism of diabetics. This is undoubtedly due to the peculiar chemical properties of vegetable starch and albumin, but chemical analyses have not yet shown in what way this starch differs from that of cereals, and why diabetics assimilate it better than milk sugar; but the chemical composition of the protein substances of dried vegetables and cereals, which comprises fewer cetogenous amino-acids than milk or meat, explains the favourable action of dried vegetables on acidosis.

Briefly put, the dried vegetable diet, which sometimes gives such excellent results in diabetes without denutrition,

and in some cases causes the glycosuria to disappear when regimens severe in appearance did not reduce it, is above all indicated in diabetes with acidosis, and is indispensable as soon as coma threatens.

5. **Fat Diet.**—From the time that Cantani, Ebstein, and Weintraud showed the advantage to be derived from a diet of fats, it has generally been conceded that a considerable quantity of fat should be given to diabetics. All the diets—mixed, modified milk regimens, cereal and vegetable—contain large amounts. When it is possible to make a patient tolerate 300 grammes of butter in some oat-flour diets, the total amount of fats ingested per day reaches 250 grammes. This is a true fat regimen. Arloing and Maignon, by recommending an emulsion of olive oil in diabetes, merely supplied a new way of absorbing fats.

6. **Fast Cures.**—The fast cure or inanition cure has been lengthily considered elsewhere (see Chapter XXV.), therefore no mention need be made of it here, nor need I again refer to potato, rice, fruit, or sugar diets, etc., because, although they have been apparently successful in obese diabetics, they have no place in the treatment of diabetes with denutrition.

Conclusions.—From a critical examination of these various diets it becomes evident that there is not one that can fulfil all the indications presented in the treatment of diabetes with denutrition. Each one has its individual advantages. The mixed diet deals best with nitrogenous denutrition and hyperglycemia; the cereal, milk, and dried vegetable regimens combat acid intoxication. Of the latter three, dried vegetables seem to me the most advantageous, because they furnish a relatively greater quantity of albumin and a lesser amount of carbohydrates than the other two, and finally because they are invariably better tolerated by patients.

When ordering a diet in diabetics with denutrition, one must take these circumstances into consideration and submit patients to various diets in succession. This is what I am in the habit of doing by ordering each month the following succession of diets: Mixed diet (one week), milk diet (three days), mixed diet (one week), and dried vegetables (three days). This first *systematic* essay, accompanied by analyses

of the urine, allows me to note the effect of each diet. Having thus determined the reactional peculiarities of the patient, I can then correctly prescribe the proper treatment of the symptoms and accidents he may present. It cannot too often be repeated that in the diet of diabetics with denutrition all idea of system should be put aside, and the treatment of the case should be entirely directed by observation.

Hygiene.

A strict hygiene is essential, as any deviation from the rules of health may be followed by serious accidents. Physical and moral rest is the basis of this hygiene; no fatiguing exercises, no travel, no intellectual or physical work, no violent emotions, no worry, and no chilling—such are the conditions that one must fulfil as far as possible. A diabetic with denutrition is a fragile subject, and he must lead a careful life.

The hygienic conditions required are frequently difficult to realize at home; the diets, fasts, and alkaline treatment necessitate close supervision, and the very special care requisite can sometimes only be carried out properly in a nursing home or by nurses having received a special education in the matter of diabetes, as Joslin has well shown.

Pharmacotherapy.

Many drugs have been lauded for diabetes. I will only envisage the principal ones.

The Arsenical Preparations.—These render good service in diabetes with denutrition; not that they influence the glycoregulator disturbance, but because they increase the appetite, restore the strength, and maintain the weight equilibrium. One may prescribe sodium arsenate, 1 centigramme per day, or sodium methylarsenate at the dose of 5 to 10 centigrammes a day given subcutaneously.

Phosphorus.—Phosphorus preparations in all their multiple forms have been recommended—namely, the glycerophosphates by mouth or subcutaneously, phosphoric acid, the vegetable phosphates, phytin, the hypophosphites, etc. Useless so far as the diabetes itself is concerned, these preparations

are of help in combating the physical depression and the often considerable asthenia of these patients.

Iron.—The ferruginous preparations may be used for the same purpose in anæmic and depressed diabetics.

Sedatives of the Nervous System.—The opiates (Dover's powder, morphine, and ext. opii), belladonna, valerian, the bromides, have been employed, even in very large doses, Tomasini having exhibited as much as 3 grammes of the extract of opium. Their action on the glycosuria has not been demonstrated, and they have the drawback of depressing and intoxicating the patients. The preparations of valerian are the only drugs fit for diabetics suffering from nervous disturbances. Bouchard used to give extract of valerian in large doses.

Antipyrine, recommended by A. Robin, at the dose of 1·5 to 2 grammes daily for five successive days, acts, according to Lépine and Porteret, by preventing the transformation of glycogen into glucose in the liver and muscles. To me its action appears most unreliable.

Sodium Salicylate and **Aspirin** have often been employed. Von Noorden and Kauffmann say that they have obtained good results with aspirin at the dose of 1 to 3 grammes daily during two to three weeks. I have not been so fortunate.

Jambul has been lauded in Germany. Von Noorden particularly recommends it in serious diabetes in which the glycosuria does not subside when carbohydrates are excluded from the diet. He prescribes extract of jambul (Merck) at the dose of a dessertspoonful in very hot water three times a day for three or four weeks. The experiments of Scott and Balfour, Coloranti, and Martz would seem to show that jambul prevents the transformation of starch into glucose by amylase.

Opotherapy.—Taking as a basis a pathogenic supposition, liver, pancreatic, intestinal, and even thyroid extracts have been given in diabetes. Hepatic opotherapy has a *raison d'être* in cases in which the liver is cirrhotic, and therefore imperfectly fulfils its functions. Pancreatic opotherapy is indicated in serious diabetes with lesions of the pancreas and digestive disturbances arising from insufficiency of the external pancreatic secretion. An improvement of the glycoregulator process is not obtained, but there is an amelioration of the

intestinal digestion. It must be remembered that during the first day of pancreatic medication a marked, but temporary, increase of the glycosuria ensues. The various pancreatins, bile extracts, and natural gastric juice can be employed for the same purpose.

The Alkalines.—Alkalines are employed in two ways—namely, in small and large doses.

In *small doses* they stimulate the liver functions, favour the fixation of glycogen in the hepatic cell, and delay the transformation of glycogen into glucose (Dufourt, Gans).

I frequently prescribe a Vichy cure at the patient's home during one month, which consists in taking a large glass of Vichy water (Hôpital spring) three times daily before each meal. The water should be heated to 104° F. before drinking, and to each bottle of water a powder composed as follows is added:

Sodium bicarb.	..	..	1 gramme.
Sodium sulphat.	..	..	4 grammes.

The following formula has also given me good results, especially in constipated patients: Take in the morning before breakfast, and for twenty days, a cup of infusion of triticum and wild pansy, to which is added a dessertspoonful of the following powder:

Sodium bicarb. Sodium citrat. Sodium sulphat.	..	..	āā 25 grammes.

In *large doses* the alkalines represent the treatment of acidosis. The bicarbonate and citrate of sodium are used. In the minor acidoses the body fluids are alkalized with 12 grammes of sodium bicarbonate daily; in serious cases from 40 to 50 grammes must be given each day in order to render the urine neutral or alkaline to litmus paper. Finally, in serious cases with threatening or even confirmed coma, much larger doses are necessary to combat the accidents; it is necessary to introduce 100 to 200 grammes of the salt into the organism within twenty-four hours.

Such large doses are often difficult for the patient to tolerate, so that, given the urgency of the condition, the salt must be given by mouth, per rectum, and intravenously. By

mouth the bicarbonate is given in doses of 5 to 10 grammes dissolved in Vichy water or an infusion of hot tea every hour; if vomiting ensues, an equal amount of sodium citrate should be mixed with it, but always remembering that the latter salt alkalizes much less than the bicarbonate. By enema a dessert-spoonful of bicarbonate dissolved in a glass of warm water should be introduced two to four times daily.

For intravenous injections I employ a 5 per cent. distilled water solution, given in doses of 500 c.c. These injections are only to be resorted to when the patient cannot tolerate the salt by ingestion.

Alkaline treatment in large doses gives brilliant results in the accidents of acidosis, and, if employed in time, will conjure the development of coma. When this has become declared one must not give up all hope, because in some exceptional cases recovery may ensue if a sufficient quantity of the salt can be introduced into the organism.

Crenotherapy.

Crenotherapy, which plays such an important part in the treatment of diabetes without denutrition, is hardly worth resorting to when denutrition exists.

When the diabetes is not excessively serious and not complicated by acidosis, the alkaline cures of Vichy, Vals, Pougues, etc., may be employed in order to stimulate the activity of the liver. But when there is acidosis, alkaline cures are useless or even dangerous. Their effect on the glycoregulator disturbance is *nil*, and, besides, diabetics of this category frequently have no liver trouble whatsoever. Finally, travel and the resulting fatigue aggravate the acidosis and occasionally induce coma.

The arsenical cures at La Bourboule and Royat are more frequently indicated in diabetes with denutrition, and are particularly to be recommended in emaciated and depressed subjects. But here, again, acidosis must not be threatening, otherwise the patient is exposed to coma from the very fact that the trip to the spa may cause it to ensue. Hence, for the majority of diabetics with denutrition hydromineral cures are contra-indicated.

CHAPTER XXV

THE FAST CURES IN DIABETICS*

THE fast cures were introduced into the treatment of diabetes by Guelpa in 1910; in France they have given rise to many protestations and have made few adepts. A paper by Rathery in March, 1921, is the only one that has appeared on the subject since Guelpa's publications.

Preconized by Allen in 1914, the fast cures have been more willingly accepted in the United States, where numerous observers, Joslin in particular, have resorted to them and have become warm partisans of the treatment. In Germany, Sweden, and Norway, those that have employed these cures have in general obtained good results. English physicians have so far been rather reserved in their opinion.

For my part, I have prescribed quite a goodly number of fast cures in diabetic subjects, so that I am in a position to discuss their therapeutical value.

There are two ways of giving a fast cure: Guelpa recommends a fast for an average of three days combined with repeated purgation; Allen advises fasting without purgation, and sometimes prolongs it for four or five days. I usually give a purgation on the first day only, as it does not seem to me that there is any advantage in repeating it. All writers are of the opinion that the fasting should be prepared by a progressive reduction in diet, and the return to food after the fast must be slowly progressive. By so doing the effects of the reduced diet are prolonged and accentuated. The return to food may, if necessary, be interrupted by a cure of green vegetables for one or several days, or even by another period of fasting. It is by daily analysis of the urine that the conduct of the treatment will be dictated.

The effects of fasting cures are very different according to whether the case is one of diabetes without denutrition or

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with nitrogenous denutrition. I shall therefore envisage each condition in succession.

I. Diabetes without Denutrition.—In this condition the fast cures are easy and give extremely good results. In the benign forms of the disease, in which the glycoregulator disturbances are moderate, the glycosuria generally subsides on the first or second day of fast. This rapid result is preferred to the slower result obtained by a reduced diet in indocile patients.

In a woman who had a real mania for food, and who had invariably refused to submit to a reduced regimen, I caused the glycosuria to drop from 297 grammes to 0 on the first day of a fast cure; it reappeared five days after the cessation of the fast, as the patient again returned to her habit of overfeeding. This shows that fasting causes the syndrome of hyperglycemia to disappear, but that it does not cure the diabetes—a fact that should be clearly explained to patients. If they will form the habit afterwards of exceeding their tolerance for carbohydrates, they may remain almost indefinitely without glycosuria.

It is in the severer forms of diabetes without denutrition, in the intermediary forms corresponding to the first phase of serious diabetes, that fast cures give the most remarkable results. When the mixed diet with reduction of the carbohydrates has improved the patient's condition and decreased the glycosuria without causing it to disappear, when it persists with disheartening fixedness, appearing to indicate a very low tolerance for carbohydrates or even none at all, a fast cure of three days will cause the glycosuria to immediately clear up and increase the carbohydrate tolerance to such an extent that in the future the patient can absorb quantities of carbohydrates, which before the cure would have resulted in an abundant glycosuria, without giving rise to any whatsoever.

The following case tables are absolutely demonstrative, and allow us to envisage the action of the fast cures from various view-points:

1. *Glycosuria.*—It always disappears, on the second day at the latest. Afterwards, when feeding is progressively carried out with green vegetables, butter, and milk, then with cheese and eggs, with meat a few days later, the glycosuria does not

reappear. It, however, occasionally happens that glycosuria returns for one to three days, and then ceases spontaneously, as if the patient needed to adapt himself to the alimentary regimen. Finally, the time comes when the glycosuria becomes definitely re-established; this is because, by increasing the carbohydrates, the patient's tolerance has been exceeded. All

TABLE I.

Date.	*Diet.*	*Carbohydrates in Grammes.*	*Weight in Kilogrammes.*	*Glucose in Grammes.*	*Gerhardt's Reaction.*	*Acetone Compounds.*	*Glycemia in Grammes.*
Dec. 16	Mixed	37	54·0	241·0	0		
,, 21	,,	35	53·7	28·0	+		
,, 25	,,	50	52·0	88·0	+ +		
,, 27	,,	43	53·0	73·0	+	6·76	
Dec. 28	Fast		52·9	0	+	0·32	
,, 29	,,		52·6	0	+	0·27	
,, 30	,,		52·0	0	+ −	0·18	
Dec. 31	Green vegetables	43	52·1	0	+ −	2·53	
Jan. 1	,, ,,	43	51·1	0	0	0·09	
,, 6	*Id.* + meat 100	43	52·3	0	0		
,, 17	*Id.* + ,, 200	44	55·1	0	0		
,, 24	*Id.* + potatoes 100	64	55·8	0	0		
Feb. 4	*Id.* + ,, 200	84	57·8	0	0		
,, 10	*Id.* + ,, 300	104	58·0	0	0		
,, 12	*Id.* + ,, 300	104	58·6	10·0	0		
,, 14	*Id.* + ,, 300	104	58·8	0	0		
,, 22	*Id.* + ,, 400	124	60·3	0	0		
,, 28	*Id.* + ,, 400	124	60·2	7·8	0		1·29
Mar. 3	*Id.* + ,, 300	104	60·0	8·0	0		1·04
,, 7	*Id.* + ,, 300	104	60·3	0	0		1·44

that is then necessary is to reduce the carbohydrates until the glycosuria subsides.

What is particularly noteworthy is that the tolerance for carbohydrates is high. Thus, in one of my patients there was a glycosuria of 33 grammes with a carbohydrate intake of 61 grammes; after a fast cure he tolerated from 42 to 53 grammes without the advent of glycosuria.

Mouly (see Table I.), who before fasting presented a glyco-

suria of 73 grammes with a daily intake of 63 grammes carbohydrates—an apparent absolute intolerance—was able to ingest 43 grammes, then 63 grammes, and finally 103 grammes carbohydrates after the fast without return to the glycosuria. In Dub's case (see Table II.) the result was still more extraordinary. Before fasting the glycosuria was 41 grammes for

TABLE II

Date.	*Diet.*	*Carbohydrates in Grammes.*	*Weight in Kilogrammes.*	*Urine in Cubic Centimetres.*	*Glucose in Grammes.*	*Gerhardt's Reaction.*	*Legal's Reaction.*	*Acetone Compounds in Grammes.*	*Glycemia in Grammes.*
Dec. 31	Mixed	187	75·0	3,000	196·0	++	++		
Jan. 1	Green vegetables, eggs, cheese	33	74·0	2,700	62·0	++	++		
,, 5	Green vegetables, eggs, cheese	33	74·0	2,600	41·0	++++	++++	13·15	
Jan. 6	Fast		72·6	2,400	11·8	++	++	17·66	
,, 7	,,		75·3	5,800	0	++	++	3·42	
,, 8	,,		73·5	2,800	0	+	+	1·41	
Jan. 9	Green vegetables	22	73·0	900	0	+	+	4·76	
,, 11	*Id.* + milk	33	72·3	1,800	3·9	++	++		
,, 14	*Id.* + eggs	33	72·8	1,000	1·4	+	+		
,, 19	,,	33	72·2	1,070	0	0	0		
,, 25	*Id.* + meat + potatoes	43	70·0	1,400	0	0	0		
,, 28	*Id.* + meat + potatoes	53	70·25	1,000	0	0	0		
Feb. 10	*Id.* + meat + potatoes	73	69·3	1,000	0	0	0		1·18
,, 19	*Id.* + meat + potatoes	93	71·5	1,000	0	0	0		
,, 28	*Id.* + meat + potatoes	113	71·0	1,200	0	0	0		0·80
Mar. 7	*Id.* + meat + potatoes	115	71·1	1,400	0	0	0		1·03

a daily intake of 33 grammes carbohydrates; after fasting the daily intake of carbohydrates could be successively increased to 33 grammes, 53 grammes, 73 grammes, and finally 200 grammes without return of the glycosuria. It is quite true that some patients did not respond so brilliantly to the fast cure, but it may be questioned whether they did not make some digressions in diet.

Such results are very difficult, not to say impossible, to obtain by a simple reduction of carbohydrates, so that the fast cure represents a particularly active treatment.

2. *Glycemia.*—Fasting influences the glycemia in the same way as the glycosuria. Thus Lag. (see Table III.) had a 2·25 per 1,000 glycemia before the fast cure; this progressively fell from the effect of the cure to 0·92 gramme—that is to say, normal—on the first day feeding was resumed; it then slowly ascended with feeding to 1·48 per 1,000. Then the glycosuria reappeared. A second fast cure lowered the glycemia to 0·85 gramme, but it went up to 1·60 grammes as soon as feeding was resumed. The type of diabetes in this case was particularly obstinate.

The study of glycemia presents a considerable practical value. The fast only gave complete results when the glycemia fell to normal—namely, from 0·90 gramme to 1·10 grammes. Under the influence of a cure by reduction, the glycosuria at first ceases, and it is only after this that the glycemia drops to normal. During the return to feeding the glycemia is the first to increase, and afterwards the glycosuria reappears. Briefly, the glycemia is a more penetrating criterion of the state of the patient than is the search for glycosuria. The true test of the cure of a hyperglycemic state is the persistence of a normal glycemia.

3. *Acidosis.*—When diabetes is not accompanied by acidosis, a fast of three days does not often cause it to appear, in spite of the fact that the Germans maintain that such is the case. Occasionally a mild acetonuria and diaceturia ensue; the reactions of urinary acidosis usually remain very slight, disappear in a few days, and never offer any gravity.

If the diabetes is complicated by acidosis, this is usually decreased by a fast cure, and in fortunate cases there is a complete disappearance of the acidosis soon after the cure. This may be judged best by the dosage of the acetone compounds following Van Slyke's method. In Dub's case (see Table II.) the acetone compounds were 32·8 grammes and 13·15 grammes before the fast cure; during the cure they were 17·6 grammes, 3·42 grammes, and 1·41 grammes; and then on the first day of feeding they reached 4·76 grammes and afterwards completely disappeared. Therefore, far from provok-

ing acidosis, the fast, on the contrary, caused it to first decrease and then to cease.

TABLE III.

Date.	*Diet.*	*Carbohydrates in Grammes.*	*Weight in Kilogrammes.*	*Urine in Cubic Centimetres.*	*Glucose in Grammes.*	*Gerhardt's Reaction.*	*Legal's Reaction.*	*Acetone Compounds in Grammes.*	*Glycemia in Grammes per Litre.*
1920:									
Jan. 8	Mixed	78	53·2	4,500	137·0				
,, 11	,,	64	55·14	2,000	55·0				
,, 15	,,	64	55·14	2,000	36·0				
,, 19	,,	64	55·6	2,000	55·0		+ −		
Jan. 20	Fast		53·2	1,500	13·7	0	+ +		
,, 21	,,		52·9	1,000	0	0	+ +		
,, 22	,,		52·9	500	0·9	0	+		
Jan. 23	Milk, green vegetables	20	52·9	1,500	0	0	+ + +		
,, 24	Milk, green vegetables	40	53·2	1,600	0	0	+ +		
,, 27	*Id.* + eggs	57	53·3	2,750	0		0		
,, 30	,, ,,	59	54·7	2,500	0		0		
Feb. 6	*Id.* + meat	59	53·5	2,100	0		+ − −		
Mar. 11	*Id.* + potatoes	77	54·6		0		0		
April 7	,, ,,	97	56·0		0		0		
,, 14	,, ,,	117	57·2		0		0		
1921:									
Feb. 11	Mixed	54	53·0	1,500	28·7	+	+ +		
,, 17	,,	54	53·6	2,000	61·0	+	+	4·22	2·14
Feb. 18	Fast	0	53·4	1,400	35·0	+ +	+ +	2·99	2·84
,, 19	,,	0	53·0	1,000	0	+	+	6·04	1·31
,, 20	,,	0	53·1	1,000	0	+ +	+ +	5·10	
Feb. 21	Green vegetables	20	51·7	1,600	0	+ +	+ + +	10·62	0·92
,, 22	*Id.* + milk	41	51·0	1,000	0	+ +	+ +	3·32	0·94
,, 28	*Id.* + eggs	51	52·1	1,500	0	+	+		1·34
Mar. 3	*Id.* + cheese	51	53·0	1,800	2·0	+	+		1·48
Mar. 4	Fast			1,500	0	+ −	+ −		
,, 5	,,		51·0	1,000	0	0	+ −		0·85
Mar. 6	Green vegetables	40	50·0	1,000	0	+ +	+ +		1·60
,, 8	*Id.* + eggs + cheese + milk	62	52·3	1,500	0	+	+		1·63
,, 9	*Id.* + eggs + cheese + milk	62			0	0	0		1·64

The excretion of ammonia and amino-acids follows a similar curve; fasting causes it to decrease.

4. *Nitrogenous Metabolism.*—Fasting causes the loss of nitrogen, but after the cure the organism is in a condition similar to that of convalescents, and again fixes nitrogen even when the diet is still very restricted.

5. *The Body Weight* decreases, but only a little. A three days' fast will cause a loss of 300 grammes to 1 kilogramme 800 grammes; the loss is greater in corpulent subjects. Occasionally there is a gain instead of loss of weight. The small loss in weight undoubtedly is due to the fact that it is concealed by hydro-retention; the hydromineral equilibrium is, in fact, very unstable in diabetic subjects. After fasting, and under the influence of feeding, the body weight increases, and usually exceeds the original weight. My patients increased in weight from 5 to 8 kilogrammes in a lapse of time varying from two to three months. A fast cure properly carried out therefore favours fattening.

6. *Blood-Pressure.*—This hardly ever drops more than 1 centimetre during the cure, and rises immediately after; it falls more markedly in diabetics with hypertension. The *pulse* becomes slower. The *temperature* drops several tenths of a degree.

7. *The General Condition.*—It is remarkable how well the patients withstand fasting. So long as the subject remains quiet in bed and warm no discomfort is complained of. On the contrary, all suffering and headache disappear. However, although the fast exercises an efficacious influence over the syndrome of hyperglycemia, increases the apparent tolerance, and causes the acidosis to subside, it possesses no curative action on the diabetes itself. The disease remains stationary, and if the case be one of serious diabetes of the progressive type, the affection will begin its fatal evolution again after an intermission of variable length.

II. Diabetes with Nitrogenous Denutrition.—In this form of diabetes, fasting will only produce a very temporary amelioration; even when it is carried out with severity it has no control over the evolution of the disease, the statements of Allen and Joslin notwithstanding. For example, I treated a woman of 30 years for a serious diabetes, and who already

in the second month of the disease presented a high-grade glycosuria and acetonuria. Each month she underwent a three days' fast; during the first two fasts the glycosuria ceased on the third day, only to reappear on the first day feeding was taken up. In the last two fasts it did not subside whatsoever. I then resorted to a five days' fast, preceded by a green vegetable diet, this time with remarkable results. The glycosuria, which was 118 grammes before fasting, fell and ceased altogether on the third day of fast, while at the same time the marked acidosis decreased and then ceased on the fifth day. The return to progressive feeding resulted only in a very slight glycosuria with a daily intake of 64 grammes of carbohydrates; the reactions of acidosis at first reappeared, and then ceased permanently. The body weight lost during the fast amounted to only 1 kilogramme, so that, all things considered, the result was very good. However, a few days later a perineal abscess developed; the acidosis suddenly returned, resulting in death from coma.

Likewise, in a young man of 19 years, in spite of repeated fastings, the diabetes continued its evolution, ending in coma and death. Several cases of diabetes with nitrogenous denutrition have given me identical results. Finally, in three patients previously treated by Guelpa himself, I witnessed the same fatal evolution regardless of repeated fasts.

From these cases one may conclude that in diabetes with nitrogenous denutrition the glycosuria only decreases during fasting without disappearing, because it is not only derived from food, but from the tissues of the organism as well. Likewise, the hyperglycemia is decreased by fasting, but does not cease. The acidosis is reduced very considerably, but does not generally disappear. Thus, in one patient the acetonuria fell from 3·9 grammes to 0·21 gramme on the third day of fasting; in another the acetone compounds fell from 7·22 grammes to 0·29 gramme on the third day; while in a third patient the acetone compounds only decreased from 36·22 to 17·94 grammes. In favourable cases the acidosis continues to decrease after the fasting when the patient is commencing to take food; in the unfavourable cases it at once assumes its initial intensity.

However, although fasting has appeared to me perfectly illusory from the view-point of the hyperglycemia, it has

seemed to me that it gives advantageous results in acidosis and postpones the danger of coma. I have never known it to cause any complications. It is usually well borne, in spite of the serious depression of the patients. But, to my mind, it should not be regarded as a systematic treatment, because it increases the nitrogenous denutrition, which is the principal danger in diabetes with denutrition.

Briefly, fast cures are an addition to the treatment of diabetes. They do not cure the disease, but they diminish its gravity. I do not think that to them alone can be attributed the amelioration of the prognosis and decrease of the mortality in diabetes, as statistics from various countries might lead one to suppose. It is an energetic therapeutical measure in the hands of the physician who knows how to employ it.

CHAPTER XXVI

SURGERY IN DIABETIC SUBJECTS*

THERE are few more difficult situations to be in than that of the physician who must decide upon the advisability of a surgical interference on a diabetic patient. Should the operation take place, or is it better to wait ? What anesthesia should be employed ? What pre-operative and post-operative treatment should be given ? Such are the serious questions that arise, and which are difficult to solve, because these different points are not settled, regardless of the important writings of Becker, Naunyn, Ruff, Karewski, Berger, and Poucel. I merely propose to present the problem and to offer a few indications based upon already rather numerous cases.

The danger of operation in diabetics depends upon two principal causes: (1) the hyperglycemia; and (2) the acidosis. I shall not speak of the danger ensuing from vascular lesions, because, although frequent in diabetics, they do not strictly belong to diabetes; they are due to accessory circumstances (syphilis, angiosclerosis, Bright's disease). Gangrene of the limbs from arteritis is not encountered in the serious diabetes of young subjects, but occurs in moderate diabetes of corpulent individuals presenting renal sclerosis as well.

I. Hyperglycemia.

Hyperglycemia favours suppuration. This is what surgeons principally feared a few years ago. Roser, Israël, and König insisted upon the necessity of reducing the glycosuria by proper diet before operating. To-day suppuration is much less feared; in aseptic operations this process is far from being fatal, and many cases could be quoted of perfect recovery with first intention. For suppuration to arise, not only is a predisposition necessary, but the bacteria as well, and a good

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operator should never introduce them into the operative wound.

The complications resulting from hyperglycemia protract healing, but usually they are not fatal. They can be dealt with by causing the hyperglycemia to subside by proper treatment, likewise the glycosuria. The treatment consists of the reduction of the carbohydrate intake. This prophylactic treatment is principally useful when the operation is to be carried out in regions which may be soiled by urine—as the perineum, for example.

