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DIABETES MELLITUS.

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PREFACE.

In the following pages I have endeavoured to present a more detailed account of diabetes mellitus than is generally found in text-books or systems of medicine.

The description of the symptoms and complications, and the statistics with reference thereto, have been based chiefly on the most severe forms of the disease, a large number of which have come under my observation during the last ten years.

The literature of diabetes is so extensive that it did not appear advisable to attempt to publish anything like a complete bibliography, especially as this can be obtained so easily by reference to the "Index Medicus" and to the "Catalogue of the Library of the Surgeon-General's Office, U.S. Army." Nevertheless, at the end of each chapter, references have been given to the more important papers. As a rule, only those articles are referred to which have been actually consulted.

Since morbid anatomy has not revealed any constant or characteristic changes in diabetes, and since the lesions found post-mortem are (with the exception of certain changes in the pancreas and about the medulla oblongata) probably nearly always secondary, or due to complications, it appeared more convenient to briefly mention these lesions in the chapter on pathological anatomy, and to give a detailed account of them elsewhere. Thus it appeared better to describe the pathological changes due to various complications just after the account of the symptoms produced thereby. But the lesions found in the pancreas and nervous system are fully described in the sections

devoted to the relation between diabetes and changes in the pancreas and in the nervous system.

In some parts of the work, the accounts of the conclusions arrived at by various physiologists and physicians will be found to be stated in almost the same words as in abstracts which have appeared in several English medical journals during the last nine years; but in all such instances the abstracts have been written by myself.

To the physicians of the Manchester Royal Infirmary—Dr. J. D. Leech, Dr. J. Dreschfeld, Dr. Graham Steell, Dr. T. Harris, Dr. J. S. Bury, and Dr. A. T. Wilkinson—I am greatly indebted, for their kindness in allowing me to record any points of interest which I may have observed in the hospital patients who have been under their care, and for the opportunity of making the pathological examination of the various organs in a considerable number of cases. I am also indebted to Dr. E. Roberts and Dr. Glascott, for kindly allowing me to examine and make sketches of the fundus oculi in several cases of diabetic retinitis. In the preparation of the work, I have further to acknowledge my indebtedness to the excellent monographs on diabetes by Frerichs, Seegen, Ebstein, and v. Noorden, and to the writings of Pavy, Sir Wm. Roberts, Dreschfeld, Minkowski, Schmitz, Saundby, and many others.

To my friend, Dr. E. Brindley, I desire to express my best thanks for his kindness in revising the proofs, and for many valuable suggestions.

R. T. W.

MANCHESTER, *March*, 1898.

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DIABETES MELLITUS.

DIABETES MELLITUS.

CHAPTER I.

INTRODUCTORY.

DIABETES MELLITUS is a disease in which grape sugar is excreted in the urine for a long period,—often for months or years,—and excreted in large quantity, or in a sufficient quantity to give a reaction with the ordinary clinical tests for sugar. But the term diabetes mellitus cannot be applied to all cases in which sugar is detected in the urine. Sugar is occasionally present in the urine, for a short period only, after febrile attacks, acute diseases, and injuries, and as a result of the action of certain toxic substances; but these are cases of *temporary glycosuria*, and not true diabetes mellitus. Then, again, after a very large quantity of saccharine food has been taken, a small amount of sugar appears in the urine of many apparently healthy persons; and if the sugar in the diet should exceed a certain limit, a small quantity of sugar will *always* be found in the urine. But these are instances of temporary alimentary glycosuria. According to some authors, a minute trace of sugar occurs in normal urine; but, if present, it is certainly too small to be detected by the usual clinical tests. In diabetes mellitus the form of sugar excreted is glucose; occasionally, however, other forms of sugar are met with in the urine, such as lactose; and a few instances have recently been recorded in which pentose has been found in the urine. Of course such cases are not to be described as diabetes, but as cases of lactosuria or pentosuria.

The term glycosuria is frequently applied to those mild forms of diabetes in which the presence of grape sugar in the urine is almost the only indication of disease. The limit between glycosuria and true diabetes is often difficult to define; but the factor of time is of the greatest importance. All cases of *permanent* glycosuria would be regarded by many authors as cases of diabetes mellitus. Other authors would apply the term chronic glycosuria to the milder forms of the disease, in which sugar is present in the urine but other symptoms absent, and they would reserve the term diabetes for the more severe form, in which the specific gravity of the urine is high, the sugar excretion abundant, and in which diuresis, thirst, and other symptoms are present.

DERIVATION OF NAME "DIABETES MELLITUS."—διά, through; βαίνω, I flow; διαβήτης, a siphon; μέλιττα, a bee; mellitus (L.), like honey.

SYNONYMS. — French, *Diabète sucre;* German, *Zuckerkrankheit, Zuckerharnruhr, Harnzuckerruhr.*

HISTORICAL NOTE.

The history of our knowledge of diabetes is of great interest. According to Hirsch (1), the earliest account of the sweet urine of the disease comes from India, and is to be found in the Ayur Veda of Susruta. Certain symptoms of diabetes were known to the Greek, Roman, and Arabian physicians, but Celsus first described the disease, or rather its most obvious symptoms, in the first century. The name diabetes (διαβήτης) is said to have been first used by Aretæus (2). He states that the disease appears "to have got the name diabetes as if from the Greek word διαβήτης, which signifies a siphon." He describes the thirst and diuresis, and adds that "the emaciation is dreadful." With reference to causation, he states, "some one of the acute diseases may have terminated in this." References to the disease also occur in the works of Galen, Avicenna, Avenzoar, and other early writers. But none of these authors appear to have been acquainted with the sweet taste of the urine.

An English physician, Thomas Willis (3), Sidley Professor in the University of Oxford, was the first European writer who mentioned the sweet taste of the urine. In his "Pharmaceutice Rationalis," published in 1679, he gives such a good account of the disease that several passages are worthy of quotation.

After alluding to the scanty references to the disease in the writings of the older physicians, he states that "Galen knew only two sick of it. But in our age, given to good fellowship and guzzling down chiefly of unallayed wine, we meet with examples and instances enough, I may say daily, of this disease." "But yet as familiar as it is . . . . . its causes and formal reason notwithstanding is almost altogether unknown." Diabetes, he tells us, is so called from διαβαίνω = *transeo*, or passing through—too swift a passage of the matter that is drunk.

Willis states that the urine is "wonderfully sweet, as it were imbued with honey or sugar," and that the patients are exceedingly thirsty and quickly grow lean. He expresses his opinion that diabetes is rather an "affection of the blood than one of the reins" (kidneys), and he ascribes "the chiefest part of the evil to the nervous juice." He attributes the disease to "an ill manner of living, and chiefly an assiduous and immoderate drinking of cider, beer, and sharp wines; sometimes sadness, long grief; also, convulsive affections and other inordination and depressions of the animal spirits are wont to beget and cherish this morbid disposition." He refers to a patient who "contracted an incurable diabetes," of which he died within a month, and to another patient who recovered, and who was treated with lime-water among other drugs.

On p. 83 he adds, in reference to the urine: "But why that it is wonderfully sweet like sugar or honey, this difficulty is worthy of explanation." The explanation was first given one hundred years later by an English physician, Matthew Dobson (4) of Liverpool. He pointed out that not only the urine, but also the serum of the blood, was sweet to the taste. By a number of experiments he showed that the urine contained saccharine matter; that, when evaporated down, a white cake was left which tasted like sugar; and that, when allowed to stand, it fermented, and the sweet taste disappeared. He concludes that the saccharine matter is a product of the animal economy, and gives a list of drugs which had been used in the treatment; amongst them were Dover's powder and tinctura thebaica.

The first detailed account of diabetes was published in 1797, by an English medical man, John Rollo (5), surgeon-general of the Royal Artillery. In his book entitled "An Account of Two Cases of Diabetes Mellitus, etc.," he gives a general review of the symptoms, and discusses the nature and treatment of the

disease. Rollo was the first to point out the importance of diet in the treatment. He advises "animal food, animal fats, and confinement, with an entire abstinence from every kind of vegetable matter," and states that the action "may be facilitated by the daily use of alkalies, calcareous and testaceous substances." "The quantity of animal food should be restricted, and given in as small quantities as possible to satisfy the stomach" (p. 261). Among the "circumstances of life which have usually preceded an attack of the disease," Rollo mentions "a free use of fermented liquors, or a uniform participation of strong vegetable food of the farinaceous kinds."

Cullen ([6]) mentions the sweet taste of the urine, but stated that he had met with one case in which the urine was insipid. Latham ([7]), in 1811, recognised two forms of diabetes—the saccharine and the serous. Gregory ([8]), in 1825, pointed out the difference between diabetes mellitus and diabetes insipidus.

Bouchardt in 1841 introduced gluten bread as an article of diet for diabetic patients.

In 1847, Claude Bernard commenced his series of famous researches on sugar formation in the organism. These researches led to the discovery of glycogen, and demonstrated the influence of puncture of the floor of the fourth ventricle in the production of glycosuria.

Ever since that time diabetes has been carefully studied experimentally and clinically; and the labours of Pavy, Seegen, Külz, Brücke, Ebstein, Cantani, Naunyn, Frerichs, Dickinson, W. Roberts, and numerous other British and continental physicians and physiologists, have greatly extended our knowledge of the disease.

Recently, the brilliant experiments of Minkowski and v. Mering (recorded in 1889–1892) have proved that diabetes mellitus can be produced experimentally in dogs by removal of the pancreas.

Chemical Note.

The presence of sugar in the urine and excess of sugar in the blood are the prominent features of diabetes mellitus.

Sugar belongs to the group of chemical substances known as carbohydrates, and some of the more important members of the group may be here briefly referred to.

Carbohydrates are compounds of carbon, oxygen, and

hydrogen; the oxygen and hydrogen being present in the same proportion as in water, *i.e.* two of hydrogen to one of oxygen.

The following are the carbohydrates of most importance to physiologists and physicians. Most of these substances have active optical properties; those which deviate the plane of polarised light to the right are marked + ; those which deviate it to the left are marked − .

CARBOHYDRATES.

I. THE AMYLOSE GROUP $(C_6H_{10}O_5)_n$.

+ Starch.	+ Glycogen.	− Inulin.
Cellulose.	+ Dextrin.	Animal gum.

II. THE SUGAR GROUP.

The Saccharoses, $C_{12}H_{22}O_{11}$.	*The Glucoses*, $C_6H_{12}O_6$.
+ Cane sugar or saccharose.	+ Grape sugar, dextrose, or glucose.
+ Milk sugar or lactose.	− Fruit sugar or lævulose.
+ Maltose.	+ Galactose.

Pentoses (*Pentaglucoses*) $(C_5H_{10}O_5)$.

+ Arabinose.
+ Xylose.

Mannite, formerly termed manna sugar, is not a sugar but a hexad alcohol, $C_6H_8(OH)_6$.

The sugars classed as glucoses are also known as *Monosaccharides*; they have the formula $C_6H_{12}O_6$.

By the combination of two molecules of glucoses, with the loss of the elements of water, sugars are formed having the formula $C_{12}H_{22}O_{11}$; these are known as *Disaccharides*—

$$C_6H_{12}O_6 + C_6H_{12}O_6 = C_{12}H_{22}O_{11} + H_2O.$$

The disaccharides, if boiled with dilute acids, take up water and form two molecules of monosaccharides.

By the action of dilute sulphuric acid on proteids, or by ferment action, Pavy[1] has been able to obtain a substance which he regards as a sugar. It reduces Fehling's solution, and with phenylhydrazin forms a crystalline osazone. It is optically inactive, however, and does not ferment with yeast.

[1] Pavy, "The Physiology of the Carbohydrates," London, 1894, pp. 28–57.

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CHAPTER II.

SUGAR TESTS.

I. Clinical Tests for Grape Sugar in the Urine.

The usual tests for sugar are so well known, that it may at first sight seem superfluous to devote any space to their consideration.

But, whilst the detection of grape sugar in the urine, in a well-marked case of diabetes mellitus, is a very simple matter, on the other hand, a very careful examination of the urine is often necessary in order to decide whether a trace or small quantity of sugar is or is not present.