When the surgeon is in presence of a suppurative process—phlegmon, carbuncle, moist gangrene—necessitating urgent interference, the cure of the hyperglycemia should be carried out as rapidly as possible. It is in these circumstances that fasting, with or without purgation, renders great service; there need be no fear of an aggravating action of the fasting on the acidosis—which has been considerably exaggerated by some—because I have been able to observe in several acidosic diabetics that an absolute fast decreased both the ammonuria and acetonuria.

II. Acidosis.

Acidosis is a far more serious menace; it causes post-operative coma, and is the cause of death of many diabetic patients. Becker, Landau, and Hoffa have recorded very impressive examples of post-operative coma occurring in diabetics, who, however, thanks to diet, no longer had any sugar in the urine. Death ensued in twenty-four hours, sometimes in several days, or at the expiration of a few hours only; the patient does not regain consciousness after the narcosis, and develops coma at once.

Various conditions influence post-operative acidosis—namely, the type of diabetes, the nature of the operation, the anesthetic used, and the treatment resorted to.

1. **The Type of Diabetes.**—In diabetics with denutrition and acidosis, the slightest operation presents exceptional gravity; chloroform is practically fatal in action; a simple incision, even without narcosis, may result in coma.

In diabetics without denutrition, but who are undergoing

an outburst of acidosis, the danger is also very great, but the resistance is better, so that the patient may survive both the operation and narcosis.

In diabetics without denutrition or acidosis, coma need not generally be feared. However, one should not be too optimistical, because an operation done in narcosis may cause acidosis to develop in a subject who previously did not have any. This I observed in a diabetic female who was given a chloroform narcosis of an hour's duration for a perineorrhaphy. Before the operation the urine did not contain any diacetic acid; at the conclusion of the operation, before consciousness was regained, the urine obtained by catheter gave a strong Gerhardt's reaction, and for three days the patient was in a dangerous condition. However, with an energetic alkaline treatment she recovered, and a few days later the acidosis decreased and finally subsided.

Hence examination of the patient before operation allows one to make a prognosis. Three degrees of gravity may be distinguished: (1) Diabetes with denutrition and acidosis; (2) diabetes without denutrition, but with an outburst of acidosis; and (3) diabetes without denutrition or acidosis.

2. **The Nature of the Operation.**—The nature and gravity of the operation influences the danger from acidosis. The major operative traumata and long interferences are the most redoubtable. The pre-operative emotion caused by the fear of the surgical act may also play a part. I saw in one case that it was the origin of an attack of serious acidosis in a diabetic without denutrition. From 0·32 gramme the acetone rose to 0·51 gramme, and a diaceturia which did not previously exist made its appearance. But, in reality, it is less the knife than the anesthetic that makes the danger of an operation in a diabetic subject.

3. **The Anesthetic.**—The most dangerous anesthetic is *chloroform*. It is even susceptible of provoking a mild acidosis in non-diabetic subjects. Rolland has found acetonuria frequently after chloroform narcosis, and diaceturia rarely. Baldwin has met with acetonuria after chloroform narcosis, as well as after the use of other anesthetics. In reality, in subjects who have neither diabetes nor other lesions of the

liver, the acidosis is merely trifling, and I have searched for it upon several occasions with Gerhardt's reagent in urine after operation without being able to detect it.

On the other hand, Nicloux, who has studied the decomposition of chloroform in the organism, has noted that it is accompanied by a removal of alkalies from the tissues in notable quantity, hence there is a tendency to acidification. If the organism is healthy, it will defend itself against acidosis and will repair its losses, but this will not take place in disease.

In diabetics, even without denutrition, chloroform may produce acidosis; the drug aggravates the intoxication and frequently causes coma. However, recovery may ensue, as I recently observed in a female with a very serious diffuse phlegmon of the forearm, which was amputated under chloroform narcosis. The stump finally underwent cicatrization; the patient still has her glycosuria, but the diaceturia has subsided.

In diabetes with denutrition complicated by acidosis, chloroform is lethal. It is also to be feared in patients with lesions of the liver. The toxic action of chloroform on the liver has been clearly set forth by Doyen, N. Fiessinger, Chevrier, R. Bénard, Sorrel, and Rolland, as well as by the cases reported by Quénu. Serious types of icterus are known to occur after narcosis with chloroform, and I have seen several cases of serious hepatic insufficiency, with or without icterus, rapidly fatal, developing after operation. Hepatic necrosis has been experimentally produced in animals, and urobilin, albumin, bile pigments, acetone, and glucose have been found in the urine after chloroform narcosis, as well as alimentary glycosuria induced by the ingestion of sugar. These findings indicate that serious functional disturbances of the liver ensue after the administration of chloroform. The tendency of chloroform to attack the liver undoubtedly is one of the principal reasons for the gravity of operations performed on this viscus.

Ether is generally supposed to have a less deleterious action than chloroform, but one must not rely upon this supposition, because I have seen death in coma take place in a woman with diabetes without denutrition, but presenting an outburst of acidosis, in whom every pre-operative and post-operative precaution had been taken.

Prolonged narcosis with *ethyl chloride* appears to be better tolerated by diabetics. I observed one case of diabetes without denutrition in which the patient withstood remarkably well a narcosis with this drug lasting fifty-five minutes for a mastoid operation. For a long time previous to the operation there had been traces of diacetic acid in the urine, and yet there were no post-anesthetic accidents, while on the day following the narcosis the diaceturia had not increased.

Boureau, who has had a very large experience in long narcoses with ethyl chloride, tells me that he has anesthetized seventeen diabetics with this drug, six of whom had acetonuria. They were all serious operations, lasting from twenty to sixty minutes, and requiring the absorption of 35 to 100 c.c. ethyl chloride. Some of the patients were quite old, yet in spite of this fact no post-operative death occurred.

Spinal anesthesia by lumbar injection of cocaine or novocaine is also to be preferred to chloroform or ether in diabetics. It was well tolerated by one of my patients who underwent disarticulation at the knee for gangrene; no acidosis reaction afterward appeared in the urine.

Local anesthesia or nerve blocking with cocaine, stovaine, or novocaine is the method of choice in diabetics. Several of my patients withstood this procedure well, and no acidosis ensued. Professor Reclus, whose large experience with this method of anesthesia is well known, tells me that he has used it with excellent results in amputations in diabetic subjects.

Pre-Operative and Post-Operative Treatment.—A vegetarian diet (dried vegetables, oatmeal) or milk diet, which combats the acidosis, and the exhibition of a large dose of sodium bicarbonate before the operation may decrease the dangers of acid intoxication. I have observed one case which furnished me with an almost schematic example. This diabetic subject with acidosis had to submit at several days' interval to amputation, with chloroform narcosis, of two toes presenting local gangrene. Both operations were exactly the same, but at the first interference I ordered 30 grammes sodium bicarbonate before operation, and the result was excellent; at the second interference this precaution was overlooked, with the result that the patient developed coma and died.

It has been suggested that injections of glucose might be

given as a prophylactic for acidosis. This is all very well for subjects who utilize the glucose, but in diabetics who do not burn it I can see no advantage, but rather disadvantage, in their use.

At any rate, surgeons appear at present to agree that a useless fast before operation is unnecessary, and some even systematically give a certain quantity of sugar immediately before operation to non-diabetic patients.

Although the general outline of the prognosis is at present known, it must not be supposed that cases always schematically follow the evolutions I have offered as examples. There are unforeseen successes and accidents due to the fact that we do not know all the conditions influencing acidosis. Otherwise put, one cannot be too prudent or far-sighted in the question of surgical interference in diabetics, and above all in the domain of narcosis.

Conclusions.

I will sum up in a few propositions the rules of conduct that appear to me to be the best for directing surgical interferences in diabetic patients:

1. Only operations of absolute necessity should be permitted in diabetes; particular reserve should be the rule in diabetes with acidosis. Nevertheless, it will sometimes be better to operate than to allow an infectious process to persist and to become generalized, hence killing the patient from septicemia or from the acidosis that the sepsis provokes.

2. If the interference is not urgent, it should be preceded by a treatment directed against the hyperglycemia and acidosis. This has as a basis: (1) A mixed diet with little meat, and reduction of carbohydrates if the patient presents no trace of acidosis, so that the hyperglycemia will disappear. (2) Dry vegetable diet, or a diet of oatmeal or milk if there is acidosis. (3) The exhibition of sodium bicarbonate in sufficient quantity to render the urine alkaline.

3. Immediately before the operation fasting is to be avoided. Forty grammes of sodium bicarbonate should be given shortly before the patient goes to the operating-room.

4. The choice of the anesthetic is of utmost importance. Local analgesia or nerve blocking with cocaine or its suc-

cedaneous products should be preferred above all, or spinal analgesia if nerve blocking is not sufficient. If general narcosis must be employed, ethyl chloride should be used, as both chloroform and ether are to be discarded in diabetes with acidosis.

5. After the operation sodium bicarbonate should be given *per os ;* but should this be impossible, an intravenous injection of a solution of the salt should be given in sufficient quantity to render the urine alkaline. If there is a strong acidosis reaction, 100 grammes of sodium bicarbonate must be introduced into the organism. As soon as the patient can be fed, he should be given vegetable soups, oatmeal mush, purées of dried vegetables, or milk. The alkaline treatment should be continued until every trace of acidosis reaction has disappeared.

[The conclusion in respect to the choice of anesthetics and analgesics arrived at by Professor Labbé has recently found absolute confirmation. In the *Presse Médicale,* May 21, 1921, a summary is given of the researches carried out by F. Widal, P. Abrami, and J. Hutinel on the hepatic changes produced by anesthetics, and communicated to the Académie des Sciences. These observers have found that hepatic insufficiency is invariably produced by chloroform, no matter for how long a time this anesthetic is given. Hepatic insufficiency is produced by narcosis with ether or protoxide of N when prolonged. On the contrary, these observers show that the hepatic cell remains uninjured when analgesia is produced by spinal or regional injections of syncaine, and they conclude: "In subjects having an hepatic taint in whom there is danger of complications due to hepatic insufficiency ensuing after general narcosis, it is interesting to note that a local analgesic, such as novocaine, even in large doses, does not determine any morbid functional change in the liver."

The results obtained by Widal, Abrami, and Hutinel have been confirmed by Jeanbrau, Cristol, and Bonnet, in a paper on "Anesthesia and Acidosis" (*Journal de Urologie,* May-June, 1921). From careful and detailed analyses of the urine in thirty-five cases of various forms of narcosis and analgesia these observers conclude: "The only product employed in our researches which does not increase the percentage of acidosis is syncaine. We can therefore conclude that spinal analgesia

with this drug produces the minimum amount of anesthetic shock . . . and *a fortiori* regional or local analgesia with syncaine is the method giving the greatest security . . . in all patients whose hepatic and renal functions are imperfect."

They also show that acidosis invariably occurs to a marked degree after chloroform narcosis, and that ether causes oscillations in the coefficient of acidosis, but not a progressive elevation, as occurs after chloroform narcosis.—EDITOR'S NOTE.]

CHAPTER XXVII

THE CLINICAL ASPECTS OF ACIDOSIS AND DIABETIC COMA

In diabetic coma the older writers distinguished between a premonitory phase and confirmed coma. Recent studies, founded on complete analysis of the urine, have justified this distinction, and show that there is reason to successively study: (1) A premonitory phase, often of very long duration, characterized by a state of acid intoxication, or, as is now commonly said, acidosis; and (2) coma, strictly speaking.

The Phase of Acidosis.

The name acidosis is given to a state of intoxication characterized by an accumulation of non-oxidised acid substances in the blood and body fluids. This denomination especially applies to intoxication from acids of the fatty acids, particularly β-oxybutyric acid and diacetic acid. The pathogenesis of acidosis being a question whose final solution has not yet been reached, I shall confine my remarks to the acetone compounds considered in the light of *stigmata of intoxication*, without deciding whether they play the principal part, or whether they are not evidences of an abnormal metabolism giving rise to other toxic substances.

The notion of chemical stigmata has resulted in the detection of the state of acidosis, even when it is larvate, to disentangle from the ensemble of symptoms observed in the course of serious diabetes those which belong to the diabetic process, and to constitute a syndrome of acidosis which occurs alone, or, what is more usual, in association with the syndrome of hyperglycemia.

The states of acidosis, larvate or complete, latent or patent, interrupted by symptomatic outbursts with a menace of coma, terminate sooner or later, but almost surely, in diabetic coma, and may last for weeks, months, or even years.

Their diagnosis and a general concept of their pathogenesis are of utmost interest to the clinician. He who knows how to recognize acidosis and treat this condition will be able to foresee the development of diabetic coma and prevent it by an appropriate hygiene and therapeutic measures.

Diabetic acidosis is made evident by a certain number of *chemical stigmata* and *clinical symptoms*. The former are constant and readily recognized; it is on them that the diagnosis of acidosis is usually based; they should be systematically searched for in every case of diabetes. The latter are inconstant, often concealed, and easily pass by unnoticed.

I. Chemical Stigmata.

The signs are derived from the urine and blood.

Urinary Acidity.—The urine is constantly acid; the percentage of the acidity is, in general, above the normal average; however, it usually does not attain very high figures. This is because the acids in excess, which are eliminated by the urine, are saturated by ammonia and other bases borrowed from the organism. The amount of 12·81 grammes, expressed in sulphuric acid, that I once met with at the onset of a diabetic coma, is exceptional.

The dosage of the acidity by Maly's procedure, modified by Denigès, gives higher percentages than those obtained by the usual methods. I have occasionally remarked a very considerable difference between the results obtained by both methods; while usually the differences are 1 to 2, they reached from 1 to 15 in one case of diabetes with acidosis. Perhaps this may have been due to treatment with sodium bicarbonate, which decreased the acidity measured by the ordinary method, while it had no action over the acidity when the dosage was made by Maly's procedure.

Resistance to Alkalization.—More characteristic is the resistance to alkalization offered by the urine by the ingestion of alkalines. When a normal subject has absorbed 10 grammes of sodium bicarbonate the urine is immediately alkaline, while in a diabetic in the state of acidosis the urine will remain acid even after rather large doses of alkalines. There are diabetics whose urine will remain acid after the absorption of 20, 50,

or even 100 grammes of sodium bicarbonate, and this very fact indicates a superproduction of organic acids difficult to saturate. However, a time always comes, excepting in fatal cases, at which the dose of bicarbonate will be found sufficiently large to saturate all the acids and to render the urine amphorteric or even alkaline.

Blum (*Therapie der Gegenwart*, March, 1910), having remarked a relationship between the dose of sodium bicarbonate necessary to alkalize the urine and the average dose of β-oxybutyric acid excreted in twenty-four hours, adopted it as a clinical procedure for approximately estimating the degree of acid intoxication. From his observations he concludes that in slight acidosis from 10 to 20 grammes of sodium bicarbonate are necessary to produce saturation, while in medium acidosis from 20 to 30 grammes will be required, and 50 grammes or more in cases of serious acidosis. Finally, in certain cases of fatal acidosis ending in coma it will be found impossible to alkalize the urine. In one case of imminent coma, from which the patient recovered by intensive alkalization, I was obliged to give a daily dose of 250 grammes sodium bicarbonate on the first day, 160 grammes on the next two days, 120 grammes on the fourth and fifth, and 100 grammes on the sixth day, when the urine at last became alkaline.

This procedure, which is exceedingly simple, gives very useful clinical data, both for the prognosis and treatment. The reaction of the urine is ascertained with litmus paper or with phenolphthalein. It should be known that the alkaline reaction with litmus is easier to obtain than with phenolphthalein; there are urines that are more distinctly alkaline to litmus and which nevertheless are acid to phenolphthalein.

Ammonuria.—The dosage of ammonia is easy to obtain with the Soerensen-Ronchèse formol technique. Precaution should be taken to collect the urine in a very clean vessel, and then to add a little xylol or chloroform to prevent ammoniacal fermentation, which would completely falsify the result.

The quantity of ammonia excreted in the urine reveals the existence and intensity of the acidosis. Walter's experiments have, in fact, shown the relationship existing between the intoxication from a mineral acid and the ammonuria; the experiments of H. Labbé and Violle have verified this fact,

and have established the existence of a proportionality between the ingestion of acid and the excretion of ammonia.

On the other hand, since Hallervorden (*Archiv für exp. Path.*, 1880) observers have noted the appearance of large quantities of ammonuria in the urine of serious diabetes, and this was one of the reasons which led Stadelmann to regard diabetic coma as the result of acidosis. From 2 to 3 grammes of ammonuria in the urine are not uncommon in cases of serious diabetes, and already indicate a mild degree of acidosis. When the intoxication is more marked, when it leads to coma, from 6 to 8 grammes will be found (Naunyn, Stadelmann, M. Lévy, von Noorden, Sandmeyer, Külz), or even as much as 12 grammes *pro die* (Stadelmann).

The increase of the ratio of ammoniacal nitrogen to the total nitrogen of the urine places this ammonuria well in evidence. Normally, this ratio equals from 5 to 6 per 100. In diabetics with acidosis it reaches from 20 to 25 per 100, and has even been known to attain 45 per 100.

The increase of the total amount of ammonuria indicates that a certain quantity of ammonia is employed for saturating acids, especially β-oxybutyric acid, which plays the chief part in diabetic acidosis, and is eliminated in combination with it. Therefore, one has attempted to calculate the quantity of oxybutyric acid according to the amount of ammonia excreted, but this method only gives very indefinite results.

The Coefficient of Ureogenic Imperfection.—Another way of calculating the elimination of ammonia consists of establishing the ratio—

$$\frac{\text{Ammoniacal nitrogen}}{\text{Ammoniacal nitrogen} + \text{uric nitrogen}},$$

that Maillard has suggested for measuring nitrogenous metabolism, and which Lanzenberg has studied under the term of the coefficient of acidosis, an unfortunate expression in my opinion, because this ratio simply indicates the quality of the nitrogenous metabolism, and that if it is high in cases of acidosis, it can likewise be so in subjects with hepatic insufficiency without acidosis. Normally, this ratio at most reaches 5 to 7 per 100; in acidosis I have seen it attain 20 to 30 per 100.

Amino-Aciduria.—In the urine of diabetes with acidosis one finds an exaggerated proportion of amino-acids. While in the normal state of health the amino-nitrogen, which represents a part of the total ammoniacal nitrogen measured by the formol method, varies from 0·05 to 0·35 gramme in twenty-four hours, and never goes beyond the latter quantity, and the ratio of amino-nitrogen to the total nitrogen, $\frac{\text{A-N}}{\text{TN}}$, varies from 1 to 3 per 100, one will find in acidosic diabetics quantities of amino-nitrogen reaching up to 3 to 4 grammes in twenty-four hours, so that the ratio $\frac{\text{A-N}}{\text{TN}}$ will attain 10 or even 20 per 100.

The amino-aciduria that I have studied with Bith in his thesis (Paris, 1913) is the index of an incomplete nitrogenous metabolism, and is only indirectly a sign of acidosis; but it is nevertheless an important one, which can serve to measure the degree of intoxication and foretell the advent of coma.

Colloidal Nitrogen.—The same can be said of colloidal nitrogen, whose excretion I have studied with Dauphin (*Annales de Médecine*, September, 1918). It corresponds to incompletely metabolized nitrogenous matters belonging to the group oxyproteic acids and polypeptids. In the normal state colloidal nitrogen reaches the urine in small amounts, and the ratio of colloidal nitrogen to the total nitrogen, $\frac{\text{CN}}{\text{TN}}$, varies from 0·25 to 1·45 per 100. In diabetics without denutrition the amounts are not much larger, being from 0·8 to 2·24 per 100. But in diabetics with denutrition and acidosis the ratio increases to 3·29 and up to 7 per 100.

β-Oxybutyric Acid.—It is especially to β-oxybutyric acid that the intoxication ending in diabetic coma is attributed, hence its dosage is extremely important, in order to characterize the acidosis. Until quite recently the procedures employed for the dosage of β-oxybutyric acid were delicate, long, and gave doubtful results; therefore we only employed them exceptionally. With Van Slyke's method, which is technically easy and sure, the dosage of this acid has become more generally resorted to. This procedure doses the total acetone compounds; to obtain the percentage of β-oxybutyric

acid, both acetone and diacetic acid must be dosed by the Messinger-Hüppert method, and then subtract the figure thus obtained from that obtained by Van Slyke's procedure. For that matter, this operation is useless, as it has seemed to me that the percentage of acetone presented little practical interest, so that I have usually been content with the dosage of the total acetone compounds, in which β-oxybutyric acid represents the major part.

The amount of β-oxybutyric acid in the urine of subjects in a state of acidosis is very variable, a few grammes to several hundred being found. The quantity of 30 grammes already indicates a serious acidosis with a menace of coma, although not immediate. Patients who have presented such high percentages do not usually survive for any length of time. The progressive increase of the acetone compounds renders the prognosis serious; it indicates an outburst of acidosis, and one never knows whether or not it may not end in coma. It is, however, susceptible of retrogression, as I once observed in a case where the acetone compounds progressively increased from 42 to 92 grammes, after which they decreased to 36 grammes.

Alkaline treatment will provoke excretion of the acetone compounds. Thus, Magnus Lévy noted that the excretion of β-oxybutyric acid reached 60 grammes daily in a child who was receiving 50 grammes sodium bicarbonate a day. In a patient menaced with coma and treated with sodium bicarbonate (250 grammes a day for the first two days) I noted on the third day an elimination of 120 grammes of acetone compounds. These are instances of diabetic coma cured by bicarbonate inducing a high excretion of acetone compounds. In a child of 13 years of age, weighing 30 kilogrammes, Magnus Lévy obtained the following figures:

Date.	*Remarks.*	*Digestion of $NaHCO_3$.*	*Diacetic Acid.*	*β-Oxybutyric Acid.*	*Total Acids.*
		Grammes.	Grammes.	Grammes.	Grammes.
1st day	Commencing coma	60	18·3	56·6	74·2
2nd ,,	Coma at maximum.	210	33·8	81·6	109·5
3rd ,,	Coma ceased ..	90	23·6	119·0	157·1
4th ,,	Recovery ..	99	25·6	57·4	88·4

In cases ending in death the excretion of β-oxybutyric acid never attains such a degree; the acids are retained in the tissues and poison the organism. Thus, Wolfe found 23 grammes in the urine of a comatose patient; Minkowski, 23 grammes and 53 grammes respectively; Baumann, 10 grammes; in nine cases Magnus Lévy found a maximum of 31 grammes of β-oxybutyric acid excreted.

During the evolution of serious diabetes, β-oxybutyric acid always appears in the urine. Magnus Lévy, Sandmeyer, Herter, and von Noorden have invariably found it; and Lévy refutes the contradictory findings of Rumpf, and Munzer and Strasser, reported at a time when the procedures of dosage were inadequate. Contrary to the opinion of some observers, it has even appeared to me that β-oxybutyric acid may appear in the urine before acetone. However, the large excretions of this acid invariably accompany acetonuria and diaceturia.

Is there a constant ratio between the amounts of the various acetone compounds excreted ? Von Noorden believed that there was, and attempted to establish a scale of proportionality between acetone and β-oxybutyric acid. My researches have shown that this constant ratio does not exist; the proportion of diacetic acid varied in its relation to that of β-oxybutyric acid to the extent of 0·54 to 55 per 100; there is always more β-oxybutyric acid than diacetic acid, and in the majority of cases the ratio is less than 15 per 100.

Diacetic Acid.—Diacetic or acetylacetic acid is found in the urine of diabetics in the state of unstable combination in the form of ether; it is an intermediary product between β-oxybutyric acid and acetone, and can be derived from either.

It is easily detected in the urine with Gerhardt's or Legal's reagents. The reaction obtained with the former is characteristic. When one drop of officinal perchloride of iron is allowed to drop into a test-tube containing urine, itself containing diacetic acid, a red colour develops similar to that of port or very old Burgundy wine; while if this acid is absent, the perchloride of iron will fall to the bottom of the tube without changing the colour of the urine.

In order that the perchloride reaction shall be significative, the patient must not have previously ingested antipyrine or

salicylic compounds, as they are susceptible of giving rise to a similar colouring. There is, however, a means by which we may know whether or not the reaction obtained is due to diacetic acid or salicylic acid. If the urine is allowed to boil for five minutes in the tube the diacetic acid will be eliminated, as it is volatile, while salicylic acid will remain, so that if the reaction does not occur after ebullition it will be due to diacetic acid. It is still simpler to carry out Legal's reaction at the same time, as it is not influenced by the presence of salicylic acid, and it never fails to be positive in the presence of diacetic acid.

Gerhardt's reaction presents a high degree of clinical interest. It very quickly reveals the existence of acidosis as well as its degree. Its prognostic value is considerable, because whenever it is present in a diabetic urine special therapeutical precautions should be at once taken. Unfortunately, it does not lend itself to the dosage of diacetic acid.

All the procedures that have been proposed for this end have been found useless; the coloured scales employed for this purpose are far from being exact, so that the results obtained are lacking in precision.

While awaiting a more perfect method, the best procedure we have for appreciating the intensity of Gerhardt's reaction is to carry out the reaction in definite proportions (9 c.c. of urine for 1 c.c. officinal perchloride of iron) in test-tubes of the same calibre, hence comparison is made easier. According to the colour comparable to port wine, Burgundy, or Malaga, the reaction is said to be indistinct, distinct, strong, and intense, and on paper by the sign +, ++, +++, and ++++.

Legal's reaction indicates the presence of acetone as well as diacetic acid, but as it gives a colouring nearly twenty times as strong when the latter is present, it is above all a reaction for diacetic acid. It has been criticized by Porcher, who makes the reproach that it is positive in the presence of substances other than acetone compounds. On the other hand, Denigès regards it as very sensitive, quite capable of revealing 1 to 2 centigrammes of diacetic acid per 1,000 c.c., and he consequently prefers it to Gerhardt's reaction.

The most practical technique for Legal's reaction is, according to my experience, that given by Imbert and Bonnamour. The formula of the reagent is:

Glacial acetic acid	10 c.c.
10 per cent. solution of sodium nitro-prussiate ..	10 ,,

This should be preserved in a yellow glass bottle.

To 10 c.c. urine in a test-tube the above reagent is added. The tube is then shaken and liq. ammoniæ is poured over the surface of the urine without mixing it. At the surface of separation of the two liquids a disk appears in from one to five minutes, at first pink and then violet, whose thickness and intensity give an approximate dosage of the diaceturia present.

The results obtained by Legal's reaction are usually comparable with those given by Gerhardt's; they corroborate each other. But Gerhardt's reaction is much less sensitive than Legal's, although in practice this is an advantage which imparts a greater prognostic value to the former. The verification of diaceturia naturally indicates that acidosis is also present. Does this imply that it is useless to search for the other stigmata ? Certainly not, because they will add to the precision of both the diagnosis and prognosis. They are all the more important because the elimination of the various abnormal substances in acidosis is far from being parallel.

Acetone.—Acetone exists in the urine of acidosic diabetics in larger amounts than normal. Its recognition and dosage are obtained by Lieben's procedure—namely, the formation of iodoform in the presence of potash lye and an iodine-iodide solution.

By carrying out this reaction according to a special technique described by Mauban, the approximate amount of acetone contained in the urine can be ascertained at the bedside. Ten c.c. of urine are mixed with 3 c.c. of potash lye, then filtered, after which Gram's fluid is allowed to drop on the surface of the urine without mixing. If the amount of acetone in the urine is above normal, a small opaque disk of iodoform forms at the line of demarcation of the two liquids. This disk does not form in normal urine, and is all the thicker the greater is the quantity of acetone. Its thickness measured in millimetres gives an approximate dosage of the acetone present.

The Messinger-Hüppert technique, now most generally employed, gives the quantity of preformed acetone in the urine, as well as the acetone resulting from the splitting up

of the diacetic acid. Hence the percentages are always higher than those obtained by Lieben's method.

Acetonuria measured by Lieben's reaction varies in the same way, but not in the same proportions, as the diaceturia estimated by Gerhardt's reaction. Even in cases of diabetic coma, the proportion of preformed acetone found in the urine, although higher than normal, always remains relatively low; it does not increase to the same degree as do diacetic acid and β-oxybutyric acid. Inversely, there are diabetics who eliminate amounts of acetone considerably higher than normal, and yet do not present any symptoms of acidosis.

Hence the true acetonuria has less value than the diaceturia in estimating the acidosis, while the exact dosage of preformed acetone by Lieben's method is less interesting than the dosage of the acetone compounds by Messinger's procedure.

The Comparative Prognostic Value of the Stigmata of Acidosis.—Of the various stigmata of acidosis, that one which best indicates the degree of intoxication and better permits of appreciating the danger is unquestionably β-oxybutyric acid, since this body appears to play the principal part in the intoxication. The most perfect datum is furnished by the dosage of the total oxybutyric acid, preformed and derived from the diacetic acid.

The dosage of the total acetone compounds by Van Slyke's procedure allows one to follow the evolution of the acidosis in diabetics with the utmost precision. The preformed acetone has no great signification; it indicates that there is acidosis, but not the degree.

Diaceturia, measured by Gerhardt's or Legal's reaction, possesses a clinical signification of the highest order, because as long as Gerhardt's reaction is negative acidosis need not be apprehended; even if there are large amounts of acetone in the urine, there will never be dangerous quantities of β-oxybutyric acid present. On the other hand, a strong Gerhardt reaction indicates a strong acidosis, and is a danger signal.

Ammonuria is quite closely related to the amount of acids eliminated, but on the condition that the patient is not at the time undergoing alkaline treatment, because in these circumstances the ammonuria loses its signification. In this

case one may, in fact, find a very mild ammonuria regardless of a high excretion of β-oxybutyric acid.

The urinary acidity is a vague indication, because the acids which are eliminated in excess are partially saturated by the ammonia, and therefore the urinary acidity does not increase in proportion to their excretion.

The resistance to alkalization unquestionably has a greater signification, but it only gives data after an alkaline treatment has been given, and the conclusions that one may come to are wanting in precision.

To conclude, I would say that acetonuria does not indicate the danger of acidosis, while diaceturia does. The excretion of β-oxybutyric acid measures the danger.

To thoroughly appreciate an acidosis the various stigmata should be estimated. In fact, they do not all vary proportionally, and, what is more, there is in the value of each of them considerable quantitative differences from one day to another—a fact that has not been explained, as is made evident by the writings of Stadelmann, Magnus Lévy, Naunyn, Schwarz, Baer, Blum, and myself (M. Labbé, H. Labbé, and F. Nepoeux, Société de Biologie, 1921).

The Cerebrospinal Fluid.—The acetone compounds, which reveal acidosis, enter the cerebrospinal fluid, and can there be revealed by their chemical reactions. I have pointed out (*Paris Médicale*, January 24, 1914) that this test can be utilized to make a diagnosis of diabetic coma in certain circumstances where doubt exists.

The Condition of the Blood.—In diabetic acidosis (1) the alkalinity is decreased, (2) the carbonic acid tension in the plasma is lowered, and (3) the serum is lactescent on account of the lipemia present.

I. The decrease of the alkalinity does not exist in ordinary diabetes, but is very marked in diabetic coma, and in no other morbid condition does it attain such a high degree. The figures obtained by various procedures by all those who have studied this question agree in this respect. Successive dosages in the same patient reveal the progressive fall of the alkalinity. From these figures it becomes evident that the alkalescence only falls at the terminal phase of coma, so that one cannot

derive any data relating to the diagnosis of acidosis from dosage of the alkalinity of the blood.

II. The decrease of carbonic acid in the blood-plasma is due to the fact that β-oxybutyric acid in excess forces the carbonic acid out of the plasma and takes the place of the latter. The dosage of the carbonic acid of the blood is therefore the index of the degree of acidosis.

It can be effected by Van Slyke's procedure. Joslin gives the proportion of 53 to 77 c.c. CO_2 per 100 c.c. in normal adults. In children the proportion is from 40 to 55 per 100. During diabetes with acidosis the percentage of CO_2 falls below 50 per 100.

The dosage can be made by either Fridericia's or Marriott's procedures, which are based upon the concordance existing between the carbonic acid of the blood and the air in the alveolæ. Austin and Jones, and Joslin, have carried out researches on this question. In the normal state the tension of CO_2 in the alveolar air, expressed in millimetres of Hg, varies between 38 and 45. A slight acidosis will lower it from 38 to 32; a medium acidosis from 32 to 28; an extreme acidosis causes it to drop below 25. Joslin has seen it as low as 15 and 9 in diabetic coma.

The study of the respiratory exchanges with Laulanié's apparatus also shows a drop in the respiratory quotient in acidosis to below normal.

III. In diabetic coma the lipemia attains a degree unknown in any other pathological condition. The serum is lactescent, the blood looks like chocolate, and when it coagulates a layer of fat forms on the surface of the clot. Chemical analysis shows, instead of 8 to 10 per 1,000 of total lipoids, 20 to 50 per 1,000, 94 per 1,000 in Bloor's case, and even to 262 per 1,000 in Klemperer's patient. The latter observer believes that true diabetic coma is accompanied by lipemia in the majority of cases. However, he has reported typical cases in which the lipemia was only 6 grammes and 7 grammes per 1,000 c.c. Dennstedt, Rumpf, and Stadelmann have noted the absence of lipemia in several cases. It would consequently seem that, although frequent in diabetic coma, it cannot be regarded as constant.

When very extreme, the lipemia can, according to Heine,

be detected by the ophthalmoscope; the vessels appear in pale, cloudy streaks against a pink fundus.

The Relationship between Acidosis and Glycosuria.—Acidosis is usually met with in serious diabetes with extreme glycosuria. However, some of these diabetes may last for a long time without presenting stigmata of acidosis. On the other hand, in diabetics in a state of acidosis the glycosuria may subside from the influence of diet. Briefly, the syndrome of hyperglycemia and the syndrome of acidosis, although often associated, may occur singly. Can it be said that there is a balancing between the two, that the cessation of the glycosuria by strict diet causes the acidosis to develop, and that the reappearance of the glycosuria causes the acidosis to subside ? Certainly not, because it is not the glycosuria that is important, but rather the tolerance of the diabetic for carbohydrates.

In reality, a distinction must be made between the acidoses of diabetes without denutrition, which are ordinarily moderate and curable, and those of diabetes with denutrition, which are generally progressive, serious, and fatal.

This is what Luthje expresses by saying that, as long as the diabetic burns the carbohydrates derived from the food—that is to say, as long as his glycosuria can be reduced by diet—he can have a mild acidosis without menace of coma; the danger begins when the patient no longer burns them, and when his glycosuria can no longer be controlled by diet. Luthje attributes this aggravation to the fact that the carbohydrates being no longer utilized, their anticetogenous action is no more in play, so that the organism does not set up a defensive action against the acidosis. Von Noorden is not of this opinion, and points out that there is no relationship between the degree of tolerance and the quantity of oxybutyric acid excreted, and he mentions instances of diabetes in which, although there was a rather high tolerance, large quantities of the acetone compounds were excreted. Magnus Lévy also refers to diabetics who eliminated notable quantities of oxybutyric acid with much acetone, and yet tolerated 40 grammes of starch without presenting glycosuria.

I have, in collaboration with H. Labbé, adduced reasons why the acidosis of diabetes cannot be attributed to the

privation of carbohydrates, but rather to the lack of their combustion. Far from being produced by fasting, this treatment decreases the acidosis.

II. Clinical Signs.

The symptomatology is often larvate. There are diabetics in whom acid intoxication reveals itself by no clinical sign whatsoever. It is only revealed by coma, which appears unexpectedly or when a search for the chemical stigmata is made.

There are other cases in which the acidosis betrays itself by a single symptom, such as headache, disturbances of vision, general depression, or emaciation, so that the diagnosis will be impossible if the urinary stigmata are overlooked.

In cases where the acidosis gives rise to a complete symptomatology, one must not expect to find an immutable clinical picture, since the accidents develop in a very variable order. Only certain of the more constant symptoms impart a peculiar clinical physiognomy to acidosis. These are particularly the physical and psychical depression, general discomfort, emaciation, anorexia, and progressive somnolence.

The General Disturbances.—Physical depression is very marked. It gives rise to a feeling of profound dejection and intense fatigue, and the patient's distress is imparted to his expression and bearing. He complains of indefinite discomfort, although unable to give it any localization; he suffers in all his organs, and refers to pain either in the head, chest, abdomen, or limbs.

Emaciation is usually rapid; it is largely due to anorexia, digestive disturbances, and difficulty in feeding. But even when the diet is closely watched, the emaciation will nevertheless continue, and, no matter what is done, the diabetic loses 2 or 3 kilogrammes a year. The emaciation involves the muscular mass, as is shown by the nitrogen balance, which is constantly deficient. There is progressive denutrition. This destruction of muscle certainly plays a part in the progressive weakening of the subject. Alkaline treatment will, in some cases, cause the emaciation to cease.

Œdemas, especially developing in the lower limbs, may hide the emaciation. When the patient is regularly weighed, the weight may sometimes be found to increase, although there is no correlative amelioration of the general health. In these circumstances one should be suspicious and look for œdemas in the declivous parts. These œdemas are often accompanied by chloride retention; a diet rich in salt favours their production; a dechloridation diet will help them to subside. Alkaline treatment plays a primordial part in their pathogenesis.

Briefly, nothing is more unstable than the weight of diabetic subjects; it increases or falls by periods, and often without any apparent reason. The instability of the ponderable equilibrium is related to the instability of the mineral equilibrium, with saline retention or discharges occurring in these subjects.

The temperature and pulse do not usually undergo any changes in acidosis unless coma ensues.

The odour of the breath is one of the symptoms which most struck the older observers. Lecorché used to say that he could make a diagnosis of diabetic coma as soon as he entered the room of a patient by the smell. It is an aromatic odour like chloroform or acetone, and is explained by the fact that the pulmonary surface is the principal channel for the excretion of acetone.

Küssmaul did not believe that this was a constant symptom, while Magnus Lévy states that he has rarely found it absent. It seems to me that its importance has been greatly exaggerated. I have seen diabetics die in acidosic coma who had never given off the odour of acetone in the breath, and upon more than one occasion I have thought that I could detect this smell in subjects who presented neither the phenomena of acidosis nor acetonuria. This strong aromatic odour of the breath is often confounded with that of patients whose tongue and mouth are dry, whether this be due to diabetic coma or some other affection.

The Nervous Disturbances.—Headache is rather frequent, but is far from having the intensity and persistency of the cephalalgia of uremia. It is rather a sensation of heaviness than true pain.

Psychical depression is very marked; the patient is incapable

of thinking or reasoning; he repeats his words, expresses himself with difficulty, and loses the thread of conversation in explanations; the memory presents lacunæ. It is to these patients that Lasègue's saying in reference to diabetics "who lack appetite for both work and thought" applies. It is as if a veil was spread over their intelligence.

Somnolence is the most characteristic phenomenon. The patient presents continual torpor and a desire to sleep. He does not come out of this state of semi-sleep excepting when spoken to, and when left to himself he drops off to sleep. This somnolence occasionally assumes the aspect of narcolepsy —that is to say, those attacks of sleep that seize people in the midst of their occupations. The somnolence tends to increase with the degree of acidosis, and if treatment is not instituted it will, little by little, give way to coma. Inversely, during the night the somnolence is replaced by insomnia.

At other times a state of excitement predominates. The subject is restless like an alcoholic, and this restlessness may develop into a maniacal paroxysm. Delirium is most uncommon.

Visual disturbances are rather frequent. The sensation of a mist before the eyes is complained of, or there may be a decrease of the visual acuity, sometimes suddenly developing amaurosis, as in uremia; or there may be vertigo accompanied by an uncertainty of gait and titubation. The condition of the pupils presents nothing characteristic, and they react normally.

Paralyses do not belong to the syndrome of acidosis, but, when they develop, uremia or cerebral hæmorrhage must be suspected. The subject of epilepsy in relation to acidosis has already been discussed in another chapter (see Chapter VIII.), so that it needs no further reference here.

I am unaware whether or not *tetany* has been mentioned by observers during acidosis. For my part, I have observed in a diabetic with acidosis a slight ictus without complete loss of consciousness, followed by a paroxysm of temporary contracture of the right arm of tetanic type, which disappeared without leaving any traces.

Can *chorea* due to acid intoxication occur ? This may be doubted, because the majority of observers do not refer to this

accident. Ramon y Cajal has recorded one case of unilateral chorea occurring suddenly in a diabetic, but in this case there was no acetonemia.

The question may nevertheless be raised. In fact, I followed the evolution of an extremely intense left-sided hemichorea lasting for more than three months in a young woman with diabetes and acidosis. There was violent agitation of the arm and leg, with continued rigidity; walking was impossible; the patient could not use her left hand; while the face was likewise involved. There were no disturbances of sensibility, reflexes, or sphincters. Insomnia was almost complete at night, while during the day there was a certain degree of somnolence. An intensive alkaline treatment had no very evident action over the chorea, so that its pathogenic connection with the acidosis is not demonstrated. But my confrère Sicard, who followed the case with me, told me that he had previously observed a similar case of hemichorea in a woman with diabetes and acidosis who died in coma. This coincidence should be noted.

Lépine observed a concordance between acetonuria and mental disturbances—melancholic delirium with suicidal ideas—in a diabetic female.

Digestive Disturbances.—These are principally characterized by severe anorexia, a disgust for any kind of food, which renders feeding very difficult and also partially explains the emaciation of the patient. The sudden appearance of inappetence in a diabetic whose appetite was previously normal or even excessive should lead the physician to fear the advent of coma.

The *tongue* is usually dry and the thirst intense.

Vomiting of food or bilious vomiting still more increases the difficulties of feeding. Their sudden onset sometimes marks the beginning of coma. Vomiting is especially frequent in diabetic children.

Diarrhœa, accompanied by sudden abdominal pain, frequently recurring, should be regarded as a signal of the development of coma. In a case of coma which ended in death in twenty-four hours, I noted an onset with incoercible diarrhœa. One should be suspicious of all forms of digestive disturbances occurring without any apparent cause in a diabetic subject

in a state of acidosis. One is apt merely to suspect a simple indigestion when, in reality, coma is developing.

The *abdominal pains* related to acidosis possess a special character. Most usually it is an epigastric pain, deep-seated, very violent, and not increased by pressure, similar to that met with in uremia. It may be accompanied by fainting. Occasionally the patient will locate the painful sensation in the right hypochondrium, or it may be general throughout the abdomen. It is either continued or intermittent. Lereboullet has pointed out the prognostic significance of this epigastralgia.

The *respiratory disturbances* are above all marked by a very special type of dyspnœa to which Küssmaul first called attention, and which for him was the signature of diabetic coma. The inspiration is deep, sighing, noisy, and followed by forced expiration, likewise loud in quality. Both phases of the respiration are separated by a pause. The rhythm is regular and not accelerated. It is the " deep respiration " of German writers. Although the patient complains of respiratory distress, and although these changes might suggest the idea of some functional obstacle, there is nevertheless no lesion of the heart or lungs, nor, for that matter, is there any cyanosis. Like the dyspnœa of uremia, that of acidosis is a dyspnœa *sine materia*.

The dyspnœa of acidosis is far from always being as characteristic as Küssmaul has described it. In some cases it can hardly be recognized, but if closely watched one will, however, detect a slightly sighing respiration, while from time to time speech is interrupted by a deep inspiration, as if the patient is out of breath from talking.

Ebstein especially has discussed the diagnostic value of this symptom. He pretends that he has seen deep respiration alternate with the Cheyne-Stokes type, or replaced by it altogether. On the other hand, he states that he has seen deep respiration in chronic nephritis. These statements appear to me to be exaggerated. It is very possible that in a diabetic there may be an association of renal lesions which would explain the production of the Cheyne-Stokes rhythm, while in uremia one sometimes meets with a loud respiration which, although not presenting the Cheyne-Stokes type, is nevertheless not identical with the respiration described by

Küssmaul. The diagnosis is not always easy between the coma of acidosis and that of uremia.

I would therefore conclude that deep respiration is a common symptom, although not constant, and that it has a great diagnostic value, but that one cannot deny, as Naunyn does, the typical character of the coma in cases where this symptom is absent. It is a bad habit to designate diabetic coma by the term of dyspnœic coma, as we have much more certain diagnostic signs to be derived from the urine.

Urinary Disturbances.—Under the heading of Chemical Stigmata I have described the chief changes of the urine in diabetes with acidosis.

A decrease in the *diuresis* has also been described. It is often only observed in the final phase, when the patient is in deep coma; or it may simply be due to a reduction of food and drink.

Decrease of the glycosuria has been met with in the premonitory phase of coma, and consequently it has been said that when the glycosuria diminishes in a diabetic subject one should become suspicious. In reality, the glycosuria does not usually decrease in diabetes with acidosis. It may persist in large amount up to the final phase of coma. It is only during the last twenty-four hours that the glycosuria markedly decreases, perhaps on account of defective elimination. When the glycosuria diminishes in the premonitory phase of coma, this is generally due to a reduction in the intake of food on account of the anorexia present. Perhaps also the decrease of the glycosuria has been wrongly interpreted, because this has often been seen to take place in diabetics who have suddenly been subjected to a strict meat diet, which may itself produce coma.

Albuminuria occurs occasionally or increases in acidosis.

Külz has described short, broad, pale granular casts in the urine of patients with diabetic coma, sometimes covered with red blood-corpuscles or renal cells; in a test-tube they form a thick, cloudy, white sediment. Although these casts may be present in the absence of coma when the patient is suddenly subjected to a too severe diet, their increase nevertheless indicates imminence of coma (Külz and Aldehoff).

The majority of observers state that they have seen these

casts in the urine of diabetic coma. They appear at the onset, or a day or two before. Aldehoff has even found them in cases where there were slight signs of acidosis, and saw them disappear with the retrogression of these signs. If by exception they are absent from the urine, they will be found at autopsy in the renal canaliculi, which they partially obstruct (Lépine). Magnus Lévy is not convinced that their production is the result of the action of the acidosis on the kidney, although he recognizes that they possess a great diagnostic value. Naunyn and Blum have never seen them. As far as I am concerned, I have found them in one case of diabetic coma, but I have not met with them in cases of acidosis without coma, although I searched for them.

The Evolution of Acidosis.

Nothing is more irregular than the evolution of acidosis. It is often interrupted by one or several outbursts of intoxication, with menace of coma; either spontaneously or influenced by treatment, the outbursts subside and the acidosis becomes latent. Sometimes at the onset the acidosis completely ceases and the chemical stigmata disappear. At a more advanced phase of the morbid process the acidosis will not disappear; quite on the contrary, it continues to increase, and if the patient escapes one menace of coma he will die in the next one.

Lecorché described a chronic, recurring type, characterized by successive attacks of acetonemia, as well as an acute form of acidosis, overwhelming coma suddenly developing in the midst of apparent health. The knowledge derived from the stigmata of acidosis shows that these chronic forms are much more frequent than was formerly supposed, and that they are the rule rather than the exception. The duration of the premonitory phase of coma is no longer counted in days, but rather in months or even years.

Coma.

Diabetic coma presents the fatal term of the states of acidosis. The depression reaches an extreme degree, anorexia is absolute, and somnolence becomes gradually more profound. It is complete annihilation.

Symptoms and Onset.—It usually succeeds a more or less long period, marked by premonitory accidents. Sometimes it commences suddenly in the midst of apparently good health in a diabetic who only offered the chemical stigmata of acidosis.

The onset is marked by intense epigastric pain, repeated vomiting, or attacks of diarrhœa, headache, or vertigo.

The coma of acidosis frequently becomes added to some complication occurring in a diabetic. During an extensive gangrene of a limb, the evolution of a carbuncle, a pneumonia, or a generalization of tuberculosis, a state of depression and somnolence develops ending in complete coma.

Phase of Full Development.—When coma has become constituted, the patient is inert, incapable of answering questions, or of swallowing food or drugs; he is insensible to pricking or pinching of the skin.

The face is violet rather than red and swollen, the skin is usually cold, the limbs slightly cyanotic.

The state of the pupils offers nothing characteristic; usually they are dilated, sometimes contracted, and not very contractile.

Krause has called attention to the considerable decrease of the tension of the globes of the eye, which he has met with in some twenty cases, a few hours before death. In accord with Blum, I consider this symptom inconstant and even rare, and I do not believe that it can be used to characterize diabetic coma.

Respiration is deep, noisy, stertorous, and often presents the rhythm described by Küssmaul.

The central temperature often remains normal. Frequently it drops. Even when it was previously febrile, it may progressively fall and become subnormal. De Gennes has seen it fall to 96° F.; Magnus Lévy mentions a case in which before death it was only 85° F. On the contrary, the temperature, which was low, rises during the phase of agony; Lecorché has seen it rise from 96° to 101·5° F. Finally, it is less uncommon than has generally been admitted to see the temperature progressively go up from the onset of the premonitory disturbances until death. In a case of coma arising during the evolution of a carbuncle of the neck the temperature, which previously was hardly more than 98·6° F., progressively ascended during

the last three days, and reached 103° F. before death. Briefly, there is no precise rule in this respect; it only can be said that thermic regulation is profoundly disturbed.

The pulse is usually accelerated, the beats ranging from 120 to 140 per minute; but here again there is nothing regular. Thus, with a temperature of 103° F. in the case I referred to, the pulse was 80. The heart sounds are regular and weak. The blood-pressure progressively falls to 12, sometimes to 7 millimetres Hg.

The diuresis usually diminishes, and may even completely cease, but a high polyuria may persist until the end. The glycosuria decreases on account of the inanition; it may even completely cease if coma supervenes in a diabetic whose tolerance for carbohydrates is not completely abolished, and if it lasts for several days. Some instances have been reported in which diaceturia was absent (Stadelmann, Wolpe), but these cases are now old, and may have been erroneously observed. I have sometimes seen weak acidosis reactions in the urine of comatose patients, but I have never known them to be absent.

The state of the reflexes is variable, and often remains as it previously was; the patellar reflexes may persist up to the time of death.

Evolution.

The evolution of diabetic coma is rapid. Its duration is difficult to fix. If it be counted from the moment at which the premonitory symptoms of acidosis develop it will be a few days, rarely more than a week, sometimes less than a day. From the time coma is confirmed death will take place in from twenty-four to forty-eight hours, often within a few hours.

Diagnosis—I. *The Premonitory Phase.*—The physician should not allow the diagnosis of acidosis to be imposed upon him by events; he should make it beforehand by a systematic examination of the urine.

When this is done, an energetic treatment can be begun without waiting for the development of confirmed coma. Although in reality there is some chance of recovery of the patient in the premonitory phase, the same cannot be said of

confirmed coma, in which recovery is rare. To await the confirmation is to allow death to come. A single symptom of approaching coma is enough to indicate energetic treatment, such as vomiting, vertigo, epigastric pain, and especially somnolence. But the true situation is very difficult to realize. Even when warned, the physician may hesitate to perceive a menace of death in the apparently benign symptoms offered by diabetes, and therefore will delay the indispensable intensive treatment. It is very difficult in practice to rid oneself of this illusion. In Chapter XXIX. I shall illustrate by several clinical examples how difficult an early diagnosis may be and upon what indications it can be made.

II. *The Phase of Coma.*—I will not insist on the various forms of coma which may be mistaken for that of diabetes.

Alcoholic coma, the coma of opium poisoning, uremic coma, the coma of cerebral or meningeal hæmorrhage or softening of the brain have their own individual signs which make them easy to diagnose.

Diabetic coma has its own symptoms, and above all its characteristic urinary stigmata. To admit the existence of true diabetic coma it is at the present time essential that the *acidosis test* shall be carried out, and that at least Gerhardt's reaction shall have been made. Therefore, if necessary, urine must be obtained by catheter, and if the bladder be empty the reaction of acidosis must be sought for in the cerebro-spinal fluid withdrawn by lumbar puncture. In other cases the acetone compounds may be sought for in the blood; both Gerhardt's and Legal's reactions can be obtained in the blood-serum after the albumin has been removed. The typical dyspnœa is certainly important for the diagnosis, but it has not a decisive value.

The presence of glucose in the urine is not enough to affirm a diagnosis of true diabetic coma. We, in fact, know that glycosuria may arise after cerebral hæmorrhage or opium poisoning. Besides, a diabetic may die in coma without dying from acidosis; diabetic patients without denutrition, but corpulent, with high blood-pressure and often chronic nephritis, are exposed to cerebral hæmorrhage and uremia. Finally, one must not confound the extreme depression bordering on coma which sometimes develops in diabetics during infectious

processes like gangrene, pneumonia, or tuberculosis, with true diabetic coma.

German observers have attempted, by the term of *atypical coma* or cardiac coma, to distinguish a special form of diabetic coma characterized by the absence of deep respiration and the existence of progressive cardiac weakness. Frerichs, Naunyn, Franck, and Blum have reported examples; Lépine has referred to a similar case.

It does not seem to me that there is any valid reason for making this distinction for these cases; almost all of them, in fact, were due to acid intoxication, which is the essential character of true diabetic coma; the absence of deep respiration is not enough for characterizing a special form, and this likewise applies to the cardiac weakness which belongs to all acidosis comas in variable degrees. Like all the syndromes, diabetic coma will clinically offer symptomatic variations from one case to another.

Prognosis.—What I have said of the evolution of acidosis shows the import of its prognosis.

It is by it that the majority of diabetics die. Of a total of 140 deaths, von Noorden found that 78, or 55·7 per cent., were the result of coma. Magnus Lévy gives a proportion of about 75 per cent.

At the phase of acidosis, survival may be long if strict precautions be taken; even the menacing accidents will have a favourable prognosis if one intervenes with active treatment. At the phase of confirmed coma, the prognosis is very bad, although the few cases of recovery obtained by alkaline treatment may be some reason for holding out very little hope.

The Determining Causes of Coma.—Although it is the inevitable outcome of acidosis, coma may develop from some determining cause, which may be trifling in nature, but repeated examples certainly prove that such factors play a part in the pathogenesis. In a patient with latent intoxication it will act like the drop of water which causes the overflow of the pail. The principal causes are:

1. Physical fatigue. Travel is often fatal for diabetics in a state of acidosis; therefore they should be warned against useless trips of any length. The preparation and other

incidents inherent to travel increase its deleterious effects. Summer heat, which increases fatigue and provokes a loss of sweat, which dries the organism, increases the danger. Any other kind of fatigue acts in the same way. In one of my patients the acidosis developed following a hunting party.

Cerebral fatigue is also detrimental; the preparation for examinations, competitive or otherwise, or business deals, etc., cause coma to develop.

2. Traumata. A fall or a fracture may induce coma. Such accidents are deleterious for diabetic subjects. Such was Spitzer's patient, with a mild diabetes, who fractured a leg, and four days later developed coma.

3. Violent emotion, worry, and grief.

4. Infectious diseases, of no matter what nature; influenza, pneumonia, etc.

Digestive disturbances seem to have the same action, but perhaps sometimes what was the initial manifestation may have been mistaken for the cause of the coma.