On commencing to examine a specimen of urine, if we find the specific gravity high—1028 or more—suspicions of the presence of grape sugar ought to be roused. The probability of the presence of grape sugar will be great if a sample of urine having the above mentioned specific gravity be clear and pale, if the quantity of urine be not diminished, and if the patient be not suffering from any febrile affection. If, however, the quantity of urine be diminished, or if the urine be high-coloured, or turbid and loaded with urates, or if the patient be suffering from some febrile affection, then a high specific gravity is no indication of the presence of sugar.

On the other hand, a low specific gravity does not exclude the possibility of the presence of sugar. It shows, however, that the case is not one presenting the typical symptoms of diabetes mellitus; but a small quantity of sugar may be present when the specific gravity is only 1010 or 1015.

Of course, more reliable indications of the presence of grape sugar are required, and the following are the chief chemical tests which are employed clinically:—

Moore's test.—When saccharine urine and liquor potassæ are mixed in equal quantities and the mixture boiled, it darkens

in colour and finally becomes brown—about the colour of brandy.

This test is now rarely used. As pointed out by Sir William Roberts (1), Moore's test is wanting in delicacy: a clear reaction is not obtained until the amount of sugar reaches 0·3 per cent. Further, all high-coloured urines of high specific gravity darken when treated with liquor potassæ. Also albuminous urines darken when boiled with liquor potassæ, and the change is especially marked if the liquor potassæ should contain lead as an impurity. This impurity is often present when the liquor potassæ has been kept in an ordinary white glass bottle for some time.

Reduction tests.—Grape sugar has a powerful reducing action on certain metallic salts in alkaline solution. The oxides of these salts are reduced to a lower degree of oxidation, or the metal itself is thrown down. Oxygen is not evolved, but it unites with glucose, and various products of the oxidation of sugar are formed.

Thus cupric oxide is reduced by glucose to cuprous oxide—

$$2\ CuO = Cu_2O + O.$$

Bismuthic oxide is reduced to metallic bismuth—

$$Bi_2O_3 = Bi_2 + O_3.$$

Grape sugar has also a reducing action on certain organic substances in hot alkaline solutions, and the colours of these solutions are changed. Thus, picric acid is reduced to picramic acid, and a dark brown coloration is produced; methylene blue, saffranin, and indigo-carmine are decolorised; orthonitrophenylpropiolic acid is reduced to indigo-blue.

Trommer's copper test.—A few drops of a copper sulphate solution are added to the suspected urine (about 1 drm.) in a test tube. Liquor potassæ (about half a drm.) is then added, and the mixture warmed. If sugar be present, a yellow precipitate of cuprous hydroxide, or a red precipitate of cuprous oxide, will be produced. The test is now seldom employed in this form in England, though it is still largely used in some parts of Germany.

Fehling's test.—This is a much more satisfactory method of applying the copper test for the detection of sugar. Fehling's copper solution is prepared as follows:—

(*a*) 34·64 grms. of pure crystallised copper sulphate are

dissolved in warm distilled water, and the solution when cold made up with distilled water to 500 c.c.

(*b*) 175 grms. of crystallised Rochelle salts (potassium and sodium tartrate) are dissolved in about 300 c.c. of hot water; 100 c.c. of caustic soda, having a specific gravity of 1·34, are added, and the mixture is diluted with water up to 500 c.c. Equal parts of the solutions (*a*) and (*b*) are mixed together. Since Fehling's solution is apt to decompose in time, the two solutions (*a*) and (*b*) may be kept separate, and mixed in equal quantities when required for use.

In testing for sugar, a test tube is filled for three-quarters of an inch with Fehling's solution, which is first boiled alone, in order to see if the solution has changed by keeping. When Fehling's solution has been kept for a long time, it decomposes partially, and oxide of copper may be thrown down by boiling, even when no urine is added. If now no oxide of copper is thrown down on boiling, the Fehling's solution has not deteriorated by keeping, and is therefore suitable for use. A few drops of the suspect urine are added, and the mixture is raised to the boiling point; yellow hydroxide, or red oxide of copper, is thrown down if sugar be present. When the amount of sugar is small, the precipitate is yellow; when large, the precipitate is red. If the quantity of sugar be very small, more than a few drops of urine must be added before the copper oxide is precipitated; but the quantity of urine should never be in excess of the Fehling's solution. When only a small amount of sugar is present, often there is no reduction of copper on boiling; but a greenish precipitate, or an opacity, appears when the test tube cools. If no oxide of copper is thrown down on boiling, and if no greenish precipitate appears when the mixture cools, then sugar is absent; or, if present, the quantity is so small as to be of no practical importance. According to Sir William Roberts, no quantity above a fortieth of a grain per cent. can escape detection by this method.

The three precautions in performing the test are, (1) to boil the Fehling's solution alone before adding the urine, (2) to see that the Fehling's solution is always in excess of the urine, (3) to avoid prolonged boiling of the mixture.

If non-saccharine urine, loaded with uric acid, be boiled with Fehling's solution *for a considerable time*, a brownish deposit may be produced, and the mixture may assume a muddy, dirty fawn

appearance, though no sugar be present. This turbidity is probably produced by the excess of uric acid, but it only occurs after *prolonged boiling.*

Of all the tests for sugar, Fehling's solution is the most *generally* useful; and if the above mentioned precautions be taken, it is, in most cases, very reliable. For clinical work, usually no other test is required. If a negative result is obtained with Fehling's test, the urine may be declared free from sugar, or free from any quantity of sugar which would be of clinical importance. If, on the other hand, a distinct precipitate of oxide of copper occurs, and if there are other indications of diabetes, the test is also sufficient. But there is a third class of cases, not infrequently met with, which is liable to cause trouble, especially in the careful examination of urine for life assurance. In these cases there are no indications of diabetes except the reduction of Fehling's solution, and this is often slight. Frequently, after the mixed urine and Fehling's solution have been raised to the boiling point, the fluid is unchanged at first; but in a short time, as the mixture cools, a greenish precipitate appears. Then the question arises, Is this slight reduction due to sugar or not? When the quantity of sugar in the urine is small, its detection with certainty is not always easy, since certain normal ingredients of the urine, such as uric acid, when present in excess, are apt to give a slight deposit in the Fehling's solution, especially if the precautions (2) and (3) above mentioned are not observed.

The following is a list of some of the substances of clinical importance which reduce Fehling's solution:—

Dextrose, lævulose, maltose, lactose, galactose, xylose, arabinose, pentose, glycuronic acid, glycosuric acid, hippuric acid, uric acid, creatin, creatinine, xanthin, and alkapton or pyrocatechin.

Glycuronic acid, $C_6H_{10}O_7$, is said to occur in the urine after the administration of certain drugs—morphine, chloroform, chloral, butylchloral, nitrobenzene, camphor, curare, sodium salicylate, salol, benzoic acid, etc. As Ashdown and others have pointed out, the reduction of Fehling's solution by the urine, which sometimes occurs after the administration of many of these drugs, is probably due to glycuronic acid, and not to sugar, as was formerly supposed. Minute traces of glycuronic acid compounds are said to exist in normal urine as indoxyl- and

skatoxyl-glycuronic acids, and in combination with urea as uro-glycuronic acid.

Glycuronic acid gives a reduction of Fehling's solution on heating, and precipitates bismuth from a hot alkaline solution of the salts of this metal. It is distinguished from grape sugar by not fermenting under the action of yeast. When the phenyl-hydrazin test is applied to a solution containing glycuronic acid, small yellow needle shaped crystals are obtained, somewhat resembling those produced by grape sugar (see p. 24). This compound of phenylhydrazin and glycuronic acid has a melting point of 114° to 115° C., whilst the compound of phenyl-hydrazin and glucose (phenylglucosazone) has a melting point of 205° C.

Glycuronic acid may therefore be a source of error in urine testing. If it exist in normal urine, as some believe, the quantity present is so small as not to interfere with the usual clinical tests for sugar. When present in sufficient quantity to give a reaction with the clinical tests for sugar, it is generally due to the administration of some of the drugs above mentioned, and if these be discontinued the excretion ceases. A case has been recorded by Ashdown (2), however, in which glycuronic acid was present in considerable quantity in the urine of a healthy man, who was not taking any drugs.

Alkapton or pyrocatechin (3) is another body which occasionally, though very rarely, occurs in the urine, and is liable to lead to confusion in a hasty examination, since it reduces Fehling's solution. When this substance is present (alkaptonuria), the urine is amber or straw coloured; and the specific gravity 1010 to 1020; it reduces Fehling's solution even when slightly warmed, but gives no reaction with Nylander's bismuth test for sugar. The urine rapidly undergoes ammoniacal fermentation; after a few hours it becomes greenish brown on the surface, and, on shaking, the colour of the urine passes from dark brown to black. This change occurs at once if a few drops of ammonia or liquor potassæ be added to, and well mixed with the urine. On the addition of yeast to urine containing alkapton, no fermentation occurs.

Modifications of Fehling's test.—Since Fehling's solution may be reduced by other substances besides sugar, the following modifications of the test have been proposed :—

(*a*) *Fehling's solution in the cold.*—Sugar reduces Fehling's

solution in the *cold*, whilst other "reducing" substances do not. This is a useful control test. The suspected urine is mixed with Fehling's solution, and allowed to stand for six to twenty-four hours without warming; a deposit of oxide of copper occurs if sugar be present. But Fehling's solution is not reduced in the cold if only a very small quantity of sugar be present. A 0·1 per cent. watery solution of grape sugar gives a very slight deposit, and one containing 0·05 per cent. gives no reduction (Seegen ([4])). The test is also less sensitive than the fermentation test. When the urine has contained a very small quantity of sugar, I have been able to obtain evidence thereof by the fermentation test, and by the phenylhydrazin test when there has been no reaction with Fehling's solution in the cold.

(*b*) *Worm-Müller's method* ([5]).—According to Worm-Müller, the possibility of an excess of uric acid in the urine, causing any reduction of Fehling's solution, may be excluded, by boiling the two fluids separately, and mixing after twenty-five seconds, whereby the temperature of the mixture sinks to 60° to 70° C. He believes that an excess of uric acid only reduces Fehling's solution at boiling temperature. (Seegen's researches, however, do not confirm this view.) Worm-Müller has proposed the following method of performing the test:—

Five c.c. of urine are boiled in a test tube.

A mixture of 1 to 3 c.c. of a 2·5 per cent. copper sulphate solution, and 2·5 c.c. of an alkaline solution of Rochelle salts (prepared by dissolving 100 grms. of tartrate of potash and soda in 1000 c.c. of normal caustic soda solution), is also boiled at the same time.

Twenty to twenty-five seconds after both have been brought to the boiling point, they are mixed together. If sugar be present, copper oxide is precipitated; if small in amount, the precipitate may not occur for five or ten minutes.

(*c*) *Fehling's test after filtration through animal charcoal.*—Trommer's test is a very delicate one, and by this means Seegen can detect with certainty 0·3 mgrms. (or 0·0046 grs.) of sugar dissolved in ten thousand times the amount of fluid. This great delicacy, however, only holds good so long as we have to do with a watery solution of sugar. For the detection of small quantities of sugar in urine, Trommer's test is not so delicate, because (1) urine contains certain substances (colouring matter, creatine) which tend to prevent the suboxide of copper, when

formed, from being precipitated; (2) uric acid also reduces copper salts slightly. Urine containing a large amount of uric acid acts on Fehling's solution like urine containing 0·1 or 0·2 per cent. of sugar.

Seegen ([6]) removes the above mentioned substances from the urine by repeated filtration through animal charcoal, and so obtains a watery solution of sugar. Animal charcoal has the property of retaining most of the constituents of urine, more especially the colouring matter and uric acid.

One or two ounces of urine are filtered several times through charcoal, until the fluid is completely colourless. This occurs in a few minutes. Then the charcoal on the filter is washed with a little distilled water, and to this water, when filtered, Trommer's test is applied. In this way 0·01 per cent. sugar may be detected. If the urine contains a little more sugar, 0·1 to 0·2 per cent., the water flowing off from the second and third washing acts even more energetically upon Fehling's solution than the first. In normal urine no change occurs, or only a slight turbidity is produced.

Seegen ([7]), in the last edition of his book, describes the test a little differently. He filters the urine several times through animal charcoal, until it is decolorised completely. Then the animal charcoal is washed with distilled water, and the *washings* and the *filtrate* are separately tested with Fehling's solution for sugar. He points out an important precaution with regard to his method, in order that success may be obtained, namely, the animal charcoal used ought to be very good blood charcoal.