Suppurations, boils, carbuncle, and gangrene are often the origin of acid intoxication. I have seen two diabetics develop coma from large carbuncles on the neck; in another case this occurred following an abscess the result of a hypodermic injection; in still a third, a simple boil on the thigh resulted in an attack of acidosis with somnolence and menaces of coma. In a diabetic whose condition had been improved by a fast cure, the unfortunate development of a perineal abscess revived the acidosis, which had disappeared, and a suddenly developing coma quickly resulted in death.

5. Surgical operations are particularly dangerous. A diabetic in a state of acidosis will almost surely die if operated on, especially if the interference is carried out in chloroform narcosis. For complete details the reader is referred to Chapter XXVI.

6. Mistakes in treatment may be the cause of coma. Prolonged exhibition of massive doses of opium have been incriminated. It has been said that untreated cases of diabetes die from tuberculosis, while, when treated, the patients die of coma. It is a fact that excessive meat diet, such as was formerly recommended, generates the acetone compounds and acid substances. Following a three months' cure of a

forced meat diet (600 grammes of meat daily), a diabetic who had been quite well up to that time developed acidosis, which progressively evolved until coma supervened. The sudden change from an ordinary diet to a severe one deprived of carbohydrates has also been incriminated. Magnus Lévy believes that this mistake has cost the life of many diabetics. I believe that such untoward results are due especially to the exaggerated quantity of meat given in certain strict diets.

7. Finally, there are cases in which nothing can be found to explain the advent of coma.

The knowledge of these numerous determining causes is important in practice. The diabetic should be treated with the greatest respect, and warned about all things that may cause the development of coma.

CHAPTER XXVIII

THE CURABLE DIABETIC ACIDOSES*

The success obtained by intensive alkaline treatment in diabetics threatened by coma, and even in cases of confirmed coma, led me to hope that if this was carried out early and in massive doses diabetic coma might be recovered from. Like all observers who have studied this subject, I have been deceived. I have seen many comatose diabetics, and even in cases in which the treatment was resorted to very early and intensively I have only obtained temporary amelioration, never recovery. On the other hand, I have continued to observe the remarkable effects of alkaline treatment in diabetics threatened by outbursts of acidosis, and I have on more than one occasion had the impression that I prevented the development of imminent coma by intensive alkalization resorted to in time.

Why is there such a difference between the results obtained when treatment is instituted in the premonitory phase and in the phase of confirmed coma ? Why does sodium bicarbonate possess no action in coma when, on the contrary, it is so potent in certain accidents of acidosis ?

To these questions I am able to reply. My observations permit me to distinguish two types of diabetic acidosis—one incurable, the other curable—and to describe the characters of each. The former are met with in diabetics with denutrition, the curable cases in diabetes without denutrition. I shall confine my remarks principally to the latter.

The Acidoses of Diabetes with Denutrition.

Patients in whom the alkaline treatment has shown itself powerless to arrest the evolution of the coma were all diabetics with denutrition. In this type of the disease the acidosis is an

* *Mouvement Médicale*, March, 1913.

almost fatal complication, and hardly ever will retrogress when it has become installed. Hence Lépine, as well as the majority of German writers, establishes almost an identity between serious diabetes and diabetes with acetonuria. For a variable length of time the patient will struggle against the acidosis; but after having been seriously threatened by it several times, unless previously carried off by some intercurrent disease—tuberculosis or an acute infection—he will finally succumb to it. Alkaline treatment will be successful in arresting the fatal arrival of coma upon one or even several occasions; it will prolong the patient's life for several months, perhaps several years, but a day will come when it will be insufficient to control the threatening acidosis and, therefore, the inevitable outcome.

The Acidoses of Diabetes without Denutrition.

In diabetics without denutrition, the development of acidosis is not a usual occurrence, but rather an accidental complication. The majority of diabetics do not die in coma; they are much more commonly carried off by tuberculosis, Bright's disease, asystolia, gangrene, or an accidental infection.

A certain number of conditions may cause the development of more or less serious acidosis in these patients, such as the infectious diseases, traumata, lesions of the nervous system, chloroform narcosis, fast cures, or a forced diet of meat.

The part played by infections is not constant. I have seen a patient present distinct reactions of acidosis in the urine at the time a moist gangrene of the leg, from which he died, developed. On the other hand, a corpulent diabetic with typhoid fever did not present throughout this infection any trace of acidosis reaction in the urine; even the acetonuria did not exceed the normal limit. In several diabetics of this kind I have seen the reaction of acidosis appear upon the occasion of a carbuncle or deep-seated suppuration; but, I repeat, this is not a constant phenomenon.

An accidental lesion of the nervous system may determine the development of acidosis. Thus, a corpulent diabetic for several days presented distinct reaction of acidosis in the urine (diaceturia and acetonuria) following cerebellar hæmorrhage and meningeal hæmorrhage; the ingestion of 20 grammes

of sodium bicarbonate daily made the urine alkaline, and caused both Gerhardt's and Legal's reaction to disappear.

Chloroform narcosis is the most frequent and surest cause in the production of acidosis, and I have insisted lengthily on this fact in Chapter XXVI., as well as the danger of ether and other procedures of narcosis and analgesia, and the facts I brought forward show that neither the operative trauma nor pre-operative fast is less to be feared than the toxic action of the anesthetic.

Fast cures and purgation during the lapse of three days, such as are advised by Guelpa, are susceptible of causing acidosis to develop in diabetics where previously it did not exist.

I saw this occur in a young woman with diabetes without denutrition with a very low tolerance. On the second day Gerhardt's reaction was positive, and continued to be so for a week following the cure.

In a corpulent diabetic without denutrition who entered hospital for gangrene of the leg, with a glycosuria of 104 grammes and a trace of diaceturia, an inanition cure with purging for two days resulted in a notable acidosis; Gerhardt's and Legal's reactions were very marked, and the ammonuria varied from 1 gramme to 1·5 grammes daily. Only at the end of a fortnight did these reactions tend to diminish, and a prolonged bicarbonate treatment was necessary in order to cause them to completely disappear one month after the fast cure. Only the reactions in the urine occurred without any clinical symptom.

Finally, I observed a woman of 25 years, diabetic without denutrition, never having had the reaction of acidosis in the urine, who developed the reaction following a fast cure of only two days. Gerhardt's reaction was of medium intensity, Legal's and Lieben's reactions were strong. A three weeks' bicarbonate treatment was necessary for these reactions to disappear.

Fortunately, the acidoses due to inanition cures appear to be deprived of gravity; they are not accompanied by any clinical symptom that could presage coma, and their duration is usually short. For that matter, their occurrence is not constant. Finally, what is still more paradoxical, these very same inanition cures generally have a favourable action on the reactions of acidosis which previously existed; they may cause them to disappear temporarily or definitely. There is consequently no reason to fear inanition cures in diabetics in imminence of acidosis or even in cases of marked acidosis.

Much more serious are the acidoses following a severe meat

diet, as they are capable of inducing coma and death. For a long time past the danger of too severe meat diets imposed upon diabetics has been pointed out; coma has been known to ensue upon a diet of overfeeding with meat. What is particularly dangerous in this diet is the abuse of meat, much more than the privation of carbohydrates. In point of fact, the carbohydrates that are not burned by the patient do not exercise an anticetogenous action; they are consequently useless; but the albumins of the meat give rise to acetone compounds and other toxic substances. If meat is absorbed in excess by patients in imminence of acid intoxication coma may ensue.

Fatigue, overwork, a trauma, or even an emotion, are probably capable of creating acidosis in diabetics. So many examples of coma arising in these conditions have been reported, that the acidogenous action of these factors cannot be denied.

The danger of travel to diabetics in a state of acidosis is well known, and it not infrequently happens that these patients, who have travelled a distance in a railway to consult a physician in a large centre or to reach some mineral-water spa, develop coma upon their arrival at their destination.

Finally, there are cases in which the origin of the acidosis escapes investigation; it develops without apparent reason, and disappears in the same way after a duration of variable length.

The intensity of the outbursts of acidosis occurring in diabetics without denutrition is very variable. In the majority of cases they are benign, fleeting, and limited to the development of the reactions in the urine without clinical symptoms, but they may assume serious forms, even resulting in death.

The acidosis of fasting is the mildest of all; no symptom reveals it, and if the urine is not systematically examined it will be overlooked. That arising in diabetics who are large meat eaters is more serious.

I had the opportunity of treating a male, æt. 44 years, active and vigorous in appearance, but diabetic for several years, having formerly had a glycosuria of over 100 grammes and intense polydipsia, and having had some accidents of hyperglycemia—loss of teeth, eruptions of boils—who presented an intense diaceturia and acetonuria, such as one is accustomed to see in diabetics in imminence of coma.

Under the influence of a reduced carbohydrate diet the glycosuria rapidly subsided, which showed that tolerance was quite high and the diabetes without denutrition. Nevertheless, Gerhardt's and Legal's reactions remained with the same intensity.

Treatment with Vichy water and sodium bicarbonate at a daily dose of 30 grammes was ordered, and I endeavoured to dissuade my patient from taking a long trip that he was contemplating. But he would not listen to reason, saying that he felt very fit since the glycosuria and thirst had ceased, and that the bicarbonate made him feel much better. He started off, and, in spite of my fears, he returned in excellent health after a tiresome trip of several months.

Why did this patient victoriously resist an acidosis which I believed was threatening him ? It was because in reality he presented a diabetes without denutrition and a very moderate disturbance of the glycoregulator function. The acidosis was merely due to an excess of food; he was a very large meat eater, and by eliminating this excess by placing him on a moderate diet the danger of acidosis was averted.

Here is a similar case:

A woman of 50 years, who previously had been a large eater and very corpulent, had become diabetic for some years, and had considerably emaciated. She consulted me for a very intense intertrigo complicated by multiple disseminated abscesses. The urine contained 40 grammes of glucose per 1,000 c.c., and presented Gerhardt's and Legal's reactions of medium intensity. The patient was in a state of somnolence, fatigue, and depression, which made me fearful of her condition.

Absolute rest in bed and local treatment were prescribed, with a reduced milk diet and 50 grammes of sodium bicarbonate daily. The somnolence rapidly disappeared, the general condition improved, likewise the intertrigo, while in ten days the glycosuria was only 20 grammes per 1,000 c.c. Gerhardt's reaction had become negative.

For several months her condition remained good; the glycosuria had ceased, the acidosis no longer existed. But during the summer, while on a trip, the patient became fatigued and committed great imprudences in diet; she consumed much meat and a goodly amount of sweets. Therefore, the accidents of hyperglycemia and acidosis returned. She came back with an intense thirst, an abundant glycosuria—60 grammes per 1,000 c.c.—a very extensive intertrigo, and a distinct acidosis—Gerhardt's, Legal's, and Lieben's reactions in medium intensity—with quite marked depression, but no somnolence.

She was put to bed with a diet and bicarbonate treatment. Her condition rapidly improved. The fatigue decreased, the thirst ceased, the intertrigo became less irritated. But at the end of a week the glycosuria was still present at the rate of 50 grammes per 1,000 c.c.,

while the stigmata of acidosis were just the same. A week later the local state continued to improve, but the acidosis persisted, the urine remaining acid in spite of the daily ingestion of 20 grammes of bicarbonate. A week later the glycosuria had considerably diminished, Gerhardt's reaction was negative, and of Legal's reaction there was only a trace. Afterwards the patient regained her strength, but the glycosuria did not disappear, and a trace of Legal's reaction remained in the urine.

This case is a very typical example of diabetes without denutrition in which curable accidents of acidosis developed on two occasions; the second time they were aggravated, because the first attack was recovered from in a fortnight, the second requiring four weeks to obtain the same result. At all events, I was happily surprised to see the accidents subside, because the first time, given the state of somnolence and the presence of the stigmata of acidosis, the prognosis seemed to me decidedly poor. If the attack of acidosis was recovered from so easily, it was because it was accidental and due to an excess of meat in a diabetic without denutrition.

I saw, with my colleague Lereboullet, a male æt. 50 years who had had diabetes without denutrition for many years, and a rather high tolerance for carbohydrates with a glycosuria always moderate. Following overwork there was an aggravation of his condition; the glycosuria increased, the body weight fell off a few kilogrammes, and the patient felt weak; there was some vertigo and a tendency to somnolence. There was a slight diaceturia and marked acetonuria. Bicarbonate in large doses controlled the accidents, but for several months depression and acidosis persisted. An improvement slowly took place, however, and to-day the patient has regained his former state of health and the acidosis has disappeared.

In diabetics without denutrition attacks of severe acidosis with threatening coma may arise without any apparent cause.

A diabetic female, æt. 40 years, was sent to me because for some time her glycosuria had been more marked and a state of fatigue with emaciation that could not be accounted for. I found a very moderate glycosuria without the reaction of acidosis in the urine.

However, the condition became rapidly worse. A few days later the patient could hardly come to my consultation. She was somnolent, extremely depressed, and complained of vertigo. This time the urine gave an intense Gerhardt's reaction. She was put on a vegetable diet and bicarbonate in large doses, but I feared that at any time coma might develop.

In a few days the condition improved, the glycosuria decreased,

Gerhardt's reaction was less strong, and the premonitory symptoms of coma disappeared. Some days later all danger had vanished, and the reactions of acidosis in the urine had completely disappeared. The acute serious acidosis underwent its evolution in three weeks.

The acidoses of diabetics without denutrition are, however, not all curable.

A woman, æt. 74 years, who had been very corpulent, lost 35 kilogrammes in a few years. She had had diabetes without denutrition with moderate glycosuria for a long time, but had always refused to submit to a diet. There was also renal sclerosis with high blood-pressure, while for the past few months the patient presented marked disturbances of the nutrition. She had rapidly emaciated, lost strength and appetite, which contrasted with her inveterate habit of overeating, and especially her indulgence in meat. Headache, some somnolence, and especially incoercible vomiting, drew her physician's attention, who was struck by the odour of acetone in the breath, the dry tongue, and the presence of a large amount of acetone in the urine.

Alkaline treatment seemed at first to cause some amelioration, and recovery was hoped for; but the accidents increased, somnolence became deep, the respiration and pulse accelerated, and anuria complete. In spite of an intravenous injection of bicarbonate and the ingestion of 100 grammes of the salt, death in complete coma supervened.

It is probable that excessive eating was the cause of the intoxication which, in this patient, produced the denutrition and coma.

I saw a male, æt. 45 years, somewhat corpulent, with a diabetes of several years' standing that he had supported very well until the time he came under observation. Regardless of his physician's advice, he refused any form of diet, and committed considerable excesses in eating. For some months the diabetes had become worse, the glycosuria abundant, and emaciation rapid. There was, however, no pulmonary tuberculosis. Finally, for a few days the patient felt extremely tired; he was somnolent during the day, and slept badly at night, complaining of dull headache. The appetite was completely lost. The distaste for food sharply contrasted with the delight in eating previously manifest. His physician had noted the acetone odour of the breath, and an analysis of the urine revealed a very strong reaction of acidosis. In spite of alkaline treatment, the accidents became worse, and in three days the patient died in coma complicated with epilepsy.

In this case there was diabetes without denutrition, badly treated, becoming worse from excessive meat eating, resulting in denutrition and fatal acidosis.

Coma arising in these cases is susceptible of cure when

properly treated, and I have met with such a case with P. Carrié:

A woman, æt. 65 years, belonged to a diabetic family, and herself had had the disease for ten years. She also had cystitis with pyelonephritis, for which she entered hospital. We at once found a marked glycosuria (110 grammes) and a notable diaceturia. Twelve days later, following a severe attack of fever, due to urinary infection, coma developed, from which it was impossible to rouse the patient. The urine presented an intense Gerhardt reaction. Although no hope was entertained, she was given bicarbonate intravenously, and afterwards by mouth, and the coma disappeared. A relapse due to premature cessation of the intravenous injections was also conjured, and the patient recovered, being discharged a month later, when all danger had been eliminated. Five months later she was in a satisfactory condition of health; the glycosuria had almost completely subsided, and the acidosis had disappeared. Two years afterwards I heard that she was still well, without any glycosuria or acidosis.

If this patient recovered after a tardy resort to alkaline treatment, this is due, in my opinion, to the fact that the coma developed in a diabetic without denutrition. From a fleeting infection, itself curable, the diabetes became aggravated and was complicated by acidosis; but an acidosis of this type is not irremediable, as when it arises in diabetes with denutrition; it represents a temporary complication. If the immediate threatening accidents are dealt with, they may retrogress and the patient recover.

Why does recovery take place, while other cases treated in the same way prove to be incurable ? It is because in diabetes without denutrition the acidosis is ordinarily a temporary accident caused by excess in eating or by some infectious disease. If by treatment the toxic products produced in excess can be neutralized, therefore eliminating imminent intoxication, complete recovery is possible.

On the contrary, in diabetes with denutrition, the acidosis is a fatally progressive process which from the day it becomes installed will continue to increase. Now, even if the evolution of coma is prevented once or several times by an intensive treatment which neutralizes the toxic bodies already produced, after this temporary recovery the acidosis continues to subsist, so that a day must come when the quantity of toxic substances circulating in the organism is such that no treatment will be of any avail.

In presence of a case of acidosis it is possible to ascertain if it belongs to the curable variety, but the prognosis is delicate to appreciate. It should be based upon the intensity of the acidosis reactions, the intensity of the symptoms, and the nature of the diabetes.

The gravity of the acidosis is usually in direct ratio to the intensity of the stigmata of intoxication—diaceturia, acetonuria, excretion of β-oxybutyric acid, ammonuria, and amino-aciduria. But one does not always possess all these elements of appreciation, especially the dosage of β-oxybutyric acid. Besides, there are cases of curable acidosis in which the reactions offer an extreme intensity, and, inversely, there are fatal cases in which the reactions of acidosis in the urine are mild, so that they should be searched for in the cerebrospinal fluid. In practice, the intensity of the reactions of acidosis indicate the imminence of coma, but in no way permit the separation of curable from the incurable acidoses in serious cases.

The intensity of the symptoms is an important factor of the prognosis; in the premonitory phase coma will frequently be recovered from; when it is confirmed it usually kills. But this is merely the ordinary rule with many exceptions. Sometimes no premonitory symptom, other than the stigmata detected in the urine, will be present, so that without any warning coma may develop and undergo its evolution without remission. On the other hand, there are diabetics who completely recover from profound coma. Clinical study of the case is not in itself capable of foretelling this evolution.

From the facts I have adduced it would appear that acidosis —after some remissions due to treatment—has a fatal evolution in diabetics with denutrition, while it may be recovered from completely, even when it has produced coma. in diabetics without denutrition. Consequently it is the nature of the diabetes which, above all, governs the gravity of the acidosis. To make a prognosis of this intoxication it is essential to measure the intensity of the glycoregulator process and establish the nitrogenous balance, and this can be done with those clinical means at present at our disposal.

CHAPTER XXIX

THE DIFFICULTIES OF EARLY DIAGNOSIS OF DIABETIC COMA*

To foresee the early development of coma in a diabetic is one of the most delicate clinical problems. It is also one of the most important, because it is necessary to act before coma is confirmed in order to obtain a therapeutical result. Hence I shall attempt to throw some light on the most significative symptoms of the imminence of coma, using some clinical histories as a means of illustrating the subject.

A few days ago my interne, Mr. Bith, called my attention to a diabetic in the male ward, and pointed out that the patient was fatigued, depressed, and had lost his appetite; he was usually a large eater, but would not touch any food at present, while his weight chart showed some emaciation. Finally, he was somewhat somnolent, and the day before he complained of feeling tired and suddenly went to sleep in the middle of the day.

When I examined the patient I was struck by his tired look and ashy tint. He complained of a feeling of general discomfort, and that his eyelids were heavy. There was no definite pain in any part of the body, but he complained of general lassitude, such as he had never experienced. Finally, he said he was very thirsty and that the tongue was dry.

The urine presented the characteristic reaction of acidosis. Gerhardt's reaction was intense, while both Legal's and Lieben's tests were strongly positive.

Given these marked reactions in the urine, which pointed to a strong acidosis, as well as the clinical signs offered by the patient, it was evident that they were all precursory indications of an attack of diabetic coma. Therefore 50 grammes of bicarbonate were ordered to be given at once by mouth, and the drug to be given intravenously should the phenomena

* A clinical lecture delivered at the Charité Hospital.

continue during the day. At the same time I replaced the mixed feeding that I had previously ordered by a milk diet, and also ordered irrigation of the colon, which resulted in an abundant expulsion of fæces.

At the same time there was a diabetic patient in the female ward whose case was much like that of the man. For about a week this woman complained of general fatigue, depression, and no longer asked to be discharged from hospital. At the same time, without any evident cause, she was seized with sadness and uneasiness; one of her relatives having called, she burst into tears, complaining of general distress and lassitude. Finally, for the past week the appetite decreased, the patient eating much less than formerly.

When the patient's bed was approached one could detect that the breath was sour, that there was some oppression, and a slight increase of the respiratory movements; the tongue was also dry. She was somewhat somnolent, although not to the extent of not answering when spoken to. Lastly, she complained of some headache and indefinite abdominal pain.

All these symptoms were trifling, indefinite phenomena, in no way disturbing in appearance, but for one who has observed many such cases they were sufficient to cause one to fear imminence of coma, a fear all the more justified because the urine gave marked reaction to Gerhardt's, Legal's, and Lieben's tests. This patient was more threatened than the man, and Mr. Bith founded this prognosis on a comparative examination of the total urinary acidity and elimination of ammonia compounds of the cases.

In the man, the total urinary acidity varied between 2·19 and 3·81 grammes; the elimination of the ammonia compounds was 2·60 to 3·20 grammes, and among these compounds there was, above all, a large proportion of amino-acids.

In the woman, the urinary acidity was higher. From 4·60 grammes on March 4, it had progressively ascended to 6·88 grammes on March 15, although the patient's diet did not contain a large proportion of albuminoids. The elimination of the ammonia compounds likewise had increased more than in the man patient: on March 4, 2·30 grammes were excreted; on March 13, it had reached 5·46 grammes,

and, as was the case with the male patient, the ammonia compounds were largely composed of amino-acids.

As the male patient had consented to take and had tolerated 45 grammes of bicarbonate by mouth, a real amelioration ensued; on the following day he was better, and complained less of fatigue and depression.

On the other hand, the woman had developed coma. She tried to take the bicarbonate ordered, but vomited it. An intravenous injection of the salt was decided on, but had to be delayed until 10 p.m. on account of an accident to the apparatus. At the time it was given the patient had already developed a rather intense dyspnœa.

Two hours after the intravenous injection complete coma ensued. The patient was absolutely inert, and did not reply to questions; the reflexes were abolished; the respiration accelerated—35 to 40 per minute—but did not present Küssmaul's classic type. A generalized eruption of the urticaria type was seen on the internal aspect of the thighs and legs and the internal surface of the arms and forearms. The hands and feet were cold and violet. The pulse was small at 136 per minute. The temperature, which had been previously subnormal, went up to 104° F. just before death took place. These hyperthermic forms are rare; usually the patient will offer a marked hypothermia. Finally, the pupils were equal.

Here, then, are two diabetic subjects who, from the clinical view-point, presented about the same prodromata which led me to fear the advent of coma within a short time. One of them recovered, while the other developed coma and died. Alone, examination of the urine of this patient, by revealing the constant progress of the urinary acidity and uninterrupted increase of the elimination of the ammonia compounds, showed that she was the most intoxicated and threatened of the two. One of the causes which hastened the end was undoubtedly her inability to tolerate sodium bicarbonate; the alkaline treatment was commenced too late. On the contrary, in the man we were able to act more rapidly, so that on the next day the menace of coma had disappeared.

These two examples are interesting because they show the difficulty experienced in making a prognosis.

Here are some other case histories that are no less instructive:

A young woman was the subject of diabetes with denutrition. For three or four years she had had glycosuria, but this could be reduced—that is to say, diminished or even made to disappear—when an appropriate diet was strictly followed. There was no acidosis. In October, I found Gerhardt's test positive for the first time; therefore a symptom of acidosis had made its appearance, while at the same time the glycosuria could not be reduced by diet. A fortnight ago the patient felt so well that she went to the theatre, but returned home feeling very weak and with a pain simulating lumbago. She passed a bad night, and on the next day the lumbar pain persisted. She felt distressed, weak, and without appetite. As these symptoms continued, I was asked to see the patient three days after their onset.

On my arrival I found a physician at the patient's bedside who had correctly diagnosed diabetic coma, and had given an intravenous injection of 500 c.c. of a 5 per cent. sodium bicarbonate solution—that is to say, 25 grammes of bicarbonate. Following the injection, which had been given at 5 p.m., a real improvement had taken place. When I saw the patient she was awake, replied perfectly to questions, but felt weak and tired. Urine was passed in large amount, was very acid, and gave an intense Gerhardt reaction.

The prognosis was evidently very unfavourable. The only remaining hope was the influence of the treatment, so I suggested that the bicarbonate should be introduced into the body by any available means—ingestion, per rectum, or by intravenous injection. The patient could not tolerate the salt by mouth, and vomited it; when given in an enema, this resulted in an abundant discharge of fæces, so that the bicarbonate was not absorbed. Therefore at 8 p.m. I ordered a second intravenous injection of 500 c.c. of a 5 per cent. bicarbonate solution. For a time following the injection the patient seemed a little better, but at about 1 a.m. true coma developed. She did not answer questions addressed by her husband, but when I pressed matters a little she finally answered me, although speech was not free, the tongue moving with difficulty, and there was profound intellectual cloudiness. Two more intra-

venous injections were given, hence the patient had four in all in twenty-four hours, thus having received 100 grammes of bicarbonate. In spite of this intensive treatment, she died in the evening of the following day.

Thus, this patient had presented minor precursory signs before the development of the coma, but they were so mild and insignificant in appearance that no disquiet was felt by the family.

The fourth case is that of a girl of 23 years with a serious diabetes with acidosis. She was being treated at a town some thirteen hours' railway travel from Paris, without result, so that it was then decided to bring her up to Paris. For a long time one hesitated to undertake the trip, fearing that it might be too tiresome for the patient, but at length it was decided on. As she was very dyspnœic and felt distressed, a morphine injection was given as she started. On her arrival in Paris the patient was very greatly distressed and had passed a bad night on the train. I saw her, with my colleague F. Bezançon, on the following morning. There were 60 respirations per minute; she had air-hunger, although there was no bronchial obstruction and not a trace of cyanosis. Pulse rapid—120 to 140—very small and depressible. Gerhardt's reaction very strong. The patient was on the point of coma.

An attempt was made to give her large doses of bicarbonate, and she took and tolerated quite a large amount by mouth; but in spite of this coma developed a few hours later, paralyis of the sphincters ensued, and urine and fæces were passed involuntarily. In the afternoon 400 c.c. of a 5 per cent. sodium bicarbonate solution were given intravenously—in other words, 20 grammes of the salt were introduced; at the same time the bicarbonate was given in solution per rectum. After the injection there was some improvement, there was less sphincteric paralysis, and the mind was less cloudy. On the next day, in spite of all treatment, the condition became worse, and the patient died forty-eight hours after the onset of the coma. In this case the premonitory symptoms of the coma vere very trifling.

The last case that I shall refer to is that of a patient seen some years ago with Dr. Vitry. It was that of a young woman with diabetes and denutrition. Formerly treated by Laignel-

Lavastine, she had improved and had returned to her work of domestic servant. Then, as she felt tired out, she entered Laennec Hospital. The urine gave a very strong Gerhardt reaction, and I should add that at this time I did not attribute the same prognostic importance to this test as I now do. One morning towards noon, before leaving the hospital, I went to see the patient with Dr. Vitry. The nurse informed me that the patient had vomited; in the night she had suffered from true abdominal colic, followed by a dozen liquid, mucous stools, almost choleriform in type.

On examination the respiration was slightly sighing; the patient complained of a very sharp pain in the epigastric region, which was increased by pressure. Gerhardt's reaction was positive. I did not believe that coma was so near to hand, so that it was not thought necessary to begin bicarbonate in large doses.

The next day I was informed that the patient died in the night, and this is what happened: In the day she continued to suffer, the diarrhœa continued. A morphine injection was given, and at about 5 a.m. coma developed, followed by death without any convulsive seizure.

These case histories are very instructive, as they show the difficulty of making a prognosis. One should never wait for all the symptoms of acidosis to develop, and in reality the signs are very variable. Sometimes dyspnœic phenomena predominate, at other times pain is in the foreground. Some patients complain of anorexia, or there may be somnolence.

However, there are a certain number of symptoms which should be discovered, because they are more frequently encountered. In the first place, there is dyspnœa. This is generally not very characteristic; one of the patients whose case I have given had Küssmaul's deep respiration, another merely had difficult breathing, the third polypnœa, while the fourth had dyspnœa resembling the Cheyne-Stokes type. Hence, always remember that any respiratory disturbance arising in a diabetic with acidosis should lead you to think of the possibility of approaching coma.

The acetone odour of the breath, likewise of the urine, has been mentioned by most writers, but their verification is personal, subjective, and subordinated to the observer. If he

should have a coryza at the time, the odour will not be detected. Personally, I only attribute a very relative importance to this symptom, and I would advise you not to wait until you find it to make a diagnosis of imminent coma.

Digestive disturbances are rather constant. In some cases vomiting occurs without any apparent cause, and continues without interruption; or there may be attacks of diarrhœa, such as arose in the last case referred to.

One very important symptom, in my opinion, is marked anorexia, and this is rarely wanting. It overwhelms the patient, and is all the more striking because it occurs in subjects who previously had a large appetite, to the extent that care had to be taken that they did not gorge themselves with food. In all the cases I have observed this symptom was found, and as far as I am concerned I attribute the greatest importance to it from the view-point of the prognosis.

A consequence of the anorexia easy to foresee is emaciation. It is a sign never to be neglected. One of my patients lost 2 kilogrammes in eight days.

Nervous disturbances also belong to the premonitory signs of diabetic coma. These consist of vertigo and an unsteady gait; sometimes there is headache, usually not so severe as that encountered in uremia. Distant pain may be complained of, sometimes at one spot, sometimes at another part of the body. One of my patients had an intense epigastric pain. Epigastralgia is a symptom to which Lereboullet attributed great importance as a premonitory sign of coma. In other cases there is a very unbearable lumbago, as in one case reported here, or there may be a pain in the thorax with a sensation of weight. These pains are not usually increased by pressure.

Epileptiform seizures sometimes occur, and urinary disturbances may arise. The amount decreases, likewise the tenor of sugar, but it would seem that the diminution of the diuresis and glycosuria is above all due to the fact that, since there is anorexia, these subjects eat and drink much less. When they still drink sufficiently, the urine is abundant up to the time of death.

Great importance is to be attached to the reactions of the urine. Külz has described hyaline casts, which accumulate

at the bottom of the tube, in diabetic urine. I have never met with them but once.

What, in my opinion, is more important is positive reactions of acidosis—Gerhardt's, Legal's, and Lieben's tests. These usually increase in intensity during the days preceding the advent of coma.

The exact dosage of acetone, diacetic acid, ammonia compounds, and the total urinary acidity are of immense prognostic value. When acetone is found to progressively increase, likewise the ammonia compounds and the amino-acids, one should be suspicious and be on the look-out for comatose phenomena.

The dosage of β-oxybutyric acid eliminated may also give warning. The German writers have maintained that by a daily dosage of β-oxybutyric acid one can estimate the evolution of the acidosis. The same can be said of the total acetone compounds estimated by Van Slyke's procedure. For controlling diabetics in a state of acidosis and the effect of diet, I usually rely on the dosage of the glycosuria and acetone compounds and Gerhardt's reaction.

Such are the principal indices that may put you in the way of making a difficult diagnosis if you are on the look-out for them. They do not all possess the same value, but each has one. In a diabetic with acidosis, when you note an abnormal symptom, no matter of what nature it may be, be suspicious and fear the advent of coma, even although the symptom be some very ordinary complication, such as an angina or bronchitis.

An early diagnosis is all the more important to make, because you can rapidly act and deal with the premonitory symptoms, which can still be controlled by treatment, while recovery from confirmed coma is exceptional. The patient must be strongly alkalinized, and you must not be imposed upon by the apparent mildness of the prodromal signs. In the first patient mentioned in this lecture we were able to overcome threatening coma by at once causing him to absorb 50 grammes of sodium bicarbonate; had this been done a day later, the golden opportunity for a successful result would have been irretrievably lost.

CHAPTER XXX

THE DIAGNOSIS OF DIABETIC COMA—THE REACTION OF ACIDOSIS IN THE CEREBROSPINAL FLUID*

When all commemoratives are wanting, the diagnosis of diabetic coma will often offer considerable difficulty. When the patient is plunged in complete coma, the symptoms are usually reduced to their simplest expression; the acetone odour of the breath may be absent—I have already stated the worth of this symptom—while at this phase the respiration presents nothing characteristic. The deep, sighing, rapid breathing described by Küssmaul is more prone to be observed at the very onset or before the development of the coma. The dyspnœa is frequently of the ordinary type, or it may assume the Cheyne-Stokes character, and hence contribute to misleading the diagnosis.

The temperature, which at times is high, at others low or even normal, will not furnish any element in the diagnosis. The same is to be said of the pulse, which is usually accelerated without any special rhythm, while the pupils are in varying states.

The commemoratives themselves will lead to nothing decisive. Unquestionably it is a good point to know that the subject has diabetes, and this notion will put the physician in the right direction for making a diagnosis; but a subject may be a diabetic and still die from cerebral or meningeal hæmorrhage. In one case that came under my observation, the diagnosis wavered because a slight deviation of the tongue pointed to cerebral hæmorrhage, while analysis of the urine indicated coma from acidosis. Likewise, one may be diabetic and die from uremic coma, and this is what actually happens to certain corpulent diabetics, who are more apt to be threatened by the bad condition of their kidneys than by their diabetes.

Most commonly, an analysis of the urine will settle the

* *Paris Médicale*, January 24, 1914. In collaboration with A. Gendron.

question, and, if necessary, the urine must be withdrawn by catheter. Albumin, glucose, and the reactions of acidosis are to be searched for. The presence of albumin does not exclude diabetic coma, neither does its absence affirm it. Glycosuria is more important, as it shows that diabetes is present, but no more than the commemoratives does it mean that the patient has diabetic coma. Besides, it must not be forgotten that certain comatigenous pathologic states, as cerebral hæmorrhage or an epileptic seizure, may be followed by a fleeting glycosuria, so that this is far from having an absolute diagnostic value.

The reactions of acidosis are more characteristic. When Gerhardt's, Legal's, or Lieben's tests are positive, revealing a large amount of a diacetic acid and acetone in the urine, it is practically certain that the case is one of diabetic coma; inversely, a negative result with these reactions does not exclude diabetic coma.

There are, however, cases in which this means does not solve the problem of diagnosis. It may happen that the reaction of acidosis exists, but is very weak, so that one may hesitate to affirm that the patient has a lethal acid intoxication. Finally, there are cases in which no urine can be obtained, thus depriving the physician of this diagnostic means.

The blood may be examined. When the albumin has been removed from the blood-serum, the reactions of acidosis can be obtained quite as well as in the urine; but the technique is delicate, and one may not have sufficient blood for carrying it out.

There then remains one more procedure—namely, the examination of the cerebrospinal fluid obtained by lumbar puncture. Besides the important data to be derived from the tension, colour, transparency, cytological examination, and search for albumin, which will confirm or eliminate the diagnosis of meningitis or meningeal or cerebral hæmorrhage, examination of the cerebrospinal fluid will also reveal the presence or absence of the stigmata of acidosis.

Gerhardt's reaction can be obtained with the greatest ease in the same way as in the urine by mixing the fluid with one-tenth of its volume of officinal perchloride of iron. Legal's

reaction can also be obtained by following Imbert and Bonnamour's technique that is used for the urine. The Lieben-Mauban reaction is readily positive if acetone is present.

Several observers have already mentioned the presence of the acetone compounds in the cerebrospinal fluid of some patients.

In 1905 Grunberger found diacetic acid in the cerebrospinal fluid in comatose diabetics, and in the same year found acetone present three times, and diacetic acid once, in cases of diabetic coma, but never β-oxybutyric acid.

Souques and Aynaud have also found acetone in the cerebrospinal fluid. In a diabetic dying in coma the dosage of acetone was 54 centigrammes per 1,000 c.c. of fluid. These observers injected acetone into the blood or subcutaneously in animals, and they found this body in the cerebrospinal fluid afterwards.

In 1910 Erben found acetone, diacetic acid, and traces of β-oxybutyric acid in the cerebrospinal fluid from a case of diabetic coma.

Derrien and Bousquet have likewise several times detected the presence of acetone in a comatous diabetic; in four cases of diabetes with acidosis, but no coma; in three non-diabetic patients (insanity with glycosuria, Addison's disease, and eclampsia in a primipara); and once the presence of diacetic acid. In all these cases the dosage showed a smaller proportion of acetone in the cerebrospinal fluid than in the urine, while, on the other hand, the proportion of acetone was the same in the cerebrospinal fluid as in the blood-serum.

Savy and Mazel found acetone in the cerebrospinal fluid and urine, but no diacetic acid, in a case of diabetic coma.

Chauffard and Rendu found acetone and diacetic acid in the cerebrospinal fluid, blood, and urine in a case of diabetic coma with eclampsia. The proportion of these bodies in the urine was larger than in the other two fluids.

I have had the opportunity of appreciating the utility of the search for acidosis in the cerebrospinal fluid in the diagnosis of diabetic coma.

Case I.—A male, æt. 36 years, treated for two years for diabetes, entered hospital in complete coma. The history was that for three weeks he had much headache, felt weak, and ate little.

The patient was inert; rather deep respiration, not accelerated, 18 to the minute. A few râles at the left pulmonary base. Temperature very low—96° F. Pulse 72; blood-pressure low, maximum 9·5. Odour of acetone in breath; gums tumefied. Patellar reflexes very weak; Achilles reflex absent on the left; cremasteric reflexes weak, abdominal reflexes *nil*. No stiffness of the neck. Pupils unequal, the left larger than right; hypertonus of the eyeballs very marked. For two days blood has come from the left ear.

Examination of the urine revealed glucose, albumin, acetone, and diacetic acid. Legal's test distinct, but not strong; Gerhardt's test practically negative.

Therefore, there was a very slight diaceturia, and the diagnosis of diabetic coma could not be affirmed. The discharge from the ear made us suspicious of meningitis.

Lumbar puncture was done, giving issue to a clear fluid, not under pressure, containing a very small amount of albumin not exceeding the norm. Therefore, there was neither meningeal hæmorrhage nor meningitis. On the other hand, Lieben's, Legal's, and Gerhardt's tests were very positive, so that no doubt existed as to the diagnosis of diabetic coma. Patient died the following day. No necropsy.

Here, then, is a case in which the positive reactions of acidosis in the cerebrospinal fluid made the diagnosis possible; Gerhardt's was very distinct, while in the urine it was doubtful. This is not usually the case. The reactions exist in the cerebrospinal fluid, but are less intense than in the urine. This is shown in the three following cases:

Case II.—Diabetes; cerebellar cortical hæmorrhage; gangrene of foot.

The cerebrospinal fluid was hæmorrhagic; after centrifugalization it became yellowish-green; it was very albuminous, and contained red blood-corpuscles and polynuclears.

	Cerebrospinal Fluid.	*Urine.*
Gerhardt's test	0	+
Legal's test	Traces	+
Lieben's test	+	+

Case III.—Diabetes without denutrition; acidosis; extreme polyphagia.

Cerebrospinal fluid flows off normally. It is hyperalbuminous, but does not contain an excess of cellular elements.

	Cerebrospinal Fluid.	*Urine.*
Gerhardt's test	0	++
Legal's test	+	++
Lieben's test	++	+

The reaction of acetone was more intense in the cerebrospinal fluid than in the urine.

Case IV.—Stenosis of œsophagus; catalepsy; non-diabetic acidosis.

Lumbar puncture gave exit to a clear, non-albuminous fluid; no leucocytosis.

	Cerebrospinal Fluid.	*Urine.*
Gerhardt's test	0	+
Legal's test	Traces	+
Lieben's test	+	++

The reactions of acidosis may be absent in the cerebrospinal fluid and present in the urine. This I found in a woman with cerebral hæmorrhage and coma, whose urine gave a strong Gerhardt reaction, which disappeared in a few days. In this case, it is true, the acidosis only played a secondary part, and perhaps did not enter at all into the pathology of the coma.

What is the diagnostic value of these reactions of acidosis in the cerebrospinal fluid? Are they met with in morbid states other than diabetic coma?

Certainly they are met with when coma does not exist in diabetics with acidosis—a fact which proves the diffusibility of acetone and diacetic acid in the humours of the organism. Assuredly they are also encountered in cases of non-diabetic acidosis, as Derrien and Bousquet have proved by several cases. But they are not present in individuals suffering from some general disease or nervous lesions which are never accompanied by acidosis.

I have searched for them in several cases of meningitis and other diseases of the nervous system requiring lumbar puncture, and I have never found them.

Cases.—I. Patient æt. 42 years. Tuberculous meningitis. Very albuminous cerebrospinal fluid. The three reactions for acidosis were negative in cerebrospinal fluid and urine.

II. Patient with disturbances of speech. General paralysis. Cerebrospinal fluid normal, no albumin, no lymphocytosis. The three tests for acidosis negative.

III. Male. Former quadriplegia. At present bilateral Argyll-Robertson; asthmatic paroxysms. Cerebrospinal fluid hardly more albuminous than normal, with two or three lymphocytes per cubic millimetre. The three reactions for acidosis are negative in cerebrospinal fluid and urine.

IV. Elderly hemiplegic female. Cerebrospinal fluid normal. The three reactions for acidosis negative.

V. Elderly hemiplegic female. Cerebrospinal fluid normal. The three reactions for acidosis negative.

VI. Labyrinthic disturbances. Albumin slightly increased in cerebrospinal fluid; 6·5 lymphocytes per cubic millimetre. The three reactions for acidosis negative.

Our control researches show that the presence of the reactions for acidosis in the cerebrospinal fluid is no ordinary occurrence. Diacetic acid is not present excepting in cases of acidosis, be it diabetic or not. Acetone will not be found unless a real excess of it is present in the urine.

The discovery of these reactions is consequently very significative, and may, in cases where it is impossible to obtain a sample of urine or in those where the reactions are doubtful in the urine, as I have shown, serve in making the diagnosis of diabetic coma.

CHAPTER XXXI

THE SYNDROME OF ACIDOSIS AND DIABETIC COMA*

MANY theories have been successively proposed for explaining the pathogenesis of diabetic coma. Most of them have now only an historical interest, but some which treat the subject more closely should still be retained.

The theory enjoying the greatest favour is that first put forward by Stadelmann, and developed more fully by Naunyn and his co-workers, which supposes that diabetic coma is an *acid intoxication* of the organism, principally caused by β-oxybutyric acid and diacetic acid. The partisans of this theory base themselves on the following arguments:

1. The increased acidity of the urine and the difficulty of making it alkaline by ingestion of large doses of sodium bicarbonate.

2. The elimination of exaggerated quantities of ammonia, which also occurs, as experiments have shown, when an animal is poisoned by an acid.

3. The decrease of the alkalinity of the blood; but it is true that this symptom is only met with in the terminal phase of coma.

4. The abnormal excretion by the kidneys of diacetic and β-oxybutyric acids, substances whose production is connected with that of acetone, and which are frequently designated by the name of acetone compounds.

5. The retention of these acetone compounds with acid functions, which can, according to Magnus Lévy, be found in the tissues when they are not eliminated in the urine.

6. Experiments that have produced comatose states by means of acids, and β-oxybutyric acid in particular, but which are curable by alkaline medication if given in sufficiently large doses and early in the process.

7. The success obtained by the treatment of diabetic coma with alkalines.

* *Presse Médicale*, April 8, 1911.

This theory of acidosis, admitted by Naunyn, Magnus Lévy, Luthje, Blum, and others, has been severely criticized. Kraus believes that it is not applicable to all cases of diabetic coma, and although Lépine accepted it, he did so under certain reserves. Hugounenq and Morel suppose that the acidosis predisposes to coma, but does not produce it, and advise the search for the pathogenic toxic substances in the group of polypeptids.

I will now review these objections, and will endeavour to discover to what extent they are founded.

The experiments that I carried out some years ago with L. Violle gave me an insight to the manner of action of various acids on the animal organism. We proposed to again carry out Walter's fundamental experiments, consisting of poisoning animals with a mineral acid—such as HCl—and then to prevent coma from developing by injecting alkalines in sufficient quantity to saturate the dose of acid injected. We were unable to obtain the expected results. HCl kills the animals when injected intravenously at the dose of 0·9 gramme per kilogramme of weight, but it acts too rapidly for an alkaline injection to have any effect; death is so rapid that there is no time for coma to develop.

But if one uses organic acids—such as lactic, propionic, butyric, or β-oxybutyric acids—a real phase of coma is induced which will end in death of the animal unless a sufficient quantity of sodium bicarbonate be injected, in which case he will recover. Hence, even when the animal is dying, recovery from the experimental acid intoxication will ensue from alkaline medication.

Some observers reproach experimental acid intoxication for killing the animals without producing the clinical picture of diabetic coma. This criticism is not founded, as I have observed animals plunged in a state of pathological sleep with complete muscular resolution following repeated injections of butyric acid. In intoxication by lactic acid I have observed dyspnœa, tremor, then slow, deep respiration and somnolence. What more can be expected ? There is nothing larvate from the symptomatic view-point, such as occurs in diabetic coma of man, and the few symptoms which precede its appearance—epigastralgia, vertigo, headache, anorexia—cannot naturally

be detected in a guinea-pig or rabbit. When Hugounenq and Morel induced comatose sleep with irregular respiratory movements by intravenous injections of peptone in a dog, they obtained nothing more similar to diabetic coma in man than the phenomena observed by Violle and myself in dogs submitted to acid intoxication.

For that matter, β-oxybutyric and diacetic acids are not the only ones that produce somnolence and coma; my experiments, and those undertaken by Ehrmann, prove that other organic acids are capable of producing the same symptoms, but that some among them are more comatigenous than others. Hugounenq and Morel's remarks even show that the comatigenous property likewise belongs to other substances as well as acids.

A more serious objection is to be found in the absence of toxicity of acetone compounds. It is certain that these substances have a low degree of toxicity; their coefficient of toxicity, which has been calculated by Desgrez and Saggio, indicates as a lethal dose for each living kilogramme: 4·35 grammes for acetone, 2·17 grammes for diacetic acid, and 1·59 grammes for β-oxybutyric acid. For the latter acid, the most potent of the three, to intoxicate a man of medium weight—60 kilogrammes—it would require about 95 grammes.

This is a very large dose. But if it is shown that such a dose is reached in diabetics dying in coma, the pathogenic action of β-oxybutyric acid will be at least possible, if not certain. Experiments which show the relative innocuousness of acids, so long as a lethal dose is not reached, show that individuals may eliminate large amounts of β-oxybutyric acid for a long lapse of time without developing coma as long as these amounts do not attain the limit of resistance of the organism.

Now, the analyses made by Magnus Lévy in patients with coma have shown that very large quantities of oxybutyric acid pass into the urine. In a child of 12 years weighing 32 kilogrammes he was able to cause, by alkaline treatment, 81 grammes of β-oxybutyric acid to be expelled, and 119 grammes on the following day. This represents a dose of 3·7 grammes per kilogramme of body weight—that is to say, twice the lethal dose. In a diabetic weighing 48 kilogrammes

who recovered from threatening coma, I found 121 grammes of total acetone compounds in the urine.

Usually, it is true, such large quantities of β-oxybutyric acid are not found in the urine in comatose patients, but in answer to this Lévy replies that oxybutyric acid is only expelled by an intensive alkaline treatment, and that such amounts only are voided in the urine in cases of recovery from coma; in fatal cases he found equivalent quantities of the acid in the tissues.

Schwarz, Geelmuyden, Joslin, Mohr, Loeb, and Grube have recorded the elimination of no less considerable quantities of β-oxybutyric acid in the urine of comatose diabetics treated by large doses of alkalines.

And what is more, if to β-oxybutyric acid the diacetic acid also found in the urine be added, one will find a still higher total of acid substances capable of intervening in the production of coma.

For a long time, it is true, the opinion in France remained doubtful because chemists rarely carried out the dosage of β-oxybutyric acid, and those who did so found much smaller amounts than those published by the Germans. H. Labbé found 24·15 grammes the day before death in one case; Guérthault, 3·93 grammes; Hugounenq, in the blood of a comatose diabetic, only found a very small percentage of oxybutyric acid. These results were due to the defective techniques of dosage employed, but at the present time with Van Slyke's procedure analyses show the presence of oxybutyric acid, in doses sufficient to produce intoxication, in the urine of comatose diabetics; hence the most serious objection that can be raised against the theory of acidosis falls to the ground.

One of the most important arguments in favour of the theory of acidosis is the excellent results of alkaline treatment. Success during the premonitory phase is frequent. Naunyn, Lévy, Lichtwitz, Lépine, Blum, and myself have reported many, whether sodium bicarbonate was given by mouth or intravenously. In the phase of confirmed coma success is exceptional, but there are some fortunate instances, two of which I shall report *in extenso* for the first time.

The partisans of the acidosis theory explain these successful

therapeutical results by direct saturation of the acids by means of the sodium set free by the bicarbonate salt. Hugounenq and Morel, although recognizing the excellent therapeutical effects obtained, give another explanation: they believe that alkalines simply favour the elimination of toxic products.

If, in fact, there was merely simple saturation of the acids, it would seem that coma freely treated by alkalines should be recovered from in every case. Violle and myself have noted that β-oxybutyric acid, when saturated by sodium, only possesses a very low toxicity—6·25 grammes per kilogramme of body weight; it would require more than 400 grammes of the saturated acid to poison a man of medium weight, and such an amount has never been met with in any case.

However, the alkaline treatment of coma suffers numerous failures; most often these can be attributed to a too small dose of bicarbonate, but they are met with in instances where sodium bicarbonate was given in sufficiently large amounts to obtain alkalization of the organism. I have recently observed two such examples, one in a very thin girl of 7 years who in twenty-four hours took over 100 grammes of bicarbonate; the second was a man who was given in twenty-four hours 30 grammes of the salt intravenously and 150 grammes by mouth, and the urine had become alkaline to litmus.

It is possible that the bicarbonate, even when introduced intravenously, does not penetrate into the tissues, and hence does not saturate the acids fixed in the cells; it is likewise possible that the cells have already undergone such profound changes from the intoxication that they cannot regain their functions. But whatever may be the explanation accepted for these therapeutical failures, they are none the less real.

Having treated a good many cases of diabetes with acidosis, I have been struck by the considerable difference existing between the results obtained by alkalization in the premonitory phase and in the phase of confirmed coma. In the former, the somnolence, vertigo, dyspnœa, and anorexia cease in their progressive evolution towards coma if a sufficient dose of sodium bicarbonate be given; the successes are so brilliant and so evident that at times one is stupefied. On the other

hand, in the phase of confirmed coma usually no result, even fleeting, is obtained.

These differences of action are to be observed in the same patient. Thus, one of my diabetics, who I had treated for several very serious attacks of acidosis by intensive alkaline medication, suddenly developed coma without any warning, and died in spite of the same intensive treatment resorted to on the previous occasions.

A girl of 7 years with diabetes was brought to me because of rapid emaciation, intolerance for any kind of food, and sleepiness. The urine gave the reaction of serious acidosis. However, a milk diet and the exhibition of a powder composed of sodium bicarbonate and citrate, at the dose of 40 grammes a day, produced a remarkable effect, the patient regaining her strength, while all the symptoms disappeared. Unfortunately, at the end of three days the child became sickened of the bicarbonate, ceased to take it, and the accidents of acidosis returned. Two days later an attack of suffocation suddenly developed in the night; the child cried out, complained of pain in the abdomen without locating the site of the pain, and went off in coma. I saw the patient in the morning, and immediately instituted an intensive alkaline treatment—over 100 grammes of bicarbonate and 50 grammes of sodium citrate in twenty-four hours—without result.

Given the difference in the effects of alkaline treatment within a few days or weeks in the same patient, it would seem as if one was not dealing with the same syndrome upon each occasion.

The clinical evolution that I have outlined in these two cases gives the same impression. Although occasionally the diabetic progressively passes from somnolence to coma, in most instances coma develops suddenly. Diabetic coma has a sudden and brutal onset in the midst of an acidosis with a progressive evolution; it does not act like an aggravation of the acidosis, but like a superadded complication.

Briefly, one has the impression that the coma is not only the fatal end of acidosis that has reached an extreme degree, but that the acidosis and coma are two distinct states, undoubtedly closely associated, but perhaps due to intoxications having different mechanisms.

I therefore believe it useful to describe the state of acidosis quite apart from diabetic coma properly speaking. The state of acidosis, the result of a non-lethal intoxication by the acetone compounds, is characterized by numerous disturbances, such as somnolence, vertigo, dyspnœa, anorexia, vomiting or diarrhœa, epigastralgia, etc. Diabetic coma ending in death has a more larvate and less significative symptomatology, consisting of muscular resolution with loss of consciousness and respiratory, circulatory, and thermic disturbances as accessory symptoms.

If the acetone compounds are not the cause of coma and death, what toxic substance should be incriminated? Hugounenq and Morel invoke complex nitrogenous substances belonging to the group of polypeptids, comparable to Witte's peptone and to various peptones resulting from the digestion *in vitro* of albuminoid matter. These products are not all very toxic; observers estimate that the average fatal dose of the commercial pepsic peptones is 1·5 grammes per kilogramme of body weight, but Witte's peptone injected in dogs at the dose of 50 centigrammes per kilogramme will cause coma to rapidly develop. Certain peptones used experimentally by Nolf are more lethal, and kill at the dose of 20 centigrammes per kilogramme. Without being violent poisons, these peptotoxins are assuredly more active than the acetone compounds.

Hugounenq and Morel also insist on the comatose state with respiratory disturbances produced by their injections, and believe that the intoxication by peptones produces the clinical picture of diabetic coma in man more than experimental intoxication by acids. I have already said that this argument did not seem to me to be convincing. If, in fact, one compares the symptoms of peptone intoxication, such as those described by Grosjean, and those of acid intoxication as were observed by Violle and myself, it will be seen that in each the narcosis and dyspnœa exist, and that one of these states cannot pretend to be a more faithful portrayal of diabetic coma than the other.

To back up their opinion, Hugounenq and Morel point out that in serious diabetes the metabolism of albuminoid substances is not less disturbed than that of the carbohydrates.

This is perfectly correct. Diabetics who die in coma generally enter into the category of patients who present nitrogenous denutrition—that is to say, who constantly and progressively destroy the proteid substances composing their tissues. Since the writings of Hallerworden, it is known that they eliminate in the form of ammonia a more or less important part of the nitrogenous matter they elaborate. The researches that I carried out with H. Bith also showed that these diabetics excrete a high proportion of amino-acids, the intermediary products of the degradation of the proteids which are almost entirely destroyed in a healthy organism. H. Labbé and Lortat-Jacob have noted a considerable increase of undosable substances in the urine in diabetics, a part of which is composed of nitrogenous matter. Finally, H. Labbé and Vitry have found a large proportion of non-dialyzable nitrogenous matter appearing to belong to the group of polypeptids in the urine of diabetics threatened by coma. With Dauphin, I have found large quantities of colloidal nitrogen in the urine of diabetics with acidosis.