Sir William Roberts ([8]) has recently described a modification of this method. He points out that urates, uric acid, and other normal constituents of the urine, which have more or less power of reducing Fehling's solution, are removed by the charcoal; but sugar, if any be present in the urine, passes freely through the charcoal, and is found in nearly undiminished proportions in the filtrate. Hence urine, after filtration through animal charcoal, is in a peculiarly favourable condition for giving a clear and definite response to the copper test. He prefers the following method of applying the test:—"A test tube is charged with Fehling's solution to the depth of about a quarter of an inch, and the filtrate is added to the depth of about two inches, and the two fluids well mixed, so as to obtain a uniform coloration. The flame of a lamp is then applied to the upper half of the column

of liquid, and this is briskly boiled for a couple of seconds. The tube is then held up to the light. If sugar be present, the boiled upper half of the column is soon seen to change—it loses its blue colour and assumes a yellowish tinge, and the earthy phosphates, which are thrown down in light flocks by the alkali of the test, are tinted more or less of a gold colour by the precipitation on them of the yellow suboxide of copper. Meanwhile the lower unheated portion of the column remains, with its blue colour unchanged."

The filtration through animal charcoal is a method which requires attention, at intervals, for some time, and hence is a rather tedious method for the medical practitioner. Also some care is required in the choice of a specimen of animal charcoal. Sometimes impurities are removed from the animal charcoal, which interfere greatly with the testing of the filtrate for sugar.

This method is of service when we wish to exclude excess of uric acid as a source of fallacy in testing for sugar.

(*d*) *Haines' fluid.*—Haines (9) employs a copper solution of the following composition in place of Fehling's solution:—

Pure copper sulphate . . .	30 grs.
Distilled water	½ oz.
Make a perfect solution, and add pure glycerin	½ oz.
Mix thoroughly, and add 5 oz. of liquor potassæ.	

In using this solution, 1 drm. is placed in a test tube and gently boiled; six to eight drops of urine are then added, and the solution again gently boiled. If sugar be present, a precipitate of copper oxide is thrown down. The test solution is said to be very stable, and to keep for a long time.

(*e*) *Pavy's modification of Fehling's solution.*—Another substitute for Fehling's solution is Pavy' fluid, which is of great service in the quantitative estimation of sugar in the urine. It will be found described on p. 42.

(*f*) *Fehling's test before and after fermentation; Worm-Müller's method.*—Worm-Müller has recommended a combination of fermentation with Fehling's test.

The urine is placed in a flask with yeast to ferment. If the fluid reduces Fehling's solution before the addition of yeast, and after the action of yeast for some time fails to do so, then sugar is indicated. The test is conclusive, providing all

the sugar has fermented. But Seegen points out that sometimes this may not occur for thirty-six or forty-eight hours; and when very minute quantities of sugar are present, fermentation may not be completed even at this time. Still, the test is of great service. A total disappearance or a very great diminution of the reducing power of the urine, after the action of yeast, indicates the presence of glucose.

Picric acid test of Braun and Johnson ([10]).—To a drachm of acid urine add its own volume of a saturated solution of picric acid and ½ drm. of liquor potassæ, and boil for a few seconds. An ordinary test tube, half an inch in diameter, is used in performing the test. If, when the tube is held up to the light, a bright red colour is visible through the middle of the column of liquid, no sugar is present. As little as 2 grs. of glucose to the ounce will render the liquid so dark that no light is transmitted through the middle of the tube. The urine of patients taking salicylate of sodium is darkened by boiling with picric acid and potash to a degree that might indicate from 1 to 2 grs. of glucose per ounce. (When the solutions are mixed before heat is applied, a slight red coloration is obtained, owing to a little reduction of picric acid by creatinine.)

Bismuth tests.—Bismuth salts are reduced to black metallic bismuth when heated in an alkaline solution in the presence of glucose.

(*a*) *Böttger's test.*—Urine and a concentrated solution of carbonate of soda are mixed in equal quantities, and a little subnitrate of bismuth is added. The mixture is then boiled; if sugar be present, the bismuth subnitrate is reduced, and the mixture becomes black. The test is less sensitive than Fehling's test; if the patient has taken rhubarb, a black precipitate may be obtained though sugar is absent. The presence of albumin also gives rise to a black deposit.

(*b*) *Nylander's* modification is said to be more accurate. Almén's fluid is used. It consists of 4 grms. of Rochelle salts (tartarated soda and potash), dissolved in 100 c.c. of a 10 per cent. solution of caustic soda. The fluid is warmed, and 2 grms. of subnitrate of bismuth added. One volume of this fluid is added to ten volumes of urine, and the mixture heated; in a few minutes (three to five) it will become black if sugar be present. The reaction will indicate the presence of 0·1 per cent. of sugar.

Nylander's test is of service chiefly as a negative test. If no reaction is obtained, then sugar is absent, or the amount is less than 0·1 per cent. If the reaction is marked, then probably sugar is present (providing the urine does not contain albumin or any drug which reduces bismuth). If the reaction be indistinct, other confirmatory tests should be tried.

Rubner's test.—To the suspected urine an equal volume of a concentrated solution of acetate of lead is added. A thick white precipitate forms; this is filtered off; and to the filtrate, in a test tube, ammonia is added drop by drop until a thick curdy white precipitate forms. The test tube is then warmed carefully to a temperature not exceeding 80° C. If grape sugar be present in the urine, the white precipitate changes to a rose-red or cherry-red colour. By heating the tube more rapidly and to a higher temperature, a coffee-brown coloration is obtained. In order that this reaction shall occur, the urine must contain 0·25 per cent. of grape sugar.

Milk sugar does not give this rose-red coloration; only a brown or yellowish-red coloration is obtained.

Indigo-carmine (*Mulder's test*).—When a solution of indigo-carmine (sulphindigotate of sodium) is boiled with a solution of carbonate of soda, the rich blue colour of the former remains unchanged, but if a drop of urine containing glucose be present in the mixture, then the blue colour disappears and the fluid becomes yellow. If the fluid be then shaken up in the test tube, the action of the oxygen of the air causes the blue colour to return. The test solutions are very liable to decompose, however, and hence in this form the test is seldom used. Its chief advantage is that the reagents can be employed in the form of dry test papers, and these have been largely used by Oliver ([11]) for the bedside testing of urine. Slips of paper are soaked in a solution of sodium carbonate; they are then dried and kept for future use. Similar papers are soaked in a solution of indigo-carmine, and dried. (Test-papers prepared according to Dr. Oliver's direction are supplied by Messrs. M. Wilson & Son, of Harrogate.)

Oliver's mode of testing.—An indigo-carmine paper is dropped into a half-inch test tube, then a carbonate of soda paper is added, and the two papers are covered by a drachm of water. Heat is applied until the water boils. If the water be soft, a transparent blue fluid is obtained; if the water be hard, then

the solution will be turbid; in this case a second carbonate of soda paper may be added. One drop of the suspected urine is allowed to fall into the tube from a pipette held vertically. The contents of the tube are again boiled freely for a few seconds, then the tube is raised and held an inch or two above the flame for a minute. If glucose be present, the rich blue colour changes to violet, then the solution becomes purple, red, reddish yellow, and finally straw yellow. The time required for the development of the above reaction depends on the amount of glucose present. If the glucose be present in large quantity (over 20 grs. to the ounce), the reaction develops in a few seconds. If the quantity of glucose be small, the reaction may not occur for thirty or sixty seconds. On shaking the test tube after the fluid has been decolorised by glucose, the blue colour returns.

Indigo-carmine is *not* decolorised by uric acid, albumin, mucus, pus, or bile; but the reaction is obtained with liquor potassæ and sodæ, dextrin, and milk sugar as well as glucose. Indigo-carmine is of service as a negative test when a great excess of uric acid has given a slight reduction of Fehling's solution. It is also useful as a positive test when lactose is present in the urine.

Hoppe-Seyler's orthonitro-phenylpropiolic acid test (12).—Baeyer has shown that orthonitro-phenylpropiolic acid is converted into indigo when heated with alkalies and a reducing substance such as grape sugar. A half per cent. solution is employed. In 100 c.c. of a 10 per cent. solution of caustic soda, 5·76 grms. of orthonitro-phenylpropiolic acid are dissolved, and water is added up to 1000 c.c. A brownish fluid is obtained, which keeps fairly well. In testing for sugar, about 1 drm. of this solution is placed in a test tube, and ten drops of the suspected urine are added. The mixture is boiled for a quarter of a minute. The fluid becomes dark blue, if the urine contains as much as 0·5 per cent. of sugar. A distinct blue colour is not obtained with normal urine. Even when large quantities are added to the test solution, only a greenish coloration is obtained. If the urine contains more than 2 per cent. of albumin, which is rare, then a dark red coloration is obtained.

The advantages of this test are said to be that the reagents keep well, that only a small quantity of urine is required. The reaction is not influenced by any ordinary amount of albumin;

it is less influenced by other reducing substances, such as creatine and creatinine, than many sugar tests, and thus has an advantage over Trommer's test, Nylander's test, etc.

The test is not so sensitive as either the phenylhydrazin or the fermentation tests, and not quite so sensitive as Fehling's solution. It is important not to add *too much* urine, otherwise no blue coloration is obtained, even when sugar is present. The test is rapidly performed, and is a good confirmatory reaction when sugar is present to the extent of 0·5 per cent. I have given it a fair trial, and never obtained any reaction with normal urines. Urine containing bile pigment gave no reaction; also the urine of patients taking sodium salicylate did not produce any blue coloration.

Methylene blue test (13).—Methylene blue is decolorised by glucose in a warm alkaline solution. In performing the test, the diabetic or suspected urine is diluted (1 part to 9 of water). Of this diluted urine, 2 c.c. are mixed with 6 c.c. of a 1 in 3000 solution of methylene blue, and 2 c.c. of liquor potassæ added. The mixture is boiled for one or two minutes, when the blue colour disappears if sugar be present. Care must be taken that the fluid is shaken as little as possible, since the blue colour returns easily, owing to the action of the oxygen of the air. It is important to dilute the urine, as all *undiluted* urine discharges the blue colour; but normal urine diluted 1 to 9 of water does not decolorise methylene blue. I have obtained a distinct reaction by this method when diabetic urine was diluted, until the percentage of sugar was only 0·07, but when further diluted until it was ·014 no reaction was obtained. I have found, however, that urine rich in urates gave a doubtful reaction when diluted 1 to 9, and I do not think the test so satisfactory as some of those already mentioned.

Saffranin test.—Saffranin when dissolved in water produces a blood-red solution, which is decolorised when heated with liquor potassæ and grape sugar. This reaction has been suggested as a test for glucose in the urine, and has recently been strongly advocated by Allen (13). In performing the test, equal parts of the suspected urine, liquor potassæ, and a 1 in 1000 watery solution of saffranin are mixed in a test tube and boiled freely, agitation being avoided as much as possible. Normal urine does not decolorise saffranin, but urine containing 0·1 per cent. of sugar causes the red colour to disappear. Urine con-

taining 0·07 per cent. almost decolorises the above mixture—only a faint red tinge remains. Uric acid, creatine, creatinine, are said not to decolorise saffranin. Albumin, however, decolorises it slowly, and hence ought to be removed before testing for sugar. I have found the test unsatisfactory, and have obtained doubtful reactions when sugar has been absent.

The fermentation test.—As a positive test, this is the most certain reaction for grape sugar in the urine. If yeast be mixed with urine containing grape sugar, and the specimen kept in a warm place, fermentation occurs; the sugar is decomposed, alcohol and carbonic acids are formed:—

$$C_6H_{12}O_6 = 2C_2H_6O + 2CO_2$$
(glucose) (alcohol) (carbonic acid).

Other changes of minor importance also occur. The liberation of carbonic acid gas indicates the presence of sugar.

The test can be performed in an ordinary test tube, which is filled with urine and a little yeast, and inverted in mercury. Or one may employ a U-shaped tube ([14]), or an inverted test tube, the lower fourth of which is filled with mercury, and the mouth closed with a stopper perforated with a glass tube bent twice at right angles, as shown in the diagram. Now, if grape sugar be present in the suspected urine, carbonic acid gas is formed, and collects at the top of the test tube or U-shaped tube (see Figs. I. 1–3). It is always important to use a *control* test tube containing yeast and normal urine, *i.e.* urine which does not give any reaction with Fehling's solution, since the yeast alone suspended in normal urine gives rise to the formation of a small bubble of gas, which collects at the top of the tube (see Fig. 1).