These findings—viz., azoturia, ammonuria, amino-aciduria, an increase of the undosable urinary substances, and polypeptiduria—show that a profound disturbance of nitrogenous metabolism exists.

Hence, many facts plead in favour of an intoxication by polypeptids in diabetic coma. But this theory is still only an hypothesis which needs clinical and experimental demonstration. It is not enough to demonstrate the possibility of an accumulation of abnormal substances in the organism belonging to the group of polypeptids; one must still prove that these substances found in the urine of diabetics are toxic and are capable of reproducing phenomena similar to diabetic coma in animals. Therefore, it will be seen what an interesting road is opened up for experimental work. Hugounenq and Morel have distinctly indicated this direction for experimental work, but at the same time they have wisely pointed out the great distance separating the hypothesis and reality.

It would be unfortunate to reject the theory of acid intoxication and adopt that of polypeptic poisoning. We should be on our guard against hasty judgments which have carried away certain less well informed observers. The theory of

acidosis possesses facts in its favour, that of peptotoxin also. The future will settle the question.

For that matter, there is no antagonism between polypeptic intoxication and acid intoxication. In point of fact, the acetone compounds are themselves derived from albuminoid matter—at the same time as fats—and their accumulation in large amounts in the organism is, in the same extent as amino-aciduria and polypeptiduria, an index to abnormal metabolism of albuminoid substances. Therefore both intoxications can and should co-exist.

If it had been demonstrated that diabetic coma is the result of a polypeptic intoxication, the importance of acidosis would assuredly be diminished, but not completely destroyed. There is a fact that cannot be denied, and that is that the stigmata of acidosis indicate the intoxication which induces the development by coma, hence diabetic coma does not occur excepting in patients offering these stigmata. Thus, the conception of acidosis has allowed one to make an interesting and practically useful grouping of the premonitory phenomena of coma. Just as in patients with Bright's disease it is important to distinguish the syndrome of nitrogenous retention from chloride retention, so in diabetics it is useful to separate the syndrome of hyperglycemia from the syndrome of acidosis. At present no one would dream of attributing Brightic coma to retention of urea in the blood-serum; nevertheless modern researches have shown how interesting the dosage of the urea in the blood is for the prognosis. The search and dosage of the acetone compounds in diabetics is none the less valuable for the prognosis.

Now, supposing that the acetone compounds are merely indices of metabolic disturbances and polypeptic intoxication, they nevertheless possess much value to the clinician. But to me they seem to have a still more important part.

I have attempted to show, by both clinical and therapeutical data, the difference existing between the premonitory symptoms of coma and the coma itself. One has the impression that they are two distinct states, clinically and pathologically: one, *diabetic acidosis*, with its train of clinical signs grouped in the form of a syndrome, derived from acid intoxication, and distinctly influenced by alkalines; the other,

diabetic coma, properly speaking, with its larvate and brutal evolution complicating and ending the acidosis, perhaps determined by a polypeptic intoxication, and usually refractory to alkaline treatment. This conception is still but an hypothesis, but it seems to me to accord quite well with the facts observed up to the present time.

CHAPTER XXXII

THE TREATMENT OF ACIDOSIS AND DIABETIC COMA

For years the medical profession was completely disarmed against diabetic coma. All known therapeutical measures at our disposal were equally ineffective. The use of general stimulants—ammonia acetate, ether, caffeine, camphorated oil, etc.—or the elimination of the toxic products by purgatives, gastric lavage, blood-letting, or blood-transfusion (Lecorché, Hilton-Fagg, Küssmaul), by subcutaneous injections of salt solution (Sahli) or intravenously, and oxygen inhalations, gave no really evident result.

At present it is different. The theory of acidosis has directed the treatment of diabetic coma on the right road. Some successful results obtained in confirmed coma, until then reputed to be incurable, by confirming the theory of acidosis, have shown that the prognosis must be changed, and that the physician must not remain inactive, but, on the contrary, should fight diabetic coma with desperation.

Alkalinotherapy.

To combat the acid intoxication by alkalines, such is the principle of the method. But it is not the timid alkaline treatment of the early days that should be given—it was never effective; the organism must be rendered thoroughly alkaline. In diabetic coma the intoxication is due to high doses of β-oxybutyric acid—above 100 grammes. To saturate this acid, considerable amounts of alkalines must be introduced. After saturation a complete recovery is not assured, and although diminished by the neutralization, the toxicity of the acids will not have completely disappeared, as Hugounenq has observed, and as Violle and I have shown; hence, it is possible that the product thus formed still represents a lethal dose in the organism. Therefore, one can foresee that cases

of diabetic coma, even when properly treated, are not all curable, and that this treatment must consequently fail in some.

The Use of Sodium Bicarbonate—Its Introduction into the Organism.—The salt most used for alkalization is sodium bicarbonate, given either by mouth, rectum, or intravenously. Unfortunately it cannot be given subcutaneously, because it irritates the tissues and in diabetics gives rise to sloughing.

By *ingestion* the bicarbonate is exhibited in doses of from 10 to 20 grammes in Vichy or some charged water or in infusions of triticum or camomile. Some persons will take it more readily in very hot fluid, which better disguises the taste. At the dose of 20 to 40 grammes a day it is usually easy to take, even over a protracted lapse of time.

Even very large doses will be absorbed by the stomach; thus, in a child weighing 24 kilogrammes, and who had ingested 220 grammes of bicarbonate in two days, Magnus Lévy only found 3 per cent. of the salt in the fæces. However, after a time the salt will not be well tolerated, and there are patients who flatly refuse it. It, in fact, provokes disgust, anorexia, and vomiting, a very uncomfortable abdominal distension and diarrhœa. It is not always possible to exhibit it in doses of 100 to 200 grammes a day, this being the necessary amount in serious cases.

Finally, in comatose patients buccal ingestion is impossible. Attempts have been made to introduce the drug in solution by the stomach-tube, but the results have been bad, as the salt is not absorbed and the gas formed distends the stomach.

Enemata of bicarbonate are preferable. Lévy advises giving one every half-hour, composed of a teaspoonful of the salt dissolved in water or tea. If the rectum is tolerant the sodium is absorbed, but usually these enemata produce diarrhœa and tenesmus, so that they cannot be repeated.

Intravenous injection of sodium bicarbonate is the procedure of choice in diabetic coma. Stadelmann proposed a solution composed of a 3 per cent. solution of bicarbonate made with a 6 per 1,000 salt solution. In order to obtain a solution isotonic with the blood-serum, Lépine employed a 1·7 per cent. solution in distilled water. Sicard and Salin, on the other hand, used solutions bordering on the maximum

of concentration at 8 per cent.; they are very hypertonic, and congeal at about −3° C. However, they do not offer any drawbacks, according to those who have used them; they do not lacker the blood-serum or produce hæmaturia, nor do they change the blood-pressure. During the injection the patient only complains of some tingling in the face and lips; after the injection there are occasionally a chill, slight rise in temperature, and a little nausea.

I usually employ a 5 per cent. solution in distilled water; this is already hypertonic; at 3 per cent. the Δ is −1·18° C. I have sometimes observed, after intravenous injections, a thermic reaction of over 1·5° F., accompanied by a chill and intense discomfort, indicating the destruction of some red blood-corpuscles.

One has advised sterilizing the solutions by heating in a closed glass receptacle to avoid dissociation of the bicarbonate. This is not indispensable, because, as Blum has shown, when the bicarbonate solution is heated to 110° C. in the autoclave, a sesquicarbonate is formed, containing 36·3 per cent. of sodium, which can very well be employed for alkalization. The solution must be tepid when injected.

The injection is usually given at the anterior fold of the elbow, and at each injection a different vein is chosen; the saphenous veins and those on the dorsum of the hand may be used. The technique of the injection is the same as that now generally employed for the introduction of the arsenical compounds in syphilis, hence further technical details are unnecessary here.

Blum states that he has several times noted a swelling of the vein at the time the injection was being given, and the flow ceased, which he attributed to an irritation of the walls of the vessel, spasm, or even a thrombus produced by a too concentrated solution. Personally, I have never had any such difficulty.

The receptacle containing the solution should be raised about 6 feet above the level of the bed; if it is too low, the solution enters too slowly or even not at all. Lépine advises not to inject too quickly when 1 or 2 litres of solution are to be introduced, so as not to overwork the heart; if a "*bruit de galop*" of the heart is heard during the injection, this is to be

momentarily stopped. Lépine takes from one hour to one hour and a half to inject 1 to 2 litres. It does not seem to me that circulatory overloading is to be greatly feared, and in practice it is better that the injection should not last too long.

The Indications for the Requisite Doses of Sodium Bicarbonate.—The necessary dose of bicarbonate varies (1) according to the case to be treated; and (2) according as to whether the salt is to be given by mouth or intravenously.

1. *Ingestion of Sodium Bicarbonate.*—(*a*) In cases of latent diabetic acidosis, revealed only by the urinary stigmata, without any other symptom, daily doses of 10 to 20 grammes of bicarbonate will usually suffice. Their action may be judged by the evolution of the urinary stigmata, which will indicate the saturation of the acids; the acidity of the urine decreases, and it may even become alkaline in reaction.

(*b*) In cases of diabetic acidosis accompanied by accidents, such as somnolence, vertigo, physical and psychical depression, etc., larger doses are necessary. At least 40 grammes of sodium bicarbonate must be ingested daily. The disappearance of the symptoms at the same time as the evolution of the urinary stigmata and appearance of an alkaline reaction will inform the physician as to the necessity of continuing treatment, to increase the dose of the bicarbonate or the propriety of decreasing it.

One of the effects of alkaline treatment in cases of diabetes with denutrition is to moderate the emaciation or even to increase the body weight. It is possible that the alkalines moderate the nitrogenous denutrition, since they decrease the quantity of nitrogen eliminated in the form of ammonia.

In the majority of cases the increase of weight is due to the development of *œdema*. One should always be suspicious when an increase of weight is too rapidly effected. The œdemas provoked by sodium bicarbonate are white, soft, and diffuse, similar to those observed in the epithelial nephritides; they develop quickly and disappear rapidly when the bicarbonate is stopped.

(*c*) When the acidosis is serious, when diabetic coma is threatening, the medium doses of bicarbonate are insufficient. One should at once exhibit 100 to 200 grammes, and occasion-

ally even more, for at least one or two days. The evolution of the symptoms and that of the urinary stigmata should be controlled daily, and will indicate whether the dose is to be increased or diminished on the following day. When the urine has become alkaline, the dose of bicarbonate is progressively diminished to 80, 60, and 40 grammes in twenty-four hours. The treatment should be continued for some time after the disappearance of the accidents, and, if possible, until the stigmata of the acidosis have likewise vanished.

By conducting the treatment in this way I have been able to forestall the danger of coma in diabetics who already presented the premonitory symptoms, such as extreme depression, deep respiration, and progressive somnolence. By the next day after treatment was begun the improvement was distinct, the somnolence disappeared, while the other symptoms began to retrogress. Lépine reports the case of a diabetic with acetonemia, presenting apathy, respiratory disturbances, and a tendency to sleep, in whom the threatened coma could be stopped by energetic bicarbonate medication, and who survived the attack of acidosis for two years.

(*d*) When the diabetic is plunged in coma the preceding doses are inadequate. I have seen a diabetic coma in a young man end in death on the sixth day, although he was given 60 grammes of sodium bicarbonate daily; the first dose produced a fleeting amelioration, but the treatment was insufficient.

The cases reported by Naunyn, Magnus Lévy, and Grube also show that recovery from coma can only be obtained by large doses. In a case I treated with Dr. Aimé it was only by the daily exhibition of 150 grammes of sodium bicarbonate for three days that the coma was recovered from. In an adult from 100 to 200 grammes by ingestion for two or three days must be considered necessary for obtaining a recovery from diabetic coma. In fatal cases in which such doses have not been reached one has no right to incriminate the untoward outcome to bicarbonate. Not that the salt is infallible; it has numerous unsuccessful results to its credit, even with doses of 113 and 140 grammes of bicarbonate in a child, as in Joslin's case, and even after the urine had become alkaline, as I have seen in several instances.

Up to the present time the fortunate results have been rare—about a dozen in all. It would seem that recovery is less difficult to obtain in children than in their elders.

After the cure of the coma, the bicarbonate is to be exhibited for a long, or even indefinite time, being guided by the results of examination of the urine for the regulation of the daily dose. The fact must never be lost sight of that a diabetic recovering from coma remains in a state of acidosis, and that the coma can return with the utmost readiness.

2. *Intravenous Injections of Sodium Bicarbonate.*—These have been especially employed in France. Upon various occasions Lépine reported the good effects obtained; Sicard advises them, and I have myself many times been witness to their effectiveness.

(*a*) In cases of slight acidosis, in which it is easy to make the urine alkaline by the exhibition of 20 to 30 grammes of bicarbonate, intravenous injections are not indispensable; however, there is no reason why they should not be used if a more rapid effect is desired. Lépine insisted on the propriety of giving alkaline injections before any premonitory symptom of coma developed, as soon as diet and medical treatment of the diabetes had shown themselves powerless.

(*b*) In cases of serious acidosis with threatening coma they are the procedure of choice. In a woman with serious acidosis and ammonuria of over 6 grammes in twenty-four hours and progressive somnolence a single intravenous injection of 15 grammes of bicarbonate produced an immediate result; the somnolence, which threatened to end in coma, and the distress having disappeared, the patient requested herself to be given a second injection, which not only was as successful as the first, but resulted in a permanent improvement. In another diabetic with acidosis I obtained a similar result with an intravenous injection of 25 grammes of sodium bicarbonate.

Given in the premonitory phase of diabetic coma, Lépine has had several cases in which the accidents retrogressed after intravenous injections. One of these patients, who was in imminent danger of death when injected, was in satisfactory health eight months later; the glycosuria was moderate and the acetonuria had almost disappeared.

Parisot observed the remarkable effects of intravenous injections in a patient in imminence of coma; two injections, one of 20 grammes, the second of 15 grammes of bicarbonate, given in one day, resulted in an attack of polyuria and overcame the somnolence.

(*c*) In the phase of confirmed coma, intravenous injections are indispensable; they represent the only treatment. Even if they do not result in recovery, they frequently produce a remarkable arrest of the evolution of the accidents. Several cases reported by Rosenstein, Lépine, Langdon Brown, Besson, and others show that consciousness is recovered for several hours before the patients again become comatose.

Recoveries ensuing from this treatment are still few. Lépine stated that he had never seen one, and was sceptical in respect to cases that had been recorded.

However, Carrié and I have reported a case (Soc. Méd. des Hôpitaux de Paris, May 19, 1911) in which upon two occasions recovery from coma ensued by intravenous injections and ingestion of sodium bicarbonate. The case was one of true acidosis, as proved by the intensity of Gerhardt's reaction.

From these various cases it is evident—and this is also Lépine's opinion—that intravenous injections of bicarbonate are far more potent in controlling acidosis than when the salt is given by mouth. They act almost instantaneously, while the effect obtained by ingestion is not noticeable for twenty-four hours. Much smaller doses of the salt are required when given intravenously. In the case of acidosis that I observed with Carrié we obtained with an injection of 15 grammes of bicarbonate an effect which would not have been produced by 100 grammes given by mouth, and also with much less rapidity. In our case of recovery from coma an injection of 15 grammes of bicarbonate was enough to cause consciousness to return. I therefore consider that this is the treatment of choice in acidosis and diabetic coma, and I am astonished that the Germans employ it so little.

The Succedaneums of Sodium Bicarbonate.—On account of the inconveniences of bicarbonate observed in certain diabetic subjects, an attempt has been made to replace it by other alkaline salts.

Lichtwitz has extolled the sodium salts of organic acids, as the citrate, tartrate, and acetate, which, from the combustion of their acid in the organism, reproduce sodium bicarbonate. The researches of Satta seem to show that sodium citrate and acetate possess an anticetogenous action. But the experiments of Baer and Blum are not favourable in respect to sodium acetate.

Sodium citrate has been the most employed. This salt is agreeable to the taste; it can readily be taken in a watery solution, acidulated with lemon juice. It does not disturb the appetite, and does not cause vomiting or diarrhœa; it even facilitates the tolerance for sodium bicarbonate. For this reason I am in the habit of prescribing a mixture of equal parts of the citrate and bicarbonate in cases where the alkaline treatment must be followed for a long time.

Lichtwitz has compared the action of the citrate with that of the bicarbonate, and it seems to him that the former is more effective. In equal doses, its composition would seem to indicate that it should be twice less alkalizing than the bicarbonate, and in practice this is true. In point of fact, in a diabetic with slight acidosis who was alkalized on the first day with a dose of 40 grammes of sodium bicarbonate, I noted that 40 grammes daily of the citrate did not make the urine alkaline even after the lapse of several days.

Solutions of sodium citrate, being practically neutral and do not decompose, may be given subcutaneously, hence facilitating the treatment of diabetic coma. In order to render it absolutely neutral and still to diminish its irritating action, Lichtwitz has proposed to saturate the solution with a little citric acid and lemon juice.

The Manner of Action of Alkaline Treatment.—The alkaline treatment of acidosis appears to act by saturating abnormal acids which poison the system, particularly β-oxybutyric and diacetic acids. The organism defends itself by neutralizing the acid products by means of the bases contained in the tissues and ammonia, from which results a loss of alkaline that is pernicious. The introduction of sodium bicarbonate, a salt easily decomposed in the system, furnishes the sodium which replaces the bases of the tissues and ammonia for the saturation of organic acids, while the liberated carbonic acid, being

volatile, is eliminated by the respiratory tract. In this way one will understand that any salt susceptible of furnishing an alkaline carbonate by combustion in the organism may play the same part.

Why is bicarbonate at the same dose when taken by mouth less effective than when given intravenously ? Theoretically, in each case the same number of alkaline ions should be placed at the disposal of the organism. But when the salt is given *per os*, so many intermediary reactions take place between the gastric mucosa and the intimacy of the tissues that we do not know if the final result can be the same. Lépine believed that the injections caused a temporary retention of sodium in the organism, which thus allowed the bicarbonate to penetrate the cells; but this occurs after ingestion as well. At all events, it is a general rule of physiology that drugs, as well as poisons, when introduced directly into the blood-stream, exercise a more intense action than when injected into the cellular tissue or absorbed by the digestive tract.

The Action of Alkaline Treatment on Urinary Excretion.— What becomes of the urinary stigmata under the influence of alkaline treatment ?

The acidity of the urine at once decreases, but the urine remains acid until a sufficient dose of the alkaline to saturate all the acids of the organism has been introduced. It is only then that the urine becomes alkaline to litmus and afterwards to phenolphthalein.

The ammonuria likewise decreases. When the acids are saturated by the sodium, the percentage of ammonia becomes normal, or even subnormal. From this it must not be concluded that the acidosis has disappeared, because if the bicarbonate is stopped, or if the dose is decreased too much, the ammonuria increases. Besides, an excretion of the acetone compounds often continues, and it is only when the acidosis is really cured that the ammonuria falls to the normal, in spite of the cessation of alkaline treatment.

The excretion of the acetone compounds increases by alkaline treatment, as is made evident by the cases recorded by Weintraud, Meyer, Schwarz, Mohr, Loeb, Luthje, Blum, and my own.

In a case of Magnus Lévy there was a distinct parallelism

between the ingestion of the bicarbonate and the excretion of diacetic and β-oxybutyric acids.

Duration of Treatment.	*Ingestion of Sodium Bicarbonate.*	*Total Elimination of β-Oxybutyric Acid.*
3 days	50 grammes.	60·0 grammes.
3 ,, ...	36 ,,	47·3 ,,
2 ,, ...	18 ,,	36·9 ,,
3 ,, ...	18 ,,	38·3 ,,
5 ,, ...	9 ,,	35·1 ,,
4 ,, ...	9 ,,	27·5 ,,
4 ,, ...	21 ,,	36·0 ,,

However, the same observers have occasionally noted that this reaction was absent, and even exceptionally may take on an inverse sense.

In cases of cured diabetic coma, Magnus Lévy has shown by dosages how great may be the elimination of diacetic and β-oxybutyric acid; the total may be over 100 grammes a day. At the same time there is an abundant diuresis. Thus, in a case of cured diabetic coma in a girl of 12 years he found:

Days.	*Ingestion of Sodium Bicarbonate.*	*Urine in c.c.*	*Total Excretion of Acids calculated in β-Oxybutyric Acid.*
1st day	15 grammes.	2,500	41·5 grammes.
2nd ,, ...	18 ,,	2,750	40·4 ,,
3rd ,, ...	18 ,,	2,600	47·8 ,,
4th ,, ...	109 ,,	6,000	93·3 ,,
5th ,, ...	102 ,,	7,100	107·6 ,,
6th ,, ...	45 ,,	4,000	37·0 ,,
7th ,, ...	36 ,,	3,950	45·8 ,,

On the other hand, in cases of fatal diabetic coma no such elimination occurs, and after death a dose of β-oxybutyric acid will be found in the tissues corresponding to that which should have been excreted. These data well show that the alkaline salts act by favouring the elimination of the acetone compounds.

What we learn from the dosage of the acetone compounds

is also to be noted when one studies the excretion of diacetic acid with Gerhardt's or Legal's tests. In spite of the improvement of the symptoms by alkaline treatment, Gerhardt's and Legal's reactions do not decrease in intensity; sometimes this even seems to increase. Or during a very larvate acidosis Gerhardt's reaction may become positive under the influence of alkaline treatment.

The study of these reactions shows the prolonged time of elimination of the acetone compounds. It is only when the acidosis has definitely subsided that this elimination stops, and for this it may require weeks or months. Lieben's test, which shows the presence of acetone, follows about the same chart curve.

Alkaline intravenous injections do not act exactly as exhibition of the salt by mouth. I have never observed the same immediate temporary action on the ammonuria; this will progressively diminish after injections, although on the day of the injection it does not appear to be especially influenced. Briefly, there is discordance between the immediate therapeutical influence on the symptoms and the more remote influence on the ammonuria.

Alkalinotherapy does not seem to influence the glycosuria. When the decrease of the glycosuria after intravenous injections is progressive, this should not be attributed to the alkaline salt, because it may depend upon a reduced diet whose effects are prolonged. Sicard also does not admit that there is a constant influence of intravenous injections on the glycosuria.

Diet.

Although alkalinotherapy is the basis of treatment of diabetic coma, there are some accessory medications that should not be disregarded. Diet is not of much importance in confirmed coma, the patient usually being incapable of taking food. In the premonitory phase when he can still eat, all deleterious substances must be avoided and meat absolutely proscribed; certain alkalizing foods, such as cereals, vegetables, and milk, may be useful; fasting with abundant fluid intake—vegetable soups, lemon juice, various infusions, and alkaline waters—is still more preferable. During the phase of acidosis,

which precedes the coma by several months, the diet, on the contrary, assumes capital importance.

I have already outlined the diet in acidosis in cases of diabetes with denutrition. I pointed out the danger of meat diets as factors in the production of acidosis; the utility of milk and vegetarian diets, especially oatmeal and vegetable cures, which alkalize the organism, and inanition cures still more so. Therefore I shall only recall the fact that a well-conceived diet may prolong the life of a diabetic for months or years, and that it is sufficient to cause the acidosis to definitely disappear in certain forms of diabetes without denutrition.

Accessory Medication.

Cardiovascular exhaustion which forms part of coma also requires treatment. The various cardiac tonics, caffeine, theobromine, sparteine, and digitalis should be exhibited. Injections of camphorated oil may be freely given. It is possible that intravenous injections of sodium bicarbonate exercise a tonic action on the cardiac and vascular systems—a fact which helps to explain their unquestioned greater effectiveness than when the salt is ingested.

During the premonitory phase of coma and phase of acidosis very great precautions must be taken; the diabetic patient should be regarded as a fragile subject, and should be protected as far as possible against infectious processes of all sorts, as well as traumata and fatigue.

CHAPTER XXXIII

SERIOUS ACIDOSIS TREATED BY INTRAVENOUS INJECTIONS OF SODIUM BICARBONATE—A BIOCHEMICAL STUDY*

THE problem of diabetic acidosis, so important from the clinical view-point, is still moot. Therefore it may not be devoid of interest to report a case in which intravenous injections of sodium bicarbonate exercised a remarkable influence over the premonitory symptoms of diabetic coma, and where we were able to regularly follow the evolution of the chemical stigmata of acidosis as influenced by treatment.

CASE REPORT.—Female, æt. 52 years, entered hospital on April 7, 1911, for a salpingitis. In presence of an abundant glycosuria the patient was transferred to the medical ward.

No hereditary taint could be found in the antecedents. At the age of 18 years she had typhoid fever; then until the age of 40 no morbid incident disturbed her health. She never married nor became pregnant. She has worked from sixteen to eighteen hours a day, and did not feel fatigued by it. Patient is a good, but not excessive, eater, and at the age of 30 she weighed 69 kilogrammes, which, on account of her short stature, represented a certain degree of corpulence.

At the age of 40 she commenced to suffer from her abdomen. In 1901 she was treated for a retroversion of the uterus, and at this time an analysis of the urine revealed an abundant glycosuria—300 grammes per day.

Shortly after this a purulent collection in the right iliac fossa obliged the patient to be admitted as an urgent case to hospital. The collection opened spontaneously into the intestine. The question of operation was discussed, but, given the glycosuria, it was rejected. The patient received local medical treatment. The diabetes was treated by a proper diet, and the glycosuria oscillated between 50 and 70 grammes in twenty-four hours. Her health improved sufficiently for the patient to return home and resume work six months later.

Two years later, in 1903, there was another attack of salpingitis, which was soon recovered from by rest. The glycosuria was abundant, but by a severe diet it disappeared.

At the end of March, 1911, severe abdominal pain developed, and the patient, who had remained in bed with ice applied to the abdomen, was admitted to hospital on April 7.

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* Soc. Médicale des Hôpitaux, June 9, 1911. In collaboration with P. Carrié.

By examination of the patient, one was at once struck by her thin, tired face. Examination of the generative organs revealed an irreducible uterine anteversion and bilateral salpingitis. There was no peritoneal reaction. Therefore the fatigue and emaciation, symptoms to which the patient drew attention, did not seem to be only due to the abdominal process.

There were some dyspeptic disturbances; the tongue was white and coated; there was some gingivitis and the teeth were loose. Appetite normal; slight polydipsia, no polyphagia.

All the tendon reflexes were normal, and there were no ocular disturbances.

Urine was voided in fair amount—1,700 c.c. in twenty-four hours—and was acid to litmus. Glycosuria abundant, with very strong Gerhardt's, Legal's, and Lieben's reactions. From these reactions it appeared legitimate to find the explanation of the fatigue and emaciation complained of by the patient. The following diet was ordered:

Meat	200 grammes.
Potatoes	100 ,,
Eggs	4 ,,
Butter	50 ,,
Cheese	60 ,,
Green vegetables	2 portions.
Broth..	1 litre.

One orange nearly every day.

No sodium bicarbonate was prescribed.

April 11.—Slight somnolence was noted; the patient did not wake well in the morning, and slept after the noon meal.

April 13.—Desire to sleep increased; distinct aromatic odour of breath.

April 16.—Somnolence more marked; patient falls asleep when sitting on a chair.