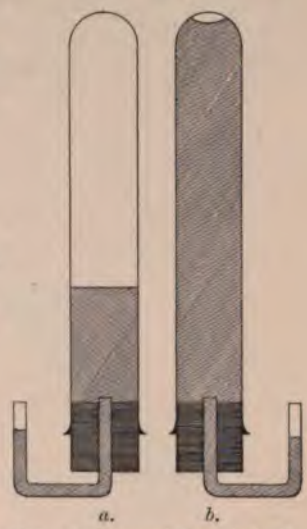


FIG. 1.—Fermentation test for sugar. *a*, test tube containing suspected urine+yeast; *b*, test tube containing normal urine +yeast. Clear part indicates amount of gas in the tubes in each case.

The use of mercury is not necessary, and the fermentation test for the detection of grape sugar can be most conveniently carried out in the following manner (Moritz):—Two ordinary

test tubes of equal size are employed. The same quantity of German yeast (weighed) is placed in the bottom of each. About one-tenth of each tube is filled with dry yeast. The one tube is then filled to the brim with the suspected urine; the other with normal urine (*i.e.* urine which gives no reaction with Fehling's solution). The mouth of each test tube is closed with an india-rubber stopper perforated with a glass tube, bent twice at right angles (see Fig. 1). A little of the fluid escapes into the glass tubes when the stoppers are inserted. The two test tubes are inverted and placed side by side in a warm place, supported in a glass tumbler, or in some other way. The atmo-

FIG. 2.—Fermentation test for sugar; another method. As the saccharine urine ferments, gas collects in the test tube and expels the fluid through the glass tubing into the wine glass.

spheric pressure keeps up the column of fluid in each test tube. At the end of eighteen to twenty hours, often long before that time, fermentation will have occurred, if sugar be present in the suspected urine. At the top of the tube containing the normal urine and yeast, a bubble of gas collects—this being given off from the yeast itself. In the other tube containing the suspected urine, if grape sugar be present, a greater quantity of gas collects at the top than in the case of the first test tube. The gas may occupy a quarter of an inch, half an inch, or an inch at the top of the tube; or if the sugar be greater in quantity, half the tube or the whole tube may be filled with gas, and the fluid expelled to a corresponding amount. Any excess of gas in the tube containing the suspected urine, beyond the small bubble

given off by the yeast itself in the tube containing the normal urine, indicates the presence of grape sugar or other fermentable sugar.

It is important that the tube be kept in a place which is *not too* warm; also the india-rubber stopper ought to fit the test tubes accurately. The control tube containing normal urine + yeast is always necessary, since the amount of gas which collects in this tube varies considerably, according to the activity of the yeast. Carried out in this simple manner, the fermentation test is most useful and reliable as a positive test. Moritz ([15, 17]) recommends that the quantity of yeast should be 2 per cent. The best temperature for fermentation is 25° C.

It is pointed out by Moritz, however, that to avoid all possible fallacies four tubes are useful, since the results might be unreliable, owing to the activity of the yeast being greatly impaired, or owing to the urine containing some substance preventing the fermentation of yeast:—

1. A tube containing normal urine + 2 p. c. of yeast.
2. „ „ „ „ + 0·1 p. c. of sugar.
3. „ „ the suspected urine „
4. „ „ „ „ + 0·1 „

Tube 1 shows the amount of gas which is given off by the yeast itself.

Tube 2 shows whether the yeast is capable of giving rise to fermentation, *i.e.* it indicates the activity of the yeast itself. If the yeast be active, the gas in Tube 2 will be in excess of the bubble of gas in the Tube 1.

Tube 3 is for comparison with Tube 1; and if an excess of gas is present in 3 beyond that in 1, sugar is indicated.

Tube 4 shows whether the suspected urine is capable of being fermented. If so, then the gas in 4 will be in excess of that in 3. If there is no formation of gas in 4, then we may conclude that there is some substance present which is checking fermentation. As a rule, however, four tubes are not necessary, and a conclusion can generally be arrived at from the result given by two tubes, as described above.

Value of the test.—As a positive reaction, fermentation is the most reliable test for sugar. If gas be given off in excess of that yielded by the yeast + normal urine, then we may conclude with certainty that sugar is present in the suspected

urine. No other substance met with in the urine ferments and gives off gas when subjected to the action of yeast.

One of the chief objections to the test is the time which is required, but this does not appear to me to be a very serious objection. The tubes as above described can be prepared in a few minutes. They are then placed aside for twenty-four hours, and, when examined at the end of that time, at a glance one can see if there is any indication of sugar.

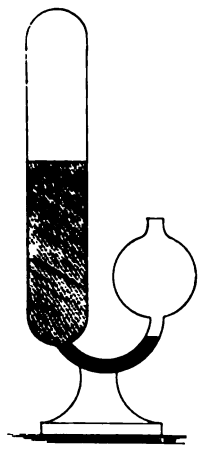


FIG. 3.—U-shaped tube for detecting sugar in the urine by the fermentation test. The narrow part of the tube contains mercury (deep black).

Another objection is, that the test is not so sensitive as many other reactions.

If no gas be liberated by the fermentation test, and if there be no source of fallacy with regard to the yeast, and if fermentation is capable of occurring in the urine when sugar is added (and these points can be determined by the four tubes recommended by Moritz and described above), we are justified in concluding that sugar is either absent or only present in very small quantity; but we cannot say that a minute quantity of sugar does not exist in the urine. In the fermentation test the fluid absorbs its own volume of carbonic acid gas, hence a very small quantity of sugar may be present and this may ferment, but all the gas may be absorbed.

By using very active yeast I have sometimes obtained a distinct reaction with the fermentation test when Fehling's solution has only given a doubtful reaction, *i.e.* when the urine has not reduced Fehling's solution at once on boiling, but has done so only as the test tube cooled. According to Sir William Roberts, if the amount of sugar be less than 0·5 per cent., it cannot be detected by the fermentation test. According to von Jaksch and Jolles ([10]), by the fermentation test 0·1 per cent. of sugar can be detected. Einhorn ([18]) states that, by boiling the urine for ten minutes before applying the fermentation test, he can detect 0·05 per cent. of sugar, and this statement is confirmed by Kobrak ([19]). Of course, as Einhorn points out, it is of great importance to place the same quantity of yeast in each tube. Einhorn also recommends the use of a large quantity of yeast—1 of yeast to 10 of fluid.

Seegen has pointed out that when only a minute quantity of sugar is present, fermentation occurs very slowly.

Moritz ([20]) recommends a combination of Nylander's test and fermentation, in order to be quite sure that a trace of sugar is not present when no gas has been liberated. Urine which gives a positive result with Nylander's test, but after fermentation no longer gives Nylander's reaction, can with certainty be declared to contain sugar. Urine which gives Nylander's reaction, but does not ferment with yeast, and after the action of yeast still gives Nylander's reaction, does not contain sugar but some other reducing body.

The phenylhydrazin test.—A confirmatory test, about which much has been recently written, is the phenylhydrazin test.

The researches of Emil Fischer ([21]) have shown that many kinds of sugar are able to combine with phenylhydrazin and form definite crystalline compounds — osazones. These compounds present minor differences in their melting points, solubility, etc., according to the form of sugar from which they have been prepared.

By the action of phenylhydrazin on grape sugar a characteristic crystalline compound is formed, phenylglucosazone. The crystals are needle-shaped and have a bright sulphur-yellow colour. This reaction was strongly recommended by von Jaksch ([22]) some years ago as the basis of a clinical test for grape sugar in the urine. The following is the method which he employs ([23]):—

Two parts of hydrochlorate of phenylhydrazin (twice as much of the phenylhydrazin salt as will lie on the point of a knife) and three of acetate of soda are placed together in a test tube containing 6 to 8 c.c. of urine. If the salts do not dissolve when the fluid is warmed, a little water is added. The test tube containing the mixture is placed for 20 to 30 minutes in boiling water. It is then taken out and placed in a vessel containing cold water. If sugar be present a yellowish deposit forms, which, on microscopical examination, is seen to contain yellow needle-shaped crystals, often in clusters, in tufts, sheaves, or rosettes. These are the crystals of phenylglucosazone, which have a melting point of 205° C.

Now, if performed in this manner, it is necessary to make use of a water-bath, and to keep the water boiling for twenty to thirty minutes. This, of course, presents no difficulty in the laboratory,

but for *clinical* work is somewhat troublesome. Also, in the hands of many medical men, the test has sometimes failed when performed in this manner, even though sugar has been present in the urine in considerable amount. One cause of failure is probably because the quantity of the reagent recommended in

FIG. 4.—The phenylhydrazin test for sugar. *a*, crystals obtained with grape sugar (phenylglucosazone); *b*, crystals obtained with lactose (simple method); *c*, minute crystals, of doubtful nature, obtained from normal urine by following the method of Moritz; not obtained in simple method of applying test.

von Jaksch's description of the test (namely, twice as much phenylhydrazin as will lie on the point of a knife) is somewhat indefinite, and this description has been copied in many accounts of the test which are given in English medical text-books.

The following is a *very simple* clinical method of performing

the phenylhydrazin test, which I have employed for seven years with the best results — a method described in foreign medical literature some years ago, but not generally referred to in English medical books.

The *simple method* to which I refer has been described in the work on urine analysis by Hoffmann and Ultzmann, and the following, which I have found so useful, is a very slight modification thereof. A test tube of ordinary size is filled for about *half an inch* with hydrochlorate of phenylhydrazin [1] (in powder); then acetate of soda in powder (or small crystals) is added for another *half inch*. The test tube is then half-filled with urine and boiled over a spirit-lamp. In performing the test I have not attempted to dissolve the salts by shaking the tube, but have simply applied the flame of the lamp to the bottom of the tube, and the powders have soon passed into solution. After the urine has reached the boiling point, I have always continued to boil for about *two minutes*. The tube is then left in the test stand and examined again some time afterwards. If sugar be present, a yellowish deposit forms at the bottom of the tube, and on microscopical examination this deposit is seen to consist chiefly of beautiful needle-shaped crystals of a bright sulphur-yellow colour. Generally the needles are arranged in tufts, sheaves, or rosettes. The crystals are found after the tube has been standing for half an hour, frequently at the end of fifteen or twenty minutes; but after boiling the tube I have generally placed it in a test stand and not examined the deposit for a few hours. If no sugar is present, only brownish amorphous globules or yellowish scales are found in the deposit.

This method is exceedingly simple, and very little time and attention are required. In four minutes the first part of the test can be easily completed; the tube is then left in the test stand and examined at a convenient time some hours later. Permanent specimens of the crystals can be prepared by drying a little of the deposit on a slide and mounting it in Canada balsam.

The value of the test.—I have used this simplified method for seven years in a very large number of urine examinations,

[1] Hydrochlorate of phenylhydrazin is a brownish powder having a peculiar smell. It is simply kept in the powdered form in a dry bottle. The acetate of soda is also kept in a dry powder in another bottle.

and have never failed to find *abundance* of the characteristic crystals on microscopical examination, if sugar has been present, even when the quantity has been very minute. The reagents are powders which usually *keep well* for months, and in this respect they have a distinct advantage over Fehling's solution, which so frequently decomposes.

The test can be performed, and the characteristic crystals easily obtained, even when the urine contains a large quantity of albumin. I have found the crystals easily in urines loaded with albumin, but which contained only a very small amount of sugar. In such cases the bright yellow crystals are easily distinguished from the amorphous granules of coagulated albumin on microscopic examination. It is always better, of course, to remove the albumin first, if the quantity should be very great.

By performing the test in the simple manner just described (*i.e.* boiling for two minutes only), I have never obtained any crystals of phenylglucosazone in normal urine. Several years ago I applied this test to the urines of fifty persons who were either in good health, or were not suffering from any disease which is accompanied by glycosuria or other diabetic symptoms. (In each case no reaction for sugar was obtained with Fehling's solution.) I was never able to find any trace of phenylglucosazone crystals in these fifty cases. Since that time I have applied the test on very numerous occasions to normal urine, but always with negative results. Hence I think this simplified method of performing the test may be regarded as quite *reliable* for clinical work, and *not too sensitive*.

A great advantage of the phenylhydrazin test is, that it gives no reaction with uric acid, creatinine, hippuric acid, pyrocatechin, etc., whilst these substances may be a source of fallacy when Fehling's test is applied.