April 17.—Prostration and somnolence still more marked; increase of aromatic odour of breath. No vertigo, no headache, no vomiting, no sighing respiration.

An intravenous injection of 500 c.c. of a 3 per cent. sodium bicarbonate solution was given. Shortly afterwards the condition improved, the sleepiness disappeared, and for the first time in eight days the patient did not sleep in the afternoon.

April 18, 19, *and* 20.—Continued to feel well; no somnolence.

April 21.—The phenomena reappeared: patient very somnolent; went to sleep during the visit, and of her own accord asked that an injection might be given; 500 c.c. of the 3 per cent. bicarbonate solution were given. The injection was followed by a chill lasting two hours, but the somnolence disappeared.

April 22.—Patient felt really well for the first time; somnolence has disappeared, strength returned, and the patient, against advice, left hospital.

The annexed table shows the amount of the glycosuria, ammonuria (dosage by Ronchèse's method), and the urinary acidity.

Date (April, 1911).	Clinical Remarks.	Treatment.	Total Amount of Urine in c.c.	Glucose in Twenty-four Hours.	NH_3 in Twenty-four Hours.	Acidity in SO_4H_2 in Twenty-four Hours.	Gerhardt's Reaction.	Body Weight in Kilogrammes.
			c.c.	Grs.	Grs.	Grs.		
9	—	—	3,425	188·27	5·82	—	Very strong	50·000
11	Slight somnolence. Wakes poorly in morning and falls asleep at noon meal	—	3,050	108·88	5·6	3·53	—	49·500
12	—	—	2,920	58·0	6·04	3·87	—	—
13	Patient notices her somnolence has increased. Slight but distinct aromatic odour of breath	—	3,760	75·0	6·32	3·49	Much stronger	—
14	—	—	3,520	64·82	3·76	2·59	—	49·600
15	—	—	3,200	54·4	6·17	2·75	—	—
16	Somnolence increased. Patient cannot sit in chair without falling asleep	—	2,600	43·57	4·24	1·53	—	—
17	Aromatic odour of breath. After injection a feeling of well-being. For the first time in eight days patient did not sleep in afternoon	12 m. injection of 15 grammes sodium bicarbonate, 3 per cent. solution	2,500	83·75	4·13	2·70	—	—
18	—	—	2,800	71·06	4·48	2·18	—	49·600
19	—	—	2,250	49·95	3·73	1·75	Less strong	—
20	Patient continues to improve. Somnolence not returned	—	2,500	62·5	3·32	1·72	,,	—
21	Somnolent in the morning. Patient requested to have another injection given	At noon intravenous injection of 15 grs. bicarbonate. Slight chill	2,510	51·2	2·91	1·83	Decrease continuous, but still very strong	51·100
22	Feels very well. No somnolence	—	2,350	42·53	2·83	1·71	Stronger	—
23	—	—	2,560	36·0	4·22	1·25	Less strong	—
24	—	—	2,560	36·0	5·04	1·4	,,	—
25	—	—	2,200	46·8	3·6	1·4	,,	50·500
26	—	— No oxylol	2,220	29·7	2·98	1·73	,,	50·500
27	—	—	2,200	26·18	2·55	1·61	,,	50·500
28	—	—	2,700	43·52	2·2	1·59	,,	51·200
29	—	—	2,900	43·52	2·22	1·86	,,	51·200
30	—	—	2,200	43·52	1·61	1·41	,,	51·200

This case history shows the action of sodium bicarbonate on acidosis.

From the clinical view-point the result was most distinct; the progressively increasing somnolence was at once stopped and the imminence of coma dispersed. The amelioration was persistent in spite of the small dose of bicarbonate injected in the vein (only 15 grammes); a much larger dose would certainly have been necessary to obtain the same result if the salt had been absorbed in the digestive tract, as our experience has shown that from 60 to 100 grammes are necessary when the salt is given *per os*. This shows the far greater effectiveness of intravenous injections than by ingestion.

The therapeutical result was so distinct that the patient herself asked for an injection four days after the first one had been given, as the acid intoxication had not been completely dispersed and somnolence recurred. This time, even with the small dose of 15 grammes, the result was definitive; the patient regained her strength, and wished to leave hospital in order to resume her work, although against advice. The stigmata of acidosis not having disappeared, it is to be feared that in absence of treatment the symptoms will recur and coma ensue.

The second injection was followed by a chill and intense distress, but temporary, perhaps due to the destruction of some red blood-corpuscles by the bicarbonate solution, which is hæmolytic, and, in point of fact, there was a temporary urobilinuria following the injection.

Such therapeutical results are not exceptional in the premonitory phase of diabetic coma; Lépine, Magnus Lévy, Blum, and Luthje have reported similar cases, and I have myself had identical success in several instances. They show that, no matter what may be the deleterious substance incriminated, the acidosis plays an important part in the intoxication leading to coma, as Naunyn and others have maintained.

The acidity of the urine, although higher than normal, was never high in the case here reported. It fell progressively from the onset, and after the first injection it could be considered normal. It is to be remarked that neither the first nor second injection produced a temporary decrease of the acidity. Their rapid and most remarkable clinical action was not accompanied by alkalization of the urine.

The ammonuria was very intense at the onset, reaching 6·32 grammes. Now if, on the one hand, one considers the amount of protein substances contained in the diet—140 grammes, which corresponds to 22 grammes of nitrogen—and, on the other, the usual proportion—5 to 6 per 100—of ammoniacal nitrogen in relation to the total nitrogen in the urine, one may conclude that a normal subject, with the same diet, would have excreted 1·60 grammes of ammonia. The excess, not contained in the diet, was therefore in this case 6·32 grammes – 1·60 grammes = 4·72 grammes. On the other hand, knowing that 1 gramme of ammonia is capable of saturating 6·1 grammes of β-oxybutyric acid, one can admit that the excess of ammonia in the urine was the index of an elimination of 30 grammes of β-oxybutyric acid. This calculation is only approximate, but several observers, von Noorden in particular, have employed it for calculating the elimination of acids by the urine in diabetics. The old experiments of Walter and the recent ones of H. Labbé and Violle on intoxication by mineral acids justify this estimate by showing that there is a relationship between the quantity of acid introduced into the organism and the amount of ammonia excreted.

Intravenous injections of sodium bicarbonate resulted in a decrease of the ammonuria. If the ammoniacal excretion in the three phases be compared, it will, in fact, be seen that:

During the 1st phase the mean of the daily excretion was	5·26 grammes.
During the 2nd phase, after the 1st bicarbonate injection, the mean was	3·61 „
During the 3rd phase, after the 2nd bicarbonate injection, the mean was	3·02 „

At the time the patient left hospital, the ammoniacal excretion had returned to the norm—1·61 grammes in twenty-four hours.

It is to be noted that the decrease of the ammonuria was progressive, and that there was no sudden decrease after the bicarbonate injections, as Blum, Luthje, and Lichtwitz have observed following the ingestion of sodium bicarbonate.

Gerhardt's reaction, the index of diacetic acid excretion, lends itself with difficulty to a quantitative estimate. However, I have attempted to make a gross estimate of its varia-

tions. In the case reported it was constantly very intense. At the onset it progressively increased; one drop of perchloride of iron gave a dark mahogany brown colour to the entire urine in the test-tube. Afterwards the intensity of the reaction diminished, but it was still strong when the patient left hospital. The bicarbonate injections did not have any distinct action over the reaction; after the first one there was a decrease of the reaction, and after the second a temporary increase ensued. What is to be especially remembered is the persistency of the diaceturia after the disappearance of the clinical symptoms and the ammonuria; this persistency should make diaceturia the most important of all the chemical stigmata of acidosis.

Legal's and Lieben's reactions, indices of acetonuria, quite closely followed the fluctuations of Gerhardt's reaction. They were likewise very intense.

The glycosuria diminished from the commencement to the end of the patient's stay in hospital. If exception be made to the two first days of diet when it was still very high, we find that it averaged:

1st phase, before the injections ..	66·09 grammes in 24 hours.	
2nd ,, after the 1st injection ..	58·67	,, ,, ,,
3rd ,, after the 2nd injection ..	37·11	,, ,, ,,

Should these figures lead one to suppose that the alkaline injections decreased the glycosuria ? This cannot be affirmed, because the reduced diet given the patient might produce the same result. The injections were not followed immediately by a fall of the glycosuria; it decreased progressively, as occurs when the patient is on a diet.

Lastly, the patient's weight was happily influenced by the injections. Although it at first fell off, it began to increase after the first injection, and when the patient left hospital she had gained 1 kilogramme 200 grammes.

Briefly, bicarbonate injections, even in small doses, exercise a manifest curative action in the premonitory phase of diabetic coma. They cause the acidity and ammonuria to drop to the norm; the diaceturia and acetonuria decrease more slowly. The clinical results of the injections are more evident than their chemical action.

CHAPTER XXXIV

TWO CASES OF DIABETIC COMA CURED BY LARGE DOSES OF ALKALINES

THE pathogenic theory of acidosis, even although it does not completely explain diabetic coma, has rendered great practical service, as it has led to a therapeutical method which has resulted in the cure of some cases of diabetic coma, until lately an incurable morbid process.

When the coma is still in the premonitory phase, recovery quite frequently ensues, provided that sodium bicarbonate is exhibited in massive doses and not timidly, as was the case a few years ago. But when coma is confirmed, recovery is very uncommon. Lépine* only obtained temporary amelioration; he mentions Rosenstein's case in which the improvement was likewise transitory, and also Besson's case in which the patient regained consciousness after an injection, but died some hours later, and Hess's case, which does not appear to have been more fortunate. Magnus Lévy in 1899 discussed Roget and Balvay's, Schmitz and Olivier's cases, but these do not seem to have been instances of diabetic coma. He rejects Hilton-Fagg's case in which there was only temporary improvement, as well as Zinn's case, which was not sufficiently characteristic. He only admits as certain the successful results obtained by Naunyn in four children, two others observed by himself, and one case reported by Mohr in a child—which is too incomplete to carry conviction—and one adult case observed by Grube. This makes a total of eight cases.

I have had two cases in which recovery ensued, and the rarity of such an outcome makes them worthy of a detailed report, all the more so because they presented different conditions. The first was a diabetic without denutrition, the second was a diabetic with the severest form of denutrition. Since this time I have become convinced, from numerous other

* Lépine, "Le Diabète Sucré," Paris, 1909 (Alcan, publisher).

cases, that these conditions have a considerable importance from the view-point of the prognosis and chance of success.

The first case was reported to the Société Médicale des Hôpitaux in July, 1911; the second one on December 12, 1913, to the same society.

Case I.—Mrs. L. entered hospital for a cystitis on November 16, 1910. As she also had diabetes, I was asked to see her.

The patient was 65 years of age, and belonged to a family of diabetics. Her father, corpulent and diabetic, died at the age of 50 with gangrene of the foot. Her mother died at the age of 23 of pulmonary tuberculosis. One of her brothers is a corpulent diabetic, another died at 50 of some hepatic process, and a sister, still living, is diabetic.

The patient has had seven children: five are living and well; one died at 30 years of pulmonary tuberculosis, another at the age of 3 years of tuberculous meningitis.

The patient had always enjoyed good health; the appetite was large, and she became slightly corpulent. At the age of 55 she was warned by an intense polydipsia that she had become diabetic, but she never submitted to any serious treatment.

The cystitis for which she entered hospital began in May, 1910.

It was at once found that she was excreting 110 grammes of glucose in twenty-four hours, and that Gerhardt's reaction was marked. A milk diet—2 litres—was ordered, with 40 grammes of sodium bicarbonate daily. Urotropin and vesical irrigations were given for the cystitis.

In spite of treatment the cystitis became worse, and was complicated by pyelonephritis; the temperature rose, and on November 25 it reached 104° F.

November 28.—Following another paroxysm of fever and chills, the patient developed a very serious condition; she was somnolent, and did not reply distinctly to questions; it was necessary to speak to her in a loud voice. Coma was imminent.

November 29.—The condition was worse. She made no answer whatever to questions, and it was difficult to make her swallow any liquid, while the bicarbonate could not be exhibited at all. The urine fell from 3,100 to 2,400 c.c., and presented an intense Gerhardt reaction.

An intravenous injection of bicarbonate was given—500 c.c. of a 3 per cent. solution—after which the condition improved a little, so that 60 grammes of the salt in an infusion of triticum and Vichy water could be given by mouth.

November 30.—There was a marked improvement. The patient was awake and replied to questions; diuresis reached 3,500 c.c. A second injection of 500 c.c. of the bicarbonate solution was given, and 60 grammes of the salt were given by mouth.

December 1.—A chill with a temperature of 103·2° F. took place. Patient exhausted but lucid; no somnolence. Injection of 500 c.c. bicarbonate solution and ingestion of 80 grammes of the salt.

December 2.—Temperature normal; patient very exhausted; urine, 3,000 c.c. Same treatment.

December 3.—Temperature normal; exhaustion; urine, 2,400 c.c. One intravenous injection, and same amount of bicarbonate by mouth.

December 4.—Temperature normal; exhaustion; urine, 3,000 c.c. No injection. Patient took only 15 to 20 grammes of bicarbonate *per os*.

December 5.—General condition again very serious. Somnolence of the evening before has now developed into coma. Urine, 2,000 c.c. Prognosis absolutely bad. Injection of 1,000 c.c. of 3 per cent. sodium bicarbonate solution and 20 grammes of the salt by ingestion.

Gerhardt's reaction, intense in the forenoon, was much less marked in the urine collected after the injection.

December 6.—No coma, only somnolence. Intravenous injection of 600 c.c. bicarbonate solution and 20 grammes of the salt *per os*.

December 7.—Considerable improvement. No somnolence. Urine, 2,500 c.c. Twenty grammes of bicarbonate by mouth.

After this the amelioration continued and the cystitis improved. Temperature oscillated between 98·6° and 101° F. Urine fell to 1,500 and 1,000 c.c.; glycosuria varied between 70 and 90 grammes in twenty-four hours with a diet comprising about 70 grammes of carbohydrates. Gerhardt's reaction, although less intense, was still positive. Dosage of acetone, 2 grammes in twenty-four hours. Patient continued to take 10 to 20 grammes of a mixture of sodium bicarbonate and citrate daily. Feeding was better.

December 28.—Patient has regained her strength, and all traces of coma have disappeared. Discharged from hospital.

May 15, five months after the accidents of coma, she was found to be in a very satisfactory condition. By the diet prescribed the glycosuria had almost disappeared, the cystitis had cleared up, and there was no menace of coma.

This was an unquestioned recovery from diabetic coma. Upon two distinct occasions the coma was dispersed by intravenous injections of sodium bicarbonate. The patient survived, and three years later she was still living. The patient recovered with relatively small doses of the bicarbonate because she had a diabetes without denutrition, and attacks of acidosis occurring in these circumstances, although they can be fatal, are susceptible of recovery or may even be definitely cured.

My second success was obtained in a case of diabetes with denutrition of the severest type in a patient with acidosis threatening for several months, and who was even intoxicated to such a degree that coma supervened when he was taking 60 grammes of bicarbonate daily.

Case II.—Male, æt. 35 years, has had diabetes for several years. At the onset the glycosuria was 85 grammes per day, and varied from 0 to 120 grammes during the first years of the disease. No treatment—because antipyrine, the cacodylates, uranium acetate, phosphoric acid, homeopathy, etc.—had been found to be without effect. The diabetes progressively became worse. Three years later, in 1911, the glycosuria could no longer be reduced; two severe Guelpa cures did not control it, and only succeeded in emaciating and depressing the patient.

I saw the patient for the first time in May, 1911; he measured 1 metre 60 centimetres, and weighed 50 kilogrammes. Digestion was poor, the stools hard and difficult; no sign of pancreatic insufficiency. Skin sallow, liver not hypertrophied, urine only contains traces of urobilin and reddish-brown pigment. Tendon reflexes normal.

A mixed diet containing 35 grammes of carbohydrates gave a glycosuria of 57 grammes; the sugar excreted was partly derived from the albumins. The nitrogenous balance showed the small deficit of 84 centigrammes a day. At this time there was no acidosis; little acetone and no diacetic acid in the urine.

The diabetes progressed. In May, 1912, the glycosuria was 150 grammes with a diet containing 110 grammes of carbohydrates. The total nitrogen showed a deficit of 1·07 grammes. Although moderate, acidosis had developed; there was a marked diaceturia and an acetonuria of 53 centigrammes.

In November, 1912, the condition was worse. The glycosuria was 167 grammes with a diet containing 123 grammes of carbohydrates. There was a nitrogen deficit of 4·89 grammes. The acidosis was intense, diaceturia abundant, acetonuria of 1·11 grammes, β-oxybutyric acid 24·78 grammes, and ammonia 3·51 grammes. Nevertheless, the patient was taking 40 grammes of a mixture of sodium bicarbonate and citrate a day.

In February, 1913, the acidosis became threatening, the appetite was mediocre, fatigue considerable, with paroxysms of oppression and intense acidosis reaction. Meat diet increased the symptoms. I was obliged to put the patient on a vegetable and milk diet or oatmeal soup, and 50 grammes of sodium bicarbonate were ordered to be taken daily for several days.

On April 26, in spite of a vegetable diet and the daily absorption of from 40 to 60 grammes of sodium bicarbonate, the patient felt worse. He came from a distant city, and the railway trip aggravated his condition, which appeared to me disquieting. He fell asleep in an armchair while in the act of speaking; speech was difficult and the memory paretic. He complained of profound anorexia, intense thirst, and extreme dryness of the mouth. Several times during the trip to Paris he almost lost consciousness, and did not realize where he was. Respiration was deep, sighing, and slow; there was a strong odour of acetone in the breath. When he arose from the chair he complained of vertigo, a hollow feeling in the head, and he staggered when he walked.

Fearing that coma might ensue at any time, he was sent to a nursing

home and immediately put to bed. An hour later, when I saw him, I found the eyes half closed, and the patient in a state of inertia, indifferent, and only awakening when shaken, afterwards becoming somnolent. The respiration was deep, sighing, and unequal; pulse 90, depressible. The tonicity of the eyeballs was normal. Patellar reflexes almost absent.

An intensive treatment was ordered, beginning with an intravenous injection of 500 c.c. of a 5 per cent. bicarbonate solution with 10 grammes of the salt by mouth, and 200 c.c. Vichy water every hour. Every three hours he was given 150 c.c. of milk. A nurse was constantly in attendance, and with much perseverance was able to carry out the treatment. By midnight the patient had taken 127 grammes of sodium bicarbonate. Condition stationary, consciousness dim, did not sleep; at times inert, at others restless; there was vertigo and a distressing occipital headache. During the night there were several fœtid liquid stools.

April 27.—A slight improvement was noted. Somnolence and subconsciousness still continued, but the respiration was more regular. Thirst intense, tongue pasty. Diarrhœa continued—eight motions in twenty-four hours, but less fœtid than on the previous day. Abdomen very distended. No vomiting. Night was better. The bicarbonate was continued to be pushed by mouth, so that in twenty-four hours 198 grammes had been ingested.

April 28.—Improvement continued. Depression less profound, consciousness returning, respiration more regular. Still some vertigo and sharp pain in right supra-orbital region. Several attacks of somnolence during the day, from which the patient could be slowly roused; he remained confused, and speech was slow and monotonous. He was incapable of co-ordinating ideas. A soft, indolent œdema began at the malleolæ and reached the legs, thighs, and scrotum. Night quieter. In the last twenty-four hours the patient absorbed 143 grammes of sodium bicarbonate.

April 29.—Improved. Vertigo and supra-orbital pain have stopped; the patient spoke more willingly, the speech was less monotonous, and he was less stupid, being more interested in conversation. Respiration still somewhat irregular, 16 to 20 to the minute. Pulse regular. No stool.

Œdema had reached the flanks, hands, and eyelids. Abdominal distension still very considerable, and distressed the patient. The skin, especially over the cheek-bones, chin, and palmar surface of the hands, presents a very pronounced dark ochre colour; however, it was not icterus, because the conjunctivæ were not yellow and the urine did not contain any bile pigment. The night was quite quiet. The dose of bicarbonate was reduced to one-half the daily amount.

April 30.—Improved. The œdema seemed to diminish a little over the thighs. The respiration was a little irregular occasionally. Pulse, 86. Temperature, 99° F. One soft motion. Patient got up for a while in the afternoon. Ordered eggs, dry vegetables, and butter. Bicarbonate continued.

May 1.—Œdema stationary. Yellow colour of integuments still present, skin dry. Pulse, respiration, and temperature normal.

Patient feels better, is more plucky, and speaks more easily. He felt that there was "a blank" in his life, and did not recall what took place after he entered the nursing home. Sleep quiet, but interrupted in the middle of the night by several paroxysms of distress with arrhythmical respiration.

Analysis of the urine made by Mr. Démelin gave the following results:

Amount	6,100 c.c.
Total nitrogen	17·93 grammes
Ureic ,,	16·10 ,,
Urea	35·0 ,,
Total ammonia (dosage with formol)	1·71 ,,
Ammonia salts	1·09 ,,
Amino-acids	0·62 gramme.
Glucose (dosage with Fehling's solution)	254·12 grammes.
,, (polarimetric dosage)	146·01 ,,
Acetone	0·75 gramme.
Diacetic acid (Legal's and Gerhardt's reactions)	Abundant.
β-oxybutyric acid	25·84 grammes.
Albumin	Imponderable trace.
Indoxyl	*Nil.*
Urobilinogen	Present.
Bile pigments	*Nil.*
Nitrogenous percentage	89·0 per 100.
Ratio of ammoniacal nitrogen to the total nitrogen	7·7 ,,
Ratio of amino-nitrogen to the total nitrogen	3·1 ,,

A study of the balance of nutrition gives the following results:

Nitrogenous balance:	
Ingested nitrogen	17·39 grammes.
Excreted nitrogen*	19·67 ,,
Deficit	2·28 ,,
Carbohydrate balance:	
CH ingested	107 grammes.
Glucose excreted	254 ,,
Deficit	147 ,,

May 2.—Colour of skin unchanged, œdema and distension the same. Respiration regular, temperature normal, pulse 82. Somnolence after meals. Patient sat in chair the greater part of the day. Slept quietly during night.

May 4.—Felt much better, but œdema, dry skin, colour of integuments, abdominal distension, and thirst persisted.

Ordered the same diet—dry vegetables, eggs, and butter; sodium

* Admitting a fæcal loss of one-tenth of ingested nitrogen.

bicarbonate, 55 grammes; Vichy water, 3,200 c.c.; calcium chloride, 3 grammes.

May 5.—Condition the same. Respiration regular, pulse 78 to 80, œdema stationary. Same treatment and throbomin 1·5 grammes.

May 6.—Œdema somewhat decreased. Same treatment.

May 8.—Strength returning, patient can walk and go upstairs. Œdema disappeared from face and hands. Blood-pressure (Pachon): maximum, 15; minimum, 6. Pulse, 80.

May 9.—Patient discharged from nursing home and returned to his home.

May 17.—I was informed that the patient bore the railway trip to his home very well, although he was greatly fatigued by it. For the next few days there was an abundant polyuria, and the œdema practically disappeared, there being only a little swelling of the legs. Sleep somewhat restless. Digestion difficult. Mixed, milk, cereal, and vegetable diets tried in turn. Sodium bicarbonate, 40 to 50 grammes daily.

July 21.—Œdema of face still persists; weakness considerable, patient can hardly walk 300 yards. Body weight is very variable from one day to another, oscillating between 45 and 47·5 kilogrammes. Analysis of urine: 11,000 c.c. in twenty-four hours; glucose, 123 grammes (the diet only contained 33 grammes of carbohydrates); β-oxybutyric acid, 20·68 grammes; acidosis reactions still very intense.

During the month of August the digestion became gradually worse, and the body weight fell to 40 kilogrammes.

On the night of August 23 severe diarrhœa developed—six to seven liquid motions—and in the morning the patient was very oppressed. At 11 a.m. coma developed, death taking place at midnight.

This case shows that recovery may ensue even in the coma of diabetics with denutrition and after the premonitory phase when complete coma has developed. The degree of acid intoxication can be surmised when it is recalled that from 150 to 200 grammes of sodium bicarbonate was necessary to alkalize the urine, while after recovery from the coma daily doses of 70 grammes did not prevent the urine from again becoming acid.

Contrary to what occurred in the first case, the intoxication continued its progress after recovery from the coma, the patient dying four months later from a second attack.

The recovery from coma in this case was unquestionably due to the treatment employed, which was energetic, massive, and prolonged. During the first three days the patient absorbed 127, 198, and 143 grammes of bicarbonate, and it was only on the third day that the organic fluids were alkalized

and the urine ceased to be acid. Such doses of an alkaline salt are considerable, representing an average of 3 grammes of bicarbonate per kilogramme of body weight per day. Besides, the treatment was prolonged, and during the ten days following the patient continued to take an average of 68 grammes of bicarbonate.

Date.	*Urine.*	*Reaction.*	*Weight.*	*CO_3NaH.*	*Treatment.*	*Diet.*	*Remarks.*
	c.c.		Grs.	Grs.			
April 26	4,400	Acid	—	127	Vichy water, CO_3NaH	Milk, 750 c.c.	Coma.
,, 27	6,500	,,	—	198	*Id.*	Milk, 2,400 c.c.	Subcoma. Diarrhœa.
,, 28	6,300	Alkaline	—	143	*Id.*	Milk, 1,950 c.c.	Somnolence. Œdema.
,, 29	6,650	,,	—	66	*Id.*	Milk, 1,800 c.c.	Improvement. Œdema more extensive.
,, 30	6,100	,,	—	66	*Id.*	Milk, 1,350 c.c.	
May 1	4,000	Weak alkaline	—	73	*Id.*	Milk, 600 c.c. + 4 eggs + dry vegetables 200 grammes	Improvement. Respiration regular. Nocturnal attacks of dyspnœa and distress.
,, 2	5,600	*Id.*	56·0	56	*Id.*	200 grammes dry vegetables + butter + 6 eggs	Patient got up.
,, 3	3,650	*Id.*	54·7	64	*Id.*	*Id.*	
,, 4	4,200	Acid	56·0	71	$CaCl_2$, 3 grammes.	*Id.*	
,, 5	6,300	Weak acid	56·7	60	$CaCl_2$, 3 grammes + theobromine, 1·5 grammes	*Id.*	
,, 6	5,750	Acid	55·0	70	*Id.*	*Id.*	
,, 7	4,900	,,	57·5	64	*Id.*	*Id.*	
,, 8	5,400	,,	57·1	63	*Id.*	*Id.*	Improvement.
,, 9	5,400	,,	56·4	63	*Id.*	*Id.*	Patient discharged.

I insist on these facts because they seem to me to give the clue to the success or failure in the treatment of diabetic coma. In both his cases of recovery, Magnus Lévy was dealing with children, aged respectively 12 and 13, and weighing 24 and 32 kilogrammes; they absorbed doses of 117 and 210 grammes

of bicarbonate per day. On the other hand, in an adult who died, only 85 grammes of the salt could be tolerated; this is unquestionably a large dose, but yet it was insufficient. In an adult weighing about 50 kilogrammes, Grube obtained a recovery with daily doses of 120 grammes of bicarbonate for two days and afterwards with 60 grammes daily. In a child weighing 22 kilogrammes, Mohr obtained recovery with a dose of 60 grammes of bicarbonate the first day and 60 grammes on the following days; hence, about 3 grammes per kilogramme of the body weight were given during the day of coma.

Are the unsuccessful results solely due to insufficient doses of alkalines? Certainly not, because there are cases in which, in spite of very large doses, only a temporary improvement results, and there are even instances in which the effect of the treatment is *nil*. Thus, I lost a young woman in a state of coma who in twenty-four hours was given 100 grammes of bicarbonate intravenously; a male adult died, although he had absorbed by mouth and by intravenous injections 200 grammes of bicarbonate in twenty-four hours and whose urine had become alkaline. A young diabetic girl was given 150 grammes of bicarbonate by mouth and intravenously, while a child of 7 years took more than 100 grammes of bicarbonate in twenty-four hours, yet neither recovered.

Although in a large number of cases failure of the treatment can be explained by the insufficiency of the dose of alkaline absorbed, this is not always so. There are cases in which the treatment was really intensive and where the organism was undoubtedly alkalized, as shown by the reaction of the urine, and yet recovery from the coma could not be obtained.

Therefore, one can never be sure of curing diabetic coma even with an energetic alkaline treatment. But this is no reason why all hope should be given up, because cases such as I have here reported will occasionally be met with and compensate the physician for his efforts. However, if one reviews the cases of diabetic coma which have resulted in recovery, it will be found that it was only by means of very large doses of alkalines that the successful outcome was obtained.

It is true that the alkaline treatment is very disagreeable for the patient, while intravenous injections are often difficult to give in fat subjects for technical reasons. Bicarbonate

enemata are not well tolerated, and one must not count on complete absorption by the rectal mucosa. By mouth the bicarbonate is always distressing to the patient, as it is prone to provoke disgust, nausea, vomiting, abdominal distension, and diarrhœa, so that after a few hours the patient may refuse to continue treatment; therefore, much persuasion and force of will will be needed to continue it.

To carry the treatment out properly, the patient should be sent to hospital or a nursing home, where discipline and adequate nursing obtain, and count for much in the success of the treatment.

CHAPTER XXXV

THE COEFFICIENT OF UREOGENIC IMPERFECTION (MAILLARD) — THE COEFFICIENT OF ACIDOSIS (LANZENBERG)*

THE procedures of Maillard, somewhat modified by Lanzenberg, may not be familiar to the English reader, and on account of their practical importance from the clinical point of view it has been thought well to consider the two methods more in detail.

The larger the amount of organic acids eliminated, the greater will be the excretion of ammonia ; otherwise put, *the greater the waste of the ureogenesis, the more intense will be the acidosis.*

From this standpoint the urine ratio that L. C. Maillard has studied under the name of *the coefficient of ureogenic imperfection* offers unusual interest in the study of diabetes. This ratio estimates that portion in 100 parts of N transformable into urea (N becoming urea+N remaining ammoniacal) which has not become transformed into urea—that is to say, has remained combined with acids in the form of ammonia. The formula is:

$$\frac{\text{N of } NH_3}{\text{N of } NH_3 + \text{N of the urea}}.$$

Lanzenberg pointed out that if the term of coefficient of ureogenic imperfection is used, it must necessarily include the ureogenous N of the amino-acids among its factors, and as this writer wished to use it as the coefficient of acidosis, he found that the ratio expressed by this formula overlooked a form of acidosis whose physiopathological importance is very great —namely, amino-aciduria. Hence, Lanzenberg's ratio is represented by the formula—

$$\frac{\text{N of } NH_3 + \text{N of the amino-acids}}{\text{N of } NH_3 + \text{N of the amino-acids} + \text{N of urea}}.$$

* Contributed by the Editor.

With this change Maillard's coefficient becomes a perfect *coefficient of acidosis*, although Professor Labbé does not approve of this term for the reasons given in Chapter XXVI.

Lanzenberg's modification of Maillard's coefficient is unquestionably the best method that has been so far proposed, as it is not influenced by variations in the amount of creatinine or purine bodies present. The reason is that only those forms of N having the same physiological destination are included among its factors.

Maillard supposed that his coefficient could estimate the *prediabetic tendency*, but Lanzenberg does not admit this, as the following case shows.

The patient was obese, with a marked heredity of diabetes. His maternal grandfather, his father and mother, were diabetics, while his sister was obese. It is therefore logical to assume, knowing what we do in respect to the transformation of carbohydrates into fats, that in the patient under consideration the corpulency indicated a latent diabetes. The patient was on a mixed diet including little meat, but Lanzenberg found the values of 6·31, 4·95, and 5·91 with Maillard's coefficient, which were quite normal for the patient's régime.

That this should be so is not to be wondered at, because we know that the state of acidosis is not a prediabetic phenomenon, but is, on the contrary, a consequence of imperfect utilization of carbohydrates. An acidosis may remain very mild for a long lapse of time in a large number of diabetics, so that Maillard's coefficient cannot measure prediabetic tendency.

In this respect the following case is instructive. Maillard's coefficient offered relatively low values, although the diabetes had been present for more than twenty years. There was no acetonuria, and the values shown by the coefficient revealed a mild acidosis.

Case I.—Female, æt. 67 years. Father died of diabetic coma at the age of 70 years. Onset of the diabetes at the age of 42 years, and at the same time the patient presented an albuminuria which never exceeded 50 centigrammes per 1,000 c.c.

The glucose was usually from 30 to 40 grammes in twenty-four hours, but two years previously there had been an outburst of 120 grammes per 1,000 c.c., which lasted about three months, coinciding with a diabetic vulvar eruption and an abscess of the labium majorum. Mixed diet. No acetonuria.

Date.	*Total Urine in 24 Hours.*	*Glucose per 1,000 c.c.*	*Urea per 1,000 c.c.*	*NH_3(F) per 1,000 c.c.*	*Urea N per 1,000 c.c.*	*N (F) per 1,000 c.c.*	*Coefficient.*
	c.c.	Grs.	Grs.	Gr.	Grs.	Gr.	
Mar. 28	1,520	29·3	12·67	0·552	5·91	0·455	7·14
,, 31	1,350	26·1	13·08	0·578	6·1	0·476	7·23

In the following case, although it was a diabetes without acetonuria, the acidosis was higher (coefficient=9·11; 8·62):

CASE II.—Male, æt. 56 years, entered hospital for emphysema. Urine contained much glucose. For that matter, the patient had all the major symptoms of diabetes—viz., polydipsia, polyphagia, and polyuria.

On April 10 the urine contained 39·5 grammes of glucose per 1,000 c.c. and 62 grammes per twenty-four hours. A diet composed of milk (1 litre), potatoes (400 grammes), butter (20 grammes), roast meat (300 grammes), spinach or cabbage (300 grammes), and two eggs per day. The polyuria progressively subsided and the glucose decreased, and for some time had not been above 37 grammes *pro die* when the patient was discharged on June 19.

Date.	*Total Urine in 24 Hours.*	*Glucose per 1,000 c.c.*	*Urea per 1,000 c.c.*	*NH_3(F) per 1,000 c.c.*	*Urea N per 1,000 c.c.*	*N (F) per 1,000 c.c.*	*Coefficient.*
	c.c.	Grs.	Grs.	Gr.	Grs.	Gr.	
June 12	1,975	17·3	9·27	0·527	4·32	0·434	9·11
,, 14	2,085	15·1	7·95	0·425	3·71	0·35	8·62

One may obtain figures comparable with Lanzenberg's by utilizing the analyses published by von Noorden* in a case of diabetes of medium intensity in which the urine gave a negative reaction to perchloride of iron. By calculating the ratio—

$$\frac{\text{Ammonia N}}{\text{Ammonia N} + \text{urea N}},$$

the coefficients are 7·15 and 7·67 with an ordinary régime. The patient was given 200 grammes of meat and two eggs plus his ordinary diet, and the coefficient rose to 9·39 per cent.

* "Handbuch der Pathologie des Stoffwechsels," second edition, vol. ii., p. 88.

The coefficient becomes much higher in diabetics in imminence of coma, with urine containing the acids ordinarily found in diabetic acidosis—acetyl-acetic acid, β-oxybutyric acid.

The following case will serve as an illustration:

Case III.—Male, æt. 61 years, and diabetic for fifteen years without any apparent discomfort, had business reverses in May, following which he enormously emaciated, and the glycosuria, which had varied between 25 and 30 grammes *per die*, increased to 100 grammes and more. A month later there was a manifest diminution of the intellectual faculties, the patient became irascible and became more and more emaciated. At this time he came under his physician's observation. The urine contained 48·2 grammes of glucose per 1,000 c.c., and gave a positive acetyl-acetic acid reaction, although not as intense as it was later on.

In July the patient's strength was declining rather fast, and there was an invincible tendency to sleep. A second analysis of the urine at this time showed that there was less glucose, but the acetyl-acetic reaction was very intense. Large doses of sodium bicarbonate were prescribed, and on the second day of treatment the somnolence was already less marked, the intelligence less nebulous, the urine was voided in larger quantity, but the acetyl-acetic acid reaction was still very intense.

This treatment was continued for a fortnight; the appetite returned somewhat, the psychic state improved, and the patient felt better. The fourth analysis of the urine still gave a strong reaction of acetyl-acetic acid.

During the month of August nothing occurred, but early in September somnolence, soon followed by coma, terminated in death on the 10th of the month.

Date.	*Total Urine in 24 Hours.*	*Glucose per 1,000 c.c.*	*Urea per 1,000 c.c.*	*NH_3(F) per 1,000 c.c.*	*Urea N per 1,000 c.c.*	*N (F) per 1,000 c.c.*	*Coefficient.*
	c.c.	Grs.	Grs.	Gr.	Grs.	Gr.	
June 12	2,700	48·2	13·05	0·765	6·09	0·630	9·37
July 20	2,400	37·8	9·27	0·867	4·33	0·714	14·16
,, 26	1,900	42·0	6·92	0·493	3·23	0·406	11·15
Aug. 4	2,150	34·5	13·31	0·649	6·26	0·532	7·83

When coma was imminent the coefficient in this case reached 14·16, but by bicarbonate treatment it fell because a portion of the acids which are eliminated in the form of ammonia salts were excreted in the form of sodium salts,

while the ammonium derived from the double splitting up was transformed into urea.

This clearly shows that there was ureogenic imperfection merely because there was acidosis. On the other hand, this datum explains why Maillard's coefficient cannot be utilized for estimating the acidosis when the patient is undergoing bicarbonate treatment.

The following is a complex case of diabetes with carcinoma of the pancreas, icterus, and advanced cachexia. Hence, the causes of the acidosis being multiple, the coefficient reached an unusually high figure—namely, 27·26. It is more than probable that in this case a rather marked amino-aciduria existed, but unfortunately it was not searched for.

Case IV.—Female, æt. 66 years. Hereditary and collateral antecedents negative. Few data could be obtained of the patient's personal antecedents. The present illness began about one year ago with marked emaciation, excessive weakness, and intense polydipsia. A physician consulted at this time found sugar in the urine.

Three months ago, while the symptoms were becoming more and more intense, a very deep jaundice developed which never retrogressed.

At present the patient is very cachectic, with a liver reaching to the umbilicus, but no ascites could be detected. There were polydipsia and polyuria. The urine was deeply pigmented, contained no albumin, but there were 15 grammes of glucose per 1,000 c.c.

A diagnosis of cancer of the head of the pancreas was made, and the patient put on a mixed diet. The following analysis was made at this time: Total twenty-four-hour urine = 2,650 c.c.; glucose = 12·5 grammes per 1,000 c.c.; urea = 2·09 per 1,000 c.c.; NH_3(F) = 0·442 gramme per 1,000 c.c.; urea N = 0·976 per 1,000 c.c.; N (F) = 0·634 per 1,000 c.c.; coefficient = 27·36.

The organism struggles against the acid dyscrasia in these patients by neutralizing the acids with ammonia, and eliminates them in the state of ammonium salts. The hyperammonuria of diabetes led to the discovery of β-oxybutyric acid. Hence came the idea of estimating the acidosis by the excretion of ammonia; and since the absolute quantity of ammonia varies with the degree of nitrogenous denutrition, the Germans adopted, as the measure of acidosis, the formula—

$$\frac{\text{Ammonia N}}{\text{Total N}}.$$

But, *a priori*, it may be supposed that certain variations in the N compounds of the urine will influence the coefficient, although not seeming to be related to the acidosis.

Hence, for example, an increase of the excretion of creatinine or the purine bases will decrease the ratio—

$$\frac{\text{N of } NH_3}{\text{Total N}},$$

although the acidosis may not have varied.

On the contrary, Maillard's ratio—

$$\frac{\text{N of } NH_3}{\text{N of } NH_3 + \text{urea N}}$$

eliminates the variations of N compounds which do not intervene in the ammoniacal neutralization of the unoxidized acids, so that it is preferable to the German coefficient for estimating the acidosis.

Lastly, it is to be recalled that the procedure adopted by Lanzenberg for determining Maillard's coefficient is:

$$\frac{\text{N by formol dosage}}{\text{Ammonia N after hydrolysis in } MgCl_2}.$$

In this form Lanzenberg believes that Maillard's coefficient presents some advantages over Maillard's first formula—

$$\frac{\text{N of } NH_3}{\text{N of } NH_3 + \text{urea N}},$$

from the view-point of diabetic acidosis.

In point of fact, dosage with formol takes the amino-acids into account, whose interference becomes an interesting subject on account of the seductive theory of diabetic coma introduced by Hugounenq and A. Morel. According to this theory, the acidosis leads indirectly to diabetic coma by disturbing the metabolism of protein substances. Hence, for this reason, Lanzenberg maintains that amino-aciduria—which clearly indicates a perturbation of nitrogenous disassimilation—should figure in the coefficient of acidosis, as it is a warning of precomatose tendencies in diabetic subjects.

It is likewise clear that by taking the amino-acids into

account the coefficient might continue to reveal an acidosis in certain diabetics, referred to by Lépine, whose organism becomes poor in calcium because these subjects at length become incapable of neutralizing acids by ammonia. Perhaps in these subjects the acidosis finally ends by inhibiting the diastases, while the NH_3 groups which would have furnished the ammonia necessary for neutralizing acids are excreted in the urine in the form of amino-acids.

CHAPTER XXXVI

THE CLINICAL SIGNIFICATION OF COLLOIDAL NITROGEN IN THE URINE*

Besides the crystalloid substances of the urine—urea, urates, salts, etc.—there exist bodies which do not dialyze, but which can be precipitated by various chemical reagents, such as alcohol, subacetate of lead, sulphate and chloride of zinc. These substances belong to the group of polypeptids, although some writers regard them as amino-carbohydrates.

The amount of these substances present in a sample of urine is easily estimated by making a dosage of the quantity of N contained in them. This particular form of N has been given the name of colloidal N. It is estimated in percentage of the total N.

The tenor of normal urine in colloid substance is small. The coefficient $\frac{CN}{TN}$ averages in normal individuals 1·2 per cent., 1·3 per cent., 1·8 per cent., and 1·9 per cent., according to the observer; in Dauphin's researches it varied from 0·25 to 1·4 per cent. The coefficient $\frac{CN}{TN}$ varies in health according to the quantity of nitrogenous substances ingested. It increases in direct proportion to the amount of meat consumed, hence it would appear to vary with the nature of the régime. A milk diet gives the lowest percentage.

In the normal state of health these substances appear to be in a large measure derived from the albumin in the food, of which they represent non-disintegrated gross fragments. Their origin in the tissues of the body, resulting from mild nitrogenous waste, is quite possible, but must be very minute.

Colloidal N is increased in a certain number of morbid processes, the most distinct results having so far been obtained

* Contributed by the Editor.

in diseases of the liver, diabetes, and malignant growths. In hepatic morbid processes colloidal N begins to increase in the urine from the time that the hepatic cells have become insufficient. It likewise increases in diseases which react secondarily on the liver. An increase of colloidal N is in all cases an indication of hepatic insufficiency.

In diabetes without acidosis colloidal N is not increased in amount, while in the intermediary forms of the disease, at the time when the urine begins to present weak positive reactions of acidosis, the coefficient $\frac{CN}{TN}$ is increased, and it continues to become more considerable as the reactions of acidosis become more and more distinct. It is invariably large in cases of confirmed acidosis, and progressively increases at the same time as the clinical symptoms become aggravated.

Colloidal N is somewhat increased in cachexia, as well as in certain morbid processes such as pneumonia, and in peritonitis during the phase of absorption of the inflammatory exudates. It is likewise increased in eclampsia, while in pregnancy it is often higher than the norm. In other diseases the results vary considerably.

In malignant disease the increase of colloidal N from the physiopathological standpoint seems to go hand in hand with the increase of neutral sulphur and the oxyproteic acids in the urine referred to by some writers.

In diabetes and affections of the liver the increase of colloidal N appears to follow that of amino-aciduria.

Practically, an increase of colloidal N in the urine is most usually due to hepatic insufficiency. Accessorily and in certain special circumstances it should lead one to suspect the possibility of a general or local destruction of the body tissues, as in cachexia or malignant neoplasms.

In the search for colloidal N in the urine of diabetics the various statistics do not mention whether the cases belonged to diabetes with or without nutrition, but some complementary data sometimes allow one to elucidate the question. In a case of diabetes Mancini found it to be 5 per cent.; Semenow found it to be 1·43 per cent. in a case of insipid diabetes, and 6·27 per cent. in a case of diabetes with acetonuria. Pibram and Löwy, in a case of insipid diabetes, found it to be 3·06 per

cent., in a diabetic with acidosis it was 11·42 per cent., while in two other cases bearing no special mention it was found to be 25·0 and 37·7 per cent. respectively.

The following cases due to Dauphin are given as illustrations:

Case I.—Diabetes without denutrition of two years' standing. Quite a large tolerance for CH. Onset of tuberculosis in the right apex. General condition fairly good.

Diet: Potatoes, butter, cheese, and meat.

Total twenty-four-hour urine	1,500 c.c.
Albumin	*Nil.*
Urobilin	*Nil.*
Acidosis	*Nil.*
TN	14·58 grammes.
CN	0·256 gramme.
$\frac{CN}{TN}$	1·8 per cent.

Case II.—Patient æt. 45 years; diabetes without denutrition treated for five years. Considerable tolerance for CH; diet caused the glycosuria to cease upon three occasions. The general health, which had been good for a long time, now tends to decline. Œdema of legs for the past few months, sight decreasing, large appetite, no thirst, liver normal. Glucose varies between 2·25 and 5 grammes *pro die*.

Diet: Meat, 200 grammes; 4 eggs; Gruyère cheese, 50 grammes; potatoes, 200 grammes; butter, 35 grammes; salt, 2 grammes; milk, 250 c.c.

Total urine	1,125 c.c.
Albumin	*Nil.*
Urobilin	*Nil.*
TN	12·46 grammes.
CN	0·28 gramme.
$\frac{CN}{TN}$	2·24 per cent.
Amino-N	0·042 gramme.
$\frac{\text{Amino-N}}{TN}$	0·45 per cent.

Case III.—Diabetes with acidosis.

Gerhardt	+ +
Lieben	+ +
Legal	+ +
Total urine	2,300 c.c.
Albumin	*Nil.*
Urobilin	*Nil.*
TN	14·0 grammes.
CN	0·744 gramme.
$\frac{CN}{TN}$	5·3 per cent.

Case IV.—Diabetes with threatening acidosis.

Gerhardt	*Nil.*
Legal	Very slight.
Lieben	*Nil.*
Total urine	1,500 c.c.
Albumin	*Nil.*
Urobilin	*Nil.*
TN	11·9 grammes.
CN	0·106 gramme.
$\frac{CN}{TN}$	0·8 per cent.

Case V.—Diabetes with quite distinct acidosis.

Gerhardt	+ +
Legal	Weak.
Lieben	+
Total urine	1,600 c.c.
Albumin	*Nil.*
Urobilin	*Nil.*
TN	7·14 grammes.
CN	0·235 gramme.
$\frac{CN}{TN}$	3·29 per cent.
Amino-N	0·21 gramme.
$\frac{Amino\text{-}N}{TN}$	2·8 per cent.

The patient being on bicarbonate treatment, the urine was weakly acid.

Case VI.—Diabetes with commencing acidosis.

Diet : 5 eggs; peas and beans.

Gerhardt	*Nil.*
Legal	*Nil.*
Lieben	+
Total urine	1,650 c.c.
Albumin	*Nil.*
Urobilin	*Nil.*
TN	14·7 grammes.
CN	0·185 gramme.
$\frac{CN}{TN}$	1·25 per cent.
$\frac{Amino\text{-}N}{TN}$	2 ,,

Case VII.—Diabetes with intense acidosis. Dried vegetable diet. Sodium bicarbonate.

Total urine	3,000 c.c.
Albumin	*Nil.*
Urobilin	*Nil.*

First dosage :

TN	21·0 grammes.
CN	0·327 gramme.
$\frac{CN}{TN}$	1·56 per cent.

Second dosage :

TN	8·82 grammes.
CN	0·436 gramme.
$\frac{CN}{TN}$	5 per cent.
Amino-N	0·903 gramme.
$\frac{\text{Amino-N}}{TN}$	10·2 per cent.

When the second dosage was made the patient's condition was bad. Sodium bicarbonate treatment.

Diet : Milk, 1,200 c.c.; cream, 120 c.c.; cheese, 60 grammes; and 4 eggs.

When the third analysis was made the patient was on an oatmeal diet of 250 grammes with eggs, and the bicarbonate treatment was being given. There was œdema, severe thirst, and imminence of coma.

Third dosage :

Total urine	5,250 c.c.
TN	9·6 grammes.
CN	0·675 gramme.
$\frac{CN}{TN}$	7 per cent.
Amino-N	0·91 gramme.
$\frac{\text{Amino-N}}{TN}$	9·4 per cent.

It is apparent that colloidal N is not increased in diabetes without acidosis. On the contrary, in acidosis it attains a very high degree, increasing as the general health declines. In intermediary cases with threatening acidosis the coefficient $\frac{CN}{TN}$ is a little high, and becomes more so as the reactions of acidosis become more marked.

CHAPTER XXXVII

THE RESIDUAL N OF THE BLOOD-SERUM IN DIABETES*

At the present time it is positively known that the liver plays a considerable part in the disassimilation of nitrogenous substances. This decomposition commences in the tissues, where, from the action of endocellular diastases, the albumins and nucleoproteins are brought in successive stages to those of amino-acids and purine bodies. This diffuse tissue phase is succeeded by the hepatic phase. By the action of the liver, the uric acid is transformed into urea or else it is disseminated —that is to say, dissociated into fatty acids and ammonia. The fatty acids split up into carbonic acid and water, while the ammonia becomes urea. Hence, hepatic insufficiency should cause an imperfection of ureogenesis.

From his long and carefully conducted researches on the residual N of the blood-serum, Brodin has shown that this residual N is hardly influenced by the nature of the patient's alimentation. In normal individuals it ranges between very restricted limits, and is always inferior to 10 centigrammes per 1,000 c.c. with the perfected technique employed by him.

In subjects with renal lesions, even when advanced, but without any appreciable morbid change in the liver, the total N and ureic N are all the higher the greater the degree of renal impermeability. On the contrary, the residual N remains constant, always inferior to 10 centigrammes.

As Widal has shown in these cases, almost all the total N is retained in the form of urea.

In chronic processes unaccompanied by hepatic changes or a marked reaction on the general health, the residual N remains at the norm. In all cases of hepatic lesions—cardiac liver, advanced cirrhosis, abscess or cancer of the liver—an increase of the percentage of residual N will be found, which

* Contributed by the Editor.

appears to be proportional to the degree of the existing hepatic morbid change.

In acute affections—pneumonia, typhoid fever, tuberculosis—the increase of residual N, although not constant, is met with in a certain number of cases. Hence, it would seem logical to admit that the liver has become involved in just the same way as the kidneys are during the evolution of infectious diseases. The peculiar gravity of these cases with the possible appearance of jaundice during infectious processes plead in favour of this hypothesis.

Experimental work has confirmed clinical observation. Brodin tied the ureters in dogs, and then found an increase of the total N and ureic N without any change in the amount of residual N. On the other hand, ligature of the choledochus, combined with angiocholitis and areolar abscesses, resulted in a high elevation of the residual N.

Briefly, it may be supposed that the increase of residual N is related to a change of the hepatic cell. Residual N is to the liver what ureic N is to the kidney, and its increase in the blood is due to a lesion of the liver, just as an increase of ureic N is the result of a renal lesion.

The following table and cases will serve to illustrate the results obtained in respect to the blood-serum content of residual N in cases of diabetes:

Case.	*Diagnosis.*	*Total N.*	*Urea N.*	*Residual N.*
		Gramme.	Gramme.	Gramme.
I.	Diabetes, mild	0·214	0·125	0·089
II.	,, denutrition	0·368	0·282	0·086
III.	,, ,,	0·425	0·262	0·163
IV.	,, ,,	0·326	0·163	0·163
V.	,, and cirrhosis	0·345	0·209	0·136
VI.	,, denutrition	0·329	0·178	0·151

Case I.—*Diabetes of Low Grade.*—Female, æt. 56 years, diabetic for several years; daily average of 30 grammes of glucose. Entered hospital complaining of visual disturbances. Ophthalmoscopic examination revealed a bilateral retinitis. Ambard's coefficient = 0·08 (normal). Cholesterin = 2·10 grammes.

Blood-serum :

TN	0·214	milligramme per	1,000 c.c. of serum.
UN	0·125	,, ,,	,,
Residual N ..	0·089	,, ,,	,,

Case II.—*Diabetes with Denutrition.*—Male, æt. 38 years, has had polyuria, polydipsia, and polyphagia with very pronounced emaciation for five months. Average amount of glucose in twenty-four hours = 300 grammes. No minor symptoms of diabetes present, excepting absence of patellar reflexes.

Blood-serum :

TN	0·368	per 1,000 c.c.
UN	0·282	„ „
Residual N	0·086	„ „

Case III.—*Diabetes with Denutrition.*—Male, æt. 36 years. For four months has complained of polyuria, polydipsia, and polyphagia with loss of strength and marked emaciation. Average amount of glucose in twenty-four hours = 600 grammes. Examination of the viscera revealed nothing abnormal. Patellar reflexes absent.

Blood-serum :

TN	0·425	per 1,000 c.c.
UN	0·262	„ „
Residual N	0·163	„ „

Case IV.—Male, æt. 37 years. Never was ill until February, 1912, when he began to emaciate rapidly and lost strength. A large amount of glucose in the urine.

When he entered hospital in December he was very thin, and incapable of the slightest effort. Urine very abundant—11 litres in twenty-four hours—containing about 650 grammes of glucose and 4 grammes of acetone compounds. No evident lesion of any of the viscera. Absence of patellar reflexes.

Blood-serum :

TN	0·326	per 1,000 c.c.
UN	0·163	„ „
Residual N	0·163	„ „

Case V.—*Diabetes and Cirrhosis.*—Male, æt. 42 years, was suddenly seized at the beginning of February, 1913, with general weakness; he emaciated and suffered from polyuria and polydipsia. A week after the onset of these symptoms patient entered hospital. Examination revealed a large and hard painless liver, extending four fingers' breadth below the ribs. Spleen not enlarged. Urine contained 100 grammes of glucose in twenty-four hours, but no albumin. Lungs and heart normal. Patellar reflexes very diminished.

Blood-serum :

TN	0·345	per 1,000 c.c.
UN	0·209	„ „
Residual N	0·136	„ „

Case VI.—*Diabetes with Denutrition.*—Male, æt. 19 years. Never had been ill. Was suddenly seized without apparent cause with

emaciation and loss of strength. At the same time there was polyuria, polydipsia, and polyphagia.

When he entered hospital he presented a serious diabetes with a polyuria of 10 to 12 litres and an average glycosuria of 400 grammes. No evident lesion could be detected in any of the viscera. Abolition of the patellar reflexes.

Blood-serum :

TN	0·329	per	1,000 c.c.
UN	0·178	„	„
Residual N	0·151	„	„

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