Now, two objections have been raised to phenylhydrazin as a clinical test for sugar in the urine—(1) It is said to give a slight reaction with many normal urines and to be *too sensitive* for clinical work. (2) It is said that glycuronic acid, if present in the urine, will give rise to crystals similar to those of phenylglucosazone.

As regards the objection that it is *too sensitive* for clinical work, it has been pointed out by many observers that a small deposit of the crystals may be obtained in many normal urines. Thus, Binet ([24]) succeeded in obtaining the crystals in one-half of

the normal urines which he examined, but the test tube was kept in a *hot-water bath for one hour.*

Moritz [25] has pointed out that if *certain proportions* of the reagents be employed, a slight deposit of minute yellow crystals can be obtained in almost *all* normal urines. These proportions are as follows:—To 10 c.c. of urine, 0·5 grm. of hydrochlorate of phenylhydrazin and 1·0 grm. of sodium acetate are added. The tube is placed in a water-bath, which is heated for one hour. I have performed the test in this manner a good number of times with perfectly normal urine, and have always succeeded in obtaining a very slight deposit of the minute yellow crystals, *when I have followed Moritz's method strictly.* But, as above mentioned, I have never succeeded in obtaining the crystals from normal urine when I have employed the *simple method*—boiling in a test tube for two minutes only.

The crystals obtained from diabetic urine are generally long fine needles (see Fig. 4, *a*), but those obtained from normal urine by Moritz's method are minute very short needles, arranged generally in rosettes, forming "thorn-apple" crystals (see Fig. 4, *c*). According to Jolles [26], the crystals obtained from normal urine are always thicker and more plump than in diabetes. Both have the same sulphur-yellow colour. Even when diabetic urine is very greatly diluted, so that the amount of sugar is only 0·015 per cent., the crystals may be still *long* fine needles; but I have always found the crystals minute and *very short* ("thorn-apple" crystals) when obtained from normal urine by Moritz's method. In cases of glycosuria, however, I have occasionally found shorter forms of crystals.

Moritz [27] points out that in normal urine, even when his sensitive method is used, the deposit of yellow crystals is *very small* in amount, whilst in glycosuria and diabetes the deposit of crystals is *very abundant.* He regards this as a point of importance in the diagnosis.

Now the question arises, What is the cause of the small deposit of minute short crystals in normal urine, when the test is carried out according to Moritz's *sensitive method*? On this point there is considerable difference of opinion. Thierfelder [28] has shown that glycuronic acid forms yellow needle-shaped crystals with phenylhydrazin. According to Flückiger [29], a very small amount of glycuronic acid is present in normal urine, and the minute crystals obtained from normal urine

by the *delicate* method of performing the phenylhydrazin test are due to this acid. Geyer ([30]) states that after the action of yeast on normal urine the crystals are still obtained, and he regards them as due to glycuronic acid, since a trace of sugar would have been destroyed by fermentation. Jolles ([31]) also believes the crystals obtained from normal urine are due to glycuronic acid. Moritz thinks they are due partly to the small amount of sugar which (according to some physiologists) is present in normal urine, partly to other substances, possibly glycuronic acid.

By a careful chemical process[1] Moritz has obtained yellow needle-shaped crystals on applying the phenylhydrazin test to a large quantity of normal urine, and has proved them to be due to sugar and not to glycuronic acid, since their melting point was 204° to 205° C. Hence he concludes that a trace of sugar is found in normal urine.

I have made several experiments on this point, but have *not* been able to confirm Geyer's statement, that these minute crystals are still obtained after the action of yeast on normal urine. It has been pointed out by Seegen, that if a fluid such as urine contains a very small amount of sugar, it ferments very slowly (thirty-eight hours may be required to complete the fermentation). If the minute crystals obtained from normal urine are due to the *trace* of sugar which some physiologists think is always present, then, in order to decompose it by fermentation, it would be necessary to submit the urine to the prolonged action of yeast; and I have found that, after the action of yeast for forty hours, these minute crystals cannot be obtained.

A quantity of normal urine recently passed was divided into two portions. One portion was placed in a bottle without the addition of any yeast. To the other portion a quantity of yeast was added, and it was kept for forty hours in a warm place. At the end of this time, 10 c.c. of the urine to which no yeast had been added were placed in a test tube, A, with 0·5 grm. phenylhydrazin hydrochlorate and 1 grm. sodium acetate. Into a second tube, B, was placed 10 c.c. of the urine to which the yeast had been added (and which had been kept warm), and 0·5 grm. of phenylhydrazin hydrochlorate and 1 grm. sodium acetate were added. Both test tubes were placed in the same water-bath and heated for one hour; the tubes were then allowed to stand until next day. The deposit in the former tube, A, contained minute yellow

[1] Described in the *Deutsches Arch. f. klin. Med.*, Leipzig, Bd. xlvi. S. 257.

crystals; while in the deposit in the latter tube, B—*i.e.* in urine which had been submitted to the action of yeast for forty hours—no crystals could be found.

Another experiment was performed in the same manner, but the specimens were tested at the end of twenty hours. Both in the urine to which the yeast had been added, and in that to which no yeast had been added, minute yellow crystals were obtained.

From these experiments we may conclude that the substance in normal urine which gives rise to the minute yellow crystals, when Moritz's delicate method of performing the phenylhydrazin test is followed, is a body which is destroyed by the action of yeast and warmth for forty hours; but it is not destroyed by the action of yeast for twenty hours.

Now, whatever may be the cause of these minute crystals, they appear to me to form a serious objection to the test if it be performed according to the delicate method, with the use of the water-bath. Though the deposit of the crystal is very small in normal urine, but always *abundant* if but a very slight degree of glycosuria exists, and though the crystals are *generally* much smaller and more plump in normal urine than in the case of glycosuria, still I think that these points are insufficient to enable any but those who have had great experience in the test to decide whether a very small pathological amount of sugar is or is not present in any suspected urine.

If, however, the water-bath be *not* used, and if the test be performed in the simple manner above described—*i.e.* boiling in a test tube for two minutes only—*this objection does not apply.* By the simple method these troublesome and dubious minute yellow crystals *are not obtained in normal urine.*

The second objection to the phenylhydrazin test is, that yellow crystals similar to those of phenylglucosazone are produced when glycuronic acid is present in the urine.

The melting point of the crystals due to glycuronic acid is 114° to 115° C., whilst that of the crystals of phenylglucosazone is 205° C. But it is evident that, for clinical work, the determining of the melting point of the crystals is too troublesome and tedious a matter.

The urine of patients taking salicylate of soda and salol generally gives a slight reduction of Fehling's solution, and this is said to be due to glycuronic acid. In these cases I have sometimes found yellow needle-shaped crystals with the

phenylhydrazin test, even when the simplified method has been employed, but only in about one-third of the cases.

The objection that glycuronic acid may give rise to fallacy is a valid one, though practically this acid is not likely to give rise to much trouble, since its occurrence in any quantity of practical importance is *generally* due to some drug, and in such cases discontinuance of the medicine causes it to disappear from the urine, and then crystals will no longer be obtained by the simplified method of testing. Still, there is the possibility of the exceedingly rare occurrence of glycuronic acid apart from any drug treatment (see p. 11).

Three cases have been recorded recently by Salkowski, in which *pentose* has been found in the urine. With phenylhydrazin it forms yellow needle-shaped crystals, which melt at 159° C. But whether such crystals would be produced by the simplified phenylhydrazin test (boiling for two minutes only), I do not know. The occurrence of this substance in the urine is probably exceedingly rare, but it is now to be borne in mind as a possible, though very improbable, source of fallacy, both in Fehling's test and in the phenylhydrazin test.

On applying the phenylhydrazin test in its simplified form (as above described, p. 25) to a solution of *lactose* in normal urine, I have never been able to obtain any *needle-shaped* yellow crystals like those characteristic of glucose, but I have found a deposit of small yellow globules with very short spines (see Fig. 4, *b*).

The delicacy of the simplified phenylhydrazin test (boiling for two minutes only).—As above mentioned, the simplified method is not too sensitive; it does not give any reaction with normal urine. Still, it is exceedingly delicate; more delicate than fermentation and than Fehling's solution, as is shown by the following experiments:—

A diabetic urine containing 7·5 per cent. of sugar was greatly diluted with water until the percentage was only 0·015. This diluted urine gave (*a*) no reaction with Fehling's solution in the cold; (*b*) no reaction with Fehling's solution on boiling; (*c*) no indication of sugar by the fermentation test; (*d*) but a distinct deposit of long yellow crystals with the phenylhydrazin test (simplified method), boiling two minutes only.

Conclusions.—1. The phenylhydrazin test, if performed according to the above-described *simplified method* (*i.e.* boiling

the reagents with the urine for two minutes only), is a most valuable confirmatory test for sugar in the urine. The reagents do not readily decompose, the test is easily carried out, and is very suitable for clinical work. It is very sensitive—*more sensitive* than Fehling's test and the fermentation test—and will give a reaction with diluted urine containing only 0·015 per cent. of sugar. But it is not too sensitive, and gives *no reaction with normal urine.*

Relative Sensitiveness of Several Urine Tests.

\+ indicates reaction ; O indicates no reaction.

Test for Sugar.	Amount of Glucose in Urine.		
	0·5 per cent.	0·1 per cent.	·05 per cent.
Fehling's solution + heat.	+	+	+
Fehling's solution in the cold.	+	Very slight.	O
Fehling's solution after filtration through animal charcoal.	+	+	+ 0·05–0·01 p.c. detected, but precipitate often occurs only 30 to 60 seconds after heating.
Fermentation	+	+ Just detected.	O
Phenylhydrazin (Simple method.)	+	+	+ Distinct crystals when urine diluted, so that only 0·015 per cent. of glucose present.

2. If in performing the test a water-bath be used, and boiling prolonged, the phenylhydrazin test is too sensitive, and is somewhat troublesome for clinical work.

3. The great value of the phenylhydrazin test (simplified method) is as a *negative test.* A urine which gives no reaction by this method may be declared quite free from sugar for practical purposes. Thus in a doubtful case, in which a slight reduction of copper oxide is produced by Fehling's test, if the simplified phenylhydrazin test gives no reaction, then the urine may be declared free from sugar, and the reduction of copper due to some other body.

4. Beside the various forms of sugar, so far as is known,

only glycuronic acid gives the phenylhydrazin reaction in the urine; but many substances which may occur in the urine reduce Fehling's solution. If the patient should be taking any drug, this must be discontinued, and the phenylhydrazin reaction would not then be obtained, if glycuronic acid due to medicine were the cause. If no drug is being taken, and the urine reacts to the simplified phenylhydrazin test, it is exceedingly probable that it contains sugar, since the occurrence of glycuronic acid in the urine in sufficient quantities to give the reactions is extremely rare.

Besides glucose, other forms of sugar are occasionally, though very rarely, met with in the urine; but at present no pathological importance can be attached to them.

Milk sugar or lactose is present in the urine of women during lactation, and especially when there is engorgement of the breast in connection therewith (see p. 88). I have found it often present in cases of abscess of the female breast.

Lactose reduces Fehling's solution on boiling. It is said not to ferment with yeast; according to some authors, however, slight fermentation does occur after the *prolonged* action of yeast. I have found that a strong solution of lactose in normal urine showed no signs of fermentation at the end of twenty-four hours, but at the end of forty hours there was a distinct but slight indication of fermentation (*i.e.* at the top of the tube containing the urine + lactose a little more gas was present than in the control tube containing the normal urine). After the action of yeast for twenty-four hours on urine containing lactose, the fluid still reduces Fehling's solution. On the application of the phenylhydrazin test in its simplified form (as described on p. 25) to a solution of lactose in the normal urine, I have never been able to obtain any needle-shaped yellow crystals like those characteristic of glucose, but I have found a deposit of small yellow globules with exceedingly short spines (see Fig. 4, *b*).

On the application of Rubner's test, no rose-red coloration is produced (as is the case with glucose), but the fluid becomes brown or yellowish red.

According to Pavy ([32]), a valuable indication of the presence of lactose is obtained by estimating the cupric-oxide reducing power of the urine before and after boiling with sulphuric acid. Taking the cupric-oxide reducing power of glucose as 100, Pavy estimates that of lactose at 60, or a little over. When

boiled with dilute sulphuric acid, lactose is converted into dextrose and galactose—

$$\underset{\text{(lactose)}}{C_{12}H_{22}O_{11}} + H_2O = \underset{\text{(dextrose)}}{C_6H_{12}O_6} + \underset{\text{(galactose)}}{C_6H_{12}O_6}$$

After boiling with dilute sulphuric acid, if the phenylhydrazin test be applied, then long straight needles and radiating clusters of yellow crystals of phenyldextrosazone and galactosazone are obtained.

Lævulose has occasionally been found in the urine, in cases of diabetes, along with grape sugar, but its occurrence is exceedingly rare. Seegen ([33]) has only met with a single example in the examination of a very large number of diabetic urines. Lævulose reduces Fehling's solution like grape sugar; it ferments with yeast, yielding alcohol and carbonic acid gas; it forms yellow needle-shaped crystals with phenylhydrazin, like those of phenylglucosazone; but it differs from glucose by rotating the plane of polarised light to the left. When present along with glucose, it will be found that the urine will fail to rotate polarised light to the left, but the degree of rotation to the right (produced by the glucose) will be greatly diminished (owing to the presence of the lævulose). In these cases the quantity of sugar indicated by the polarimeter will be markedly less than that indicated by the quantitative analysis with Fehling's solution.

Cane sugar is said to be met with occasionally in the urine of persons who have taken large quantities of cane sugar in their food. It ferments, but does not reduce Fehling's solution, and forms no compound with phenylhydrazin.

Pentose.—As previously mentioned (on p. 30), Salkowski ([34]) has recorded three cases in which pentose was found in the urine, and several have been reported since. No definite pathological importance can be attached to its occurrence, however. The urine reduces Fehling's solution, but does not ferment under the action of yeast. Pentose forms yellow needle-shaped crystals with phenylhydrazin, which melt at 159° C., and which are soluble in hot water. I have not had an opportunity of trying whether the phenylhydrazin test in its simplified form, as described on p. 25, will give any reaction with pentose.

Urines containing pentose give a red coloration when warmed with phloroglucin and hydrochloric acid. Phloroglucin is dissolved in 5 or 6 c.c. of strong warm hydrochloric acid;

it is added in excess, so that a small quantity is left over undissolved. The solution is divided into two portions, and allowed to cool. To one-half of the solution in a test tube, about half a c.c. of the suspected urine is added. To the other half of the fluid a similar quantity of normal urine is added. The test tubes are placed in a beaker containing boiling water. In a few seconds the suspected urine presents a bright red coloration if pentose be present, whilst the normal urine remains unchanged.

Table showing Reactions given by Various Substances which may be mistaken for Grape Sugar in the Urine.

\+ indicates reaction ; 0 indicates no reaction.

	Reduction of Fehling's Solution.	Fermentation with Yeast.	Phenylhydrazin test : *simplified* method.	Other Tests.
Glucose (dextrose)	+	+	+ Needles, sheaves, rosettes.	Rotates the plane of polarised light to the right. Reaction with Nylander's and Rubner's tests. Reaction with Fehling's solution after filtration through animal charcoal. No reaction to phenylhydrazin test, to Fehling's solution, and other tests after fermentation.
Lævulose . .	+	+	+ Needles, sheaves, rosettes.	Rotates the plane of polarised light to the left ; this and other tests fail after fermentation.
Lactose . . .	+	0	Globules with very short spines.	No reaction with Rubner's test ; brown coloration only. Converted into dextrose and galactose by boiling with dilute sulphuric acid. Reactions for glucose then obtained.
Cane sugar . .	0	+	0	...
Pentose . . .	+	0	Simplified method (?)	Red coloration with phloroglucin and hydrochloric acid.
Uric acid in great excess.	+ Slight.	0	0	Separated by filtering urine through animal charcoal. Filtrate does *not* reduce Fehling's solution.
Glycuronic acid	+	0	+ Slight deposit of crystals.	Generally due to administration of drugs. Fehling's test, obtained after action of yeast.
Dextrin . . .	+	0	0	After isolation, brown coloration with iodine.
Alkapton or pyrocatechin.	+	0	0	No reaction with Nylander's test. Urine becomes dark on standing, or on addition of liquor potassæ or ammonia.

II. On the Detection of Small Quantities of Grape Sugar in the Urine.

When sugar is present in the urine in large quantities, its detection is easy; but if only small quantities or traces be present, their detection with certainty is often troublesome. In the latter case, in spite of the great number of tests for sugar, often a satisfactory conclusion cannot be arrived at, unless the medical man be prepared to devote some time and care to the urine examination.

No single sugar test is quite satisfactory in all cases. The best tests we possess have some weak points when applied to the detection of minute quantities of sugar in the urine. Either they are not sufficiently sensitive, or they occasionally give reaction with other substances besides grape sugar.

During the last eight years I have devoted a considerable amount of time to the examination of urine specimens which have been thought to contain small quantities of sugar, and have given a fair trial to all of the sugar tests just described; but I have found Fehling's solution, the phenylhydrazin test, and fermentation by far the most satisfactory. By these three tests, employed and combined in the order and manner which will be described, it is nearly always possible to decide with certainty whether a small quantity of sugar is present or absent in a suspected urine. I have found this combination exceedingly useful, convenient, and reliable for clinical work, and the time actually taken up in performing the several tests will not amount to many minutes, though it may be necessary to wait twenty-four hours before a decision can be given.

In examining a suspected urine—

1. *Apply Fehling's test*, taking the usual precautions. For most cases no other sugar test is needed. If a negative result be obtained, the urine may be declared free from sugar in the clinical sense. A well-marked reduction of oxide of copper, when other indications of diabetes are present, may be taken as evidence of the presence of grape sugar. But, as mentioned already, it is a third class of cases which is especially liable to cause trouble. There are often no indications of diabetes or glycosuria, except the reduction of Fehling's solution, and frequently this reduction is slight. After the urine has been raised to the boiling point, the fluid may be unchanged at first, but when the test

tube is allowed to cool, it becomes turbid, greenish, or greenish yellow.

In these cases sometimes the reduction of copper is due to a small quantity of grape sugar, sometimes to other substances. As mentioned above, Fehling's solution may be slightly reduced, if the urine contain a great excess of uric acid or urates,[1] especially when boiling is prolonged and when too much urine is added. It is also reduced by glycuronic acid, alkapton, or pyrocatechin; slightly by creatine, creatinine, xanthine; and by the following varieties of sugar besides glucose:—lactose, maltose, lævulose, galactose, and pentose. Lactose is often present in the urine during lactation and in cases of abscess of the breast. The presence of glycuronic acid in the urine is generally due to the administration of some drug (see p. 10), but Ashdown has shown that it may be occasionally met with when no drug is being taken.

When the patient is under the influence of any of the drugs which are liable to cause the appearance of glycuronic acid in the urine, it is well to discontinue the treatment, and to test a second sample of urine. But this is not always possible, since an opinion must often be given on one specimen only.

In the cases in which there are no indications of diabetes beyond the reduction of Fehling's solution, and especially if the reduction be slight or of an indefinite nature, it is evident, therefore, that some other test is necessary before coming to a decision.

2. *Apply the phenylhydrazin test*, employing the simplified method of boiling for two minutes, without the use of a water-bath (for description, see p. 25).

Whilst many substances may reduce Fehling's solution slightly, the majority of these give no reaction with the phenylhydrazin test. Thus uric acid, urates, creatine, creatinine, hippuric acid, xanthine, maltose, cane sugar, give no reaction.

Now, phenylhydrazin is a most useful test for sugar when applied in the simple manner above described. It is exceedingly

[1] When the urine contains an excess of uric acid and urates, these can be removed by filtration several times through animal charcoal, whilst glucose passes through in the filtrate, and may then be readily detected by Fehling's solution. When a slight reduction of Fehling's solution is due to excess of uric acid or urates in the urine, the reduction will not be obtained after filtration through good animal charcoal (see p. 13).

Urine which contains alkapton or pyrocatechin becomes greenish-brown on standing. It changes to deep brown or black on the addition of a few drops of liquor potassæ or ammonia.

sensitive, but not too sensitive for clinical work. A distinct reaction is obtained even when the urine contains only 0·015 per cent. of sugar, and no reaction is obtained with normal urine when this simple method of performing the test is followed.

It is of value chiefly as a *negative* test. If no reaction be obtained, we *can state with certainty that glucose is entirely absent*, and that the reduction of the Fehling's solution was *not* due to glucose. If, then, no deposit of crystals be found in the test tube when examined half an hour (or perhaps better, one hour) after the test has been performed, *no further testing is required.* If the sulphur-yellow, needle-shaped crystals form, they generally do so in fifteen or twenty minutes. These crystals would indicate glucose almost with certainty, if numerous or large; but there is just the possibility of glycuronic acid being the cause, especially when the crystals are very scanty or small, and this is the weak point of a positive reaction with the phenylhydrazin test. If the crystals consist of globules with short spines as in Fig. 4, *b*, lactose may be suspected. If a positive reaction be obtained, and we wish to be quite certain that it is due to glucose, we must employ the next test.

3. *Apply the fermentation test*, using two test tubes, one containing normal urine for control, as described on p. 19, and taking the precautions there mentioned. If there should be a greater quantity of gas at the top of the tube containing the suspected urine, sugar is *certainly present*, and no further testing is required.

A positive reaction is often obtained in one, two, or three hours, but twenty-four hours may be necessary. The weak point of this test is, that it will not give any reaction if the amount[1] of sugar should be less than 0·1 per cent.

4. If no reaction is obtained by the fermentation test, *apply Fehling's test to the suspected urine, which has been submitted to the action of yeast* in the test tube for twenty-four hours. If now no reaction should be obtained with Fehling's solution, the urine has contained glucose. A urine which has reduced Fehling's solution, however slightly, before fermentation, but which, after the action of yeast for twenty-four hours in the test tube, no

[1] Of course, reliable results will only be obtained when the yeast is active. There is no difficulty in obtaining active yeast, however. If the yeast should be suspected, a third test tube, containing the urine + yeast and a little glucose, would show whether it is capable of giving rise to fermentation.

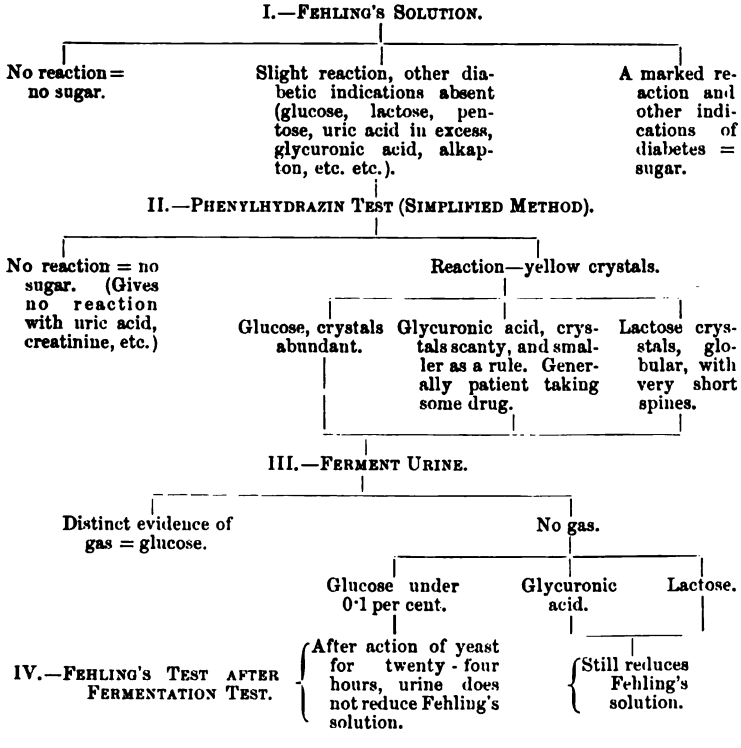
longer reduces Fehling's solution, may with certainty be stated to have contained sugar, even though no evidence thereof, by excess of gas, can be obtained by the fermentation test alone. Glycuronic acid and lactose do not ferment, and therefore after the action of yeast for twenty-four hours the urine still reduces Fehling's solution.

I have made a number of experiments on the value of this combined method, by adding a few drops of diabetic urine to a large quantity of normal urine. By trial I have thus obtained samples of urine which contained so little sugar that they gave only a very indefinite reaction with Fehling's solution, *i.e.* a slight greenish opacity, which did not appear at once on boiling, but only developed after the urine was allowed to cool. A well-marked reaction was obtained in these cases by the phenylhydrazin test (characteristic crystals). Now, such urines gave no evidence of the presence of sugar, by excess of gas, when the fermentation test was applied in a test tube in the manner above described. Yet the mixed urine and yeast, taken from the test tube at the end of twenty-four hours, failed to reduce Fehling's solution.

In these experiments the urine, before fermentation, contained a quantity of sugar, so small that only a very slight reaction was obtained by Fehling's test (*i.e.* when the fluid began to cool after boiling). Any quantity of sugar less than this, as Sir William Roberts points out, is of no clinical importance. Hence this combination of tests is sufficient to give definite results, when the urine contains the smallest quantity of sugar of any clinical importance.

When the tests are performed in the above order, the phenylhydrazin test at once eliminates the majority of the substances, other than sugar, which cause the reduction of Fehling's solution. Very often a negative result is obtained, and no further testing is required; no fermentation is necessary, and thus much time is saved. In case a positive result should be obtained with phenylhydrazin, the application of the fermentation test may be necessary. It may or may not reveal the presence of sugar. In either case, if the urine no longer reduces Fehling's solution (after the action of yeast), sugar is indicated. By the application of the above combination of tests, in the order and manner described, I believe small quantities or traces of sugar can be detected with greater certainty and with less actual expenditure

of time than by any other means, though it may be necessary in some cases to allow twenty-four hours to elapse before an opinion can be given; still the time actually expended in performing the test is but little, and the methods are very simple and convenient for clinical work.



III. Quantitative Estimation of Sugar in the Urine.

By the intensity of the reaction to the ordinary tests we may determine whether the urine contains merely a trace of sugar, or a large quantity; but often it is of service to determine the exact amount, since the quantity of sugar excreted daily is one indication of the severity of the case and of the course of the disease, as will be pointed out in a subsequent chapter.

The following are the methods chiefly used for the quantitative estimation of glucose in the urine:—

1. *Fermentation method of Sir William Roberts* ([35]).—This is the most simple method. It gives results which, though not quite

accurate, are still sufficient for clinical purposes. The whole time actually required for the estimation is not more than four or five minutes, but it is necessary to wait for twenty-four hours for the complete destruction of the sugar by fermentation.

As a method of estimating the daily sugar excretion, in order to judge of the value of various methods of treatment in reducing glycosuria, the fermentation test is most convenient. The method is founded on the diminution of the specific gravity which occurs in saccharine urine after fermentation with yeast. The sugar is decomposed, and alcohol and carbonic acid are formed. The reduction of specific gravity is due to (1) the destruction of glucose, (2) to the presence of alcohol formed by fermentation. Sir William Roberts pointed out, many years ago, that *each degree of specific gravity lost by saccharine urine, through fermentation, corresponds practically to one grain of sugar to the ounce.*

The following is the method of performing the test. About 4 oz. of the diabetic urine are placed in a 12-oz. bottle, and a piece of German yeast about the size of a small walnut is added. Into the mouth of the bottle is placed a cork which is nicked, in order that the carbonic acid gas which is formed by fermentation may escape. The bottle is put in some warm place, so that fermentation may occur. A second bottle, containing 4 oz. of the diabetic urine, without any yeast, is placed beside the first bottle. At the end of twenty-four hours the urine in the first bottle will have fermented, the sugar will have been decomposed, and the specific gravity will be diminished. Two urine glasses are taken; one is filled with the fermented urine, the other with the unfermented urine. The specific gravity of each is ascertained by the urinometer. The difference of the two will indicate the number of grains of sugar per ounce.

For example—

Specific gravity of unfermented urine	.	1040
„ of fermented „	. .	1005
Difference	. . .	35° of sp. gr.

∴ Urine contains 35 grs. of sugar to the ounce.

If the total quantity of urine for the twenty-four hours be 200 oz., for example, then the total excretion of sugar for the day will be 7000 grs.

In taking the specific gravity, the ordinary urinometer may

be used, but for greater accuracy urinometers have been made with very long scales, so that a difference of a quarter of a degree of specific gravity can be readily detected.

There is one important precaution in employing this method: it is necessary to see that the urine to which yeast has been added has completely fermented. It sometimes happens that the sugar has not all been decomposed, and then, of course, the results are unreliable, the figures being too low. Hence, before taking the specific gravity, it is well to test the urine specimen to which yeast has been added, for sugar. If it should still reduce Fehling's solution on boiling, then the sugar has not been completely decomposed, and the bottles should be put back for some time in order that fermentation may be completed. *Before the specific gravity is taken, the urine to which yeast has been added should be quite free from sugar when tested with Fehling's solution.*

Should it be desired to record the percentage of sugar in the urine, it is only necessary to multiply the difference in the specific gravity of the fermented and unfermented urines (*i.e.* the number of grains of sugar per ounce) by 0·23. Thus, if the difference of the specific gravity of the two be 35, then the percentage of sugar will be $35 \times 0{\cdot}23 = 8{\cdot}05$.

2. *Estimation by Fehling's solution.*—One volume of diabetic urine is well mixed with nine volumes of water. A burette graduated in cubic centimetres is filled with the diluted urine. Ten c.c. of Fehling's solution are placed in a flask or white porcelain capsule and diluted with about twice their volume of water. Now the Fehling's solution is of such a strength that all the copper which is contained in 10 c.c. is reduced by 0·05 grms. of glucose (see p. 9 for composition of Fehling's solution). In estimating the amount of sugar by this method, it is simply necessary to find the quantity of urine which is needed to reduce completely this 10 c.c. of Fehling's solution. Such a quantity of urine must contain 0·05 grms. of sugar.

In performing the test, the diluted Fehling's solution is raised to the boiling point, and then a little of the diluted diabetic urine is allowed to drop in from the burette. The Fehling's solution is again raised to the boiling point, when oxide of copper is precipitated; it is then allowed to stand for a few seconds. If the blue colour still remains, more of the dilute urine should be added, and the mixture again boiled. This proceeding is repeated, time after time, until at length the blue

colour entirely disappears; and after standing, when the oxide of copper falls to the bottom, the fluid is colourless. Then we know that all the copper has been reduced in the 10 c.c. of Fehling's solution. From the strength of this solution (as above stated) we know that 0·05 grms. of sugar are required to reduce the 10 c.c. This quantity of sugar is contained, therefore, in the amount of diluted urine added. Thus, for example, if the amount of urine required to reduce the Fehling's solution be 15 c.c., we know that 15 c.c. of the diluted urine contains 0·05 grm. of sugar. But this 15 c.c. contains one-tenth of its volume of urine, *i.e.* 1·5 c.c. Therefore 1·5 c.c. must contain 0·05 grm.

The following proportion gives the percentage of sugar:—

$$1{\cdot}5 : 100 :: 0{\cdot}05$$

$$\frac{100 \times {\cdot}05}{1{\cdot}5} = 3{\cdot}3 \text{ per cent. of sugar.}$$

In some cases, when the urine contains only a small quantity of sugar, it is difficult to estimate it exactly by Fehling's solution, since the copper oxide remains suspended in the fluid, and it is impossible to say when the blue colour has disappeared. But in such cases I have found Pavy's method to be satisfactory.

3. *Pavy's method* ([36]) is of great service in estimating the quantity of sugar in the urine. He employs a solution of copper sulphate containing ammonia, in place of Fehling's solution. When the copper sulphate is reduced to cuprous oxide by glucose, no precipitation occurs, since the ammonia in the solution dissolves the oxide formed; but the solution loses its blue colour. In making an analysis, the fluid containing the glucose is simply dropped into the boiling test solution until its blue colour completely disappears. Hence the troublesome waiting until the oxide of copper subsides, in order to ascertain whether the blue colour of the solution has disappeared, is no longer necessary when Pavy's solution is used.

Composition of Pavy's Ammoniated Cupric Test Solution.

Metrical System.

Cupric sulphate	4·158 grms.
Potassic sodic tartrate (Rochelle salt) . .	20·400 „
Potash (caustic)	20·400 „
Strong ammonia (specific gravity, 0·880) .	300 c.c.

Water, 1 litre.

English System.

Cupric sulphate	36½ grs.
Potassic sodic tartrate (Rochelle salt) . . .	178 „
Potash (caustic)	178 „
Strong ammonia (specific gravity, 0·880) . . .	6 fluid oz.
Water, to 1 pint.	

"Dissolve the potassic sodic tartrate and potash together in a portion of the water, and the cupric sulphate with the aid of heat in another portion; pour the solution of cupric sulphate into the mixture of potassic sodic tartrate and potash; when cold, add the ammonia; and finally, with water, bring the volume of the liquid to the bulk specified."

Pavy's solution does not deteriorate on keeping, if preserved in a properly stoppered bottle.

Ten c.c. of the solution are decolorised by 0·005 grm. of glucose. In applying the test the urine is diluted with water; if only slightly saccharine 1 in 10, if strongly saccharine 1 in 20 or 1 in 40. The diluted urine is then placed into a burette tube.

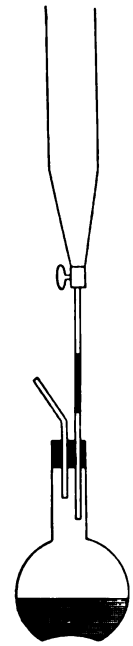


FIG. 5.—Apparatus for quantitative estimation of sugar, by Pavy's method.

The 10 c.c. of the test liquid are now measured out and placed in a flask, such as that represented in Fig. 5; the stopper being perforated by two pieces of glass tubing. Then 20 c.c. of water are added, and by the water thus used the c.c. measure is rinsed out. The flask is now connected with the burette by a piece of tubing, and heat from a spirit lamp or gas burner applied underneath. When its contents have well commenced to boil, the urine is allowed to escape by drops at the rate of about 60 to 100 per minute into the Fehling's solution, until the contents of the flask are brought to the colourless state of water. Towards the end, the dropping has to be conducted more slowly than at first, so as to avoid going beyond the exact point required. The level of the diluted urine in the burette having been read off before starting, a second reading at the termination gives the amount which has been required to decolorise the 10 c.c. of the test fluid, and which therefore contains 0·005 grms. of glucose.

If, in performing the analysis, the contents of the burette are dropped in too slowly, and the boiling becomes too prolonged, the suboxide falls, in consequence of the dissipation of ammonia before the operation is completed. Should this event occur, a fresh analysis must be performed, and the contents of the burette dropped in a little more quickly.

The chief precautions are not to drop in the urine from the burette so rapidly as to run the risk of passing beyond the point required for decoloration, and at the same time not to drop it in so slowly as to lead to a deposition of suboxide, owing to the expulsion of the ammonia.

With everything conveniently at hand, a few minutes only are required for the performance of the analysis from beginning to end.

Air ought to be excluded from the flask as much as possible during the analysis, since Pavy's fluid, after becoming decolorised, soon absorbs oxygen and turns blue again.

From the amount of diluted urine required to decolorise the 10 c.c. of Pavy's solution, the percentage of sugar is easily calculated. Supposing 5 c.c. of diluted urine be required to decolorise the 10 c.c. of Pavy's solution, then we know (from the strength of the Pavy's solution) that this quantity of urine must have contained 0·005 grm. of sugar. If the urine has been diluted in the proportion of 1 to 10, the 5 c.c. of the diluted urine corresponds to 0·5 c.c. of the undiluted urine. Therefore this quantity must contain 0·005 grm. of sugar, and the percentage of sugar can be easily calculated.

$$0{\cdot}5 : 100 : : 0{\cdot}005$$

$$\frac{100 \times 0{\cdot}005}{0{\cdot}5} = 1 \text{ per cent. of sugar.}$$

4. *Gerrard's cyanocupric method.*—This method, published by A. W. Gerrard ([37]) in 1892, has been since improved, and by some chemists is considered superior to the two methods just described. The following account is taken from the description of Allen ([38]), by whom it has been slightly modified and largely used.

When a solution of potassium cyanide and a cupric salt are mixed together, a double cyanide of potassium and copper is formed.

$$CuSO_4 + 4KCN = Cu(CN_2)2KCN + K_2SO_4$$

The double cyanide is colourless or faintly yellow. If Fehling's solution be used instead of sulphate of copper, the colourless double cyanide is also formed, and oxide of copper is not thrown down when this mixed solution is boiled with grape sugar. If an excess of Fehling's solution be present, then this extra quantity will be reduced by boiling with glucose, but the oxide of copper formed will be dissolved. When the Fehling's solution has been completely reduced, the blue colour will disappear. The method, therefore, resembles that of Pavy. The copper oxide is not precipitated, and the end of the reaction is indicated by the disappearance of the blue colour. But it has the advantage that no ammonia is given off; also reoxidation of the reduced solution proceeds so slowly that, if the test be performed fairly quickly, it is not necessary to prevent the ingress of air, and a porcelain capsule may be employed.

Ten c.c. of Fehling's solution are placed in a porcelain dish with 40 c.c. of water, and the mixture boiled. A 5 per cent. solution of potassium cyanide is added gradually until the blue colour of the liquid just disappears, or only a slight tinge of blue remains. Excess of cyanide must be carefully avoided. Another 10 c.c. of Fehling's solution are now added, and the mixture then becomes blue. The urine is rapidly dropped in from a burette, until the blue colour disappears, the mixture being kept in ebullition and constantly stirred. When this occurs, we know, from the strength of the test solution, that the quantity of urine added must have contained 0·05 grm. of grape sugar.

5. *Picric acid method.*—Sir G. Johnson ([39]) recommended the picric acid test (p. 15) as a means of estimating the quantity of sugar in the urine, since the depth of the colour produced by the reaction is proportionate to the amount of sugar present. A standard solution is prepared, which has the same dark red colour as that produced by boiling picric acid and potash with urine which contains a grain of glucose to the ounce, "four times diluted by the reagents and water in the boiling tube." As all saccharine solutions containing not less than a grain of sugar to the ounce are similarly diluted in the process of analysis, the standard represents one of a grain to the ounce.

The standard solution consists of liquor ferri perchloridi fort., sp. gr. 1·42, 1 drm.; glacial acetic acid, sp. gr. 1·058,

4 drms.; liquor ammoniæ, sp. gr. 0·959, 100 minims; distilled water to 4 oz.

The suspected urine, liquor potassæ, and saturation solution of picric acid are boiled together; then the mixture is diluted with water and placed in a graduated glass vessel, and the colour compared with that of the standard solution. From the amount of dilution which is necessary before the tints are the same, the quantity of sugar present is estimated.

6. *Polarimetric method.*—Grape sugar possesses the power of rotating the plane of polarised light to the right, and this fact forms the basis of a method for the quantitative estimation of sugar in diabetic urine.

Various forms of apparatus—the polarimeters or saccharimeters of Lippich, Soleil, and others—have been constructed for this purpose; but the instruments are expensive, and the method is open to fallacy, though it is said to give good, if not quite accurate, results when the amount of sugar is not too small. But when only a small quantity of sugar is present, the results are said to be unreliable.

In severe cases of diabetes, β-oxybutyric acid is often present in the urine. Occasionally, though very rarely, lævulose is present in addition to glucose. Both of these bodies rotate the plane of polarisation to the left, and therefore, if present in the urine examined, the results of the polarimetric estimation of glucose would be too small.

The method is rarely employed clinically, since others are more reliable. Hence it is not necessary to devote further space to the description of the apparatus and to the manner of employing it. For such a description the reader may consult works on physics.

IV. The Presence of a Trace of Sugar in Normal Urine.

It is undisputed that normal urine gives no reaction with Fehling's solution and the ordinary chemical tests for sugars, when applied in the usual way. But it was stated by Brücke, long ago, that a trace of sugar is present in normal urine, and this view has been supported by Bence Jones, Kühne, and by numerous physiologists and physicians more recently; whilst others still hold that normal urine is free from any trace of

sugar. Not long ago, the question whether a trace of sugar is or is not present in normal urine, was the subject of considerable correspondence in the *Lancet* (July–December 1894, and January, February, March 1895).

Pavy ([40]), who investigated the subject carefully many years since, supports the statement of Brücke, and still considers his methods satisfactory. Brücke devised a process for removing the supposed trace of sugar from normal urine by precipitating it with oxide of lead (for details see Pavy's recent work [41]). Pavy, by using large quantities of normal urine (100 litres), has satisfied himself of the truth of Brücke's statement. The product which he obtained gave the ordinary reactions for sugar with liquor potassæ, nitrate of bismuth, and Fehling's solution. At first no reaction was obtained with the fermentation test; the product was strongly acid, however, and on neutralising it with sodium carbonate, and then applying the fermentation test, a distinct reaction was obtained. Further, this product, obtained from normal urine by special treatment, gave a reaction with the phenylhydrazin test.

Pavy states that the amount of sugar in normal urine is 0·5 parts per 1000.

Benzoyl chloride precipitates carbohydrates from the urine, and this forms an exceedingly delicate test. Wedenski ([42]), by shaking up large quantities of normal urine with benzoyl chloride, has obtained a white granular precipitate like that yielded by glucose. By a special process applied to a large quantity of normal urine, Moritz ([43]) has obtained yellow needle-shaped crystals by the phenylhydrazin test. These crystals are not due to glycuronic acid, since their melting point is 204° to 205° C.—the same as that of phenylglucosazone. Hence he concludes that a trace of sugar is present in normal urine.

Indications of traces of sugar have been obtained only when large quantities of urine have been examined and the supposed sugar isolated. Certainly Pavy's estimate, 0·5 per 1000, appears remarkably high. By the phenylhydrazin test, performed according to the simplified method, 0·015 per cent. of sugar can be easily detected in saccharine urine greatly diluted with water. But the test applied in the same manner to normal urine gives no reaction. One would expect it to do so, if normal urine contained the amount of sugar stated by Pavy (·05 per cent.).

G. Stillingfleet Johnson and Sir G. Johnson ([44]) deny that

normal urine contains a trace of sugar. They state that after the urine has been treated with mercuric chloride, or a mixture of sodium acetate and mercuric chloride (according to the method proposed by G. Stillingfleet Johnson), and the creatinine thereby separated, it fails to give any reaction for sugar.

Seegen ([45]) points out that his very sensitive test—Fehling's test after filtration through animal charcoal—fails to give any reaction with normal urine; hence he concludes that normal urine cannot contain any quantity of sugar above 0·01 per cent.

It is sufficient for clinical work to know that the ordinary tests for sugar, performed in the usual manner, fail to indicate the presence of sugar in normal urine. Whether a minute trace of sugar be present or absent is a question of interest to the physiologist, but is not one of any great importance to the clinician, and at present opinions are divided. A full discussion of the subject is given in the works of Seegen, Allen ([46]), and Pavy.

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CHAPTER III.

PHYSIOLOGICAL CONSIDERATIONS.

In health the blood contains a small and fairly constant quantity of grape sugar; but the exact source, the destiny of this sugar, the nature of the glycogenic function of the liver, and many physiological problems connected therewith, have been the subject of endless discussion during the last fifty years. And since there is still such a great divergence of opinion on these physiological questions, it will only be possible, in a work devoted to the clinical and practical side of diabetes mellitus, to very briefly refer to some of the more important facts and theories bearing on the physiology of sugar formation.

1. The carbohydrates derived from food articles are carried from the alimentary canal by means of the portal vein to the liver. These carbohydrates vary in quantity and nature. They consist of glucose, lævulose, saccharose, lactose, maltose, and traces of dextrin. Naturally the amount of carbohydrates in the portal vein varies much at different times, and with different articles of food.

2. The liver of man and the lower animals contains a carbohydrate substance allied to starch, which has been named glycogen by its discoverer, C. Bernard (1). If the liver of one of the lower animals be removed immediately after death, rapidly cut into small pieces, thrown into boiling water and broken up, a decoction can be obtained, which, after filtration, is opalescent, and contains *glycogen*. An iodine solution gives a brownish-red or port-wine colour with this decoction, owing to the presence of glycogen. When tested with Fehling's solution, the decoction is found to contain only a small amount of sugar. The glycogen can be precipitated by alcohol, and after washing and purification a white powder is obtained, which gives a port-wine coloration with iodine, but no reaction with Fehling's solution or other sugar tests.

Sugar is produced by the action of saliva, or some other amylolytic ferment, on the separated glycogen, or on the decoction obtained from the liver. The opalescent solution becomes clear, and the chemical reactions for sugar are obtained.

Glycogen is allied to starch; it is often termed animal starch, and its chemical formula is $C_6H_{10}O_5$, or some multiple thereof.

If the liver be allowed to remain in the body for several hours after death, especially if the body be kept in a warm place, a decoction of this organ will be no longer opalescent. It will be clear, and there will be little or no port-wine coloration with iodine; but the solution will contain a very considerable amount of sugar. After death the glycogen in the liver rapidly diminishes, and the sugar increases. It is generally believed that glycogen is gradually converted into sugar, post mortem, though this view is not held by some observers. The transformation is arrested by a high temperature (100° C.), and is supposed to be due either to the action of the liver cells, or to some ferment not yet isolated.

The amount of glycogen in the liver is very variable (²). It depends on the quantity and nature of food previously taken, and it disappears during starvation. If an animal be starved so that all the glycogen may be assumed to be absent from the liver, and then a diet rich in carbohydrates be given, a large amount of glycogen is found in this organ. Starch and various kinds of sugar, therefore, cause an accumulation of hepatic glycogen—sometimes a very rapid accumulation.

A nitrogenous diet also causes an accumulation of glycogen in the liver, but to a much less extent than is caused by a carbohydrate diet. Flesh meat contains a certain amount of carbohydrate in some form; and if animals are fed on proteid such as fibrin, casein, or albumin in place of meat, the amount of glycogen in the liver becomes still smaller, though it is stated to be more than during starvation.

Gelatin leads to the formation of some glycogen in the liver, but nitrogenous food and gelatin are far less powerful than carbohydrates in producing hepatic glycogen. Fats do not give rise to the formation of glycogen, and an animal fed on fat alone has no more glycogen in its liver than a starving animal.

Thus the amount of glycogen in the liver depends largely on the food. It is least when the animal is fed on fatty food; it

is greater when the diet consists of fleshy food; it is much more abundant when the diet consists chiefly of starch; but it is greatest when the diet consists of carbohydrates which can be rapidly absorbed, such as sugar and dextrin (Seegen,[3]).

Probably glycogen is derived from sugar absorbed from the intestines. When sugar is injected into the jugular vein, glycosuria may be produced, but a very considerable quantity may be injected into the portal vein without any glycosuria occurring. Apparently the liver fixes the sugar, and converts it into glycogen. As already mentioned, glycogen is also formed from proteids.

The liver appears to act as a storehouse for the excess of glycogen; a considerable amount is stored also in the muscles. Next to the liver, the muscles form the second great storehouse for glycogen. The amount of muscle glycogen is said to be influenced by food; by feeding animals on rice and cane sugar, it is greater than when the diet consists of fat and fibrin. During starvation the muscle glycogen disappears. Glycogen is a normal constituent of muscle, though it is not invariably present, and the amount varies in different animals and in different muscles. The muscles of the embryo contain a large amount. When the nerve to a muscle is divided, the glycogen is increased; rigor mortis causes it to diminish or to disappear entirely; apparently the muscle glycogen is then converted into dextrose.

Glycogen cannot be regarded as a necessary part of ordinary muscle substance, since muscles free from glycogen may be able to carry on long-continued contractions.

As Michael Foster ([2]) puts it, the glycogen in the muscles of the embryo and of the adult is probably a local branch of the great carbohydrate bank; it appears to be a store of carbohydrate material, like vegetable starch, packed away so that it can be drawn upon when required.

3. What becomes of the glycogen in the liver, and what are the functions of the liver with reference to sugar formation, are vexed questions. There are two chief views on the subject:—

(*a*) According to one view, which was first put forward by Claude Bernard ([1]), the glycogen in the liver is gradually transformed into sugar, which is paid out into the blood, and conveyed through the hepatic vein to the right side of the heart, and then to the lungs, where it is burnt up. Afterwards Bernard modi-

fied this view, and concluded that sugar is distributed to the tissues of the body, and burnt up in the capillaries thereof. The liver is therefore a storehouse of reserve glycogen, which is paid, as required, into the hepatic vein, and thus the amount of sugar in the blood is kept within a certain normal limit. (*b*) Pavy and many other experimenters believe, however, that the liver is a sugar absorbing organ, and that instead of throwing sugar into the system, it prevents sugar passing into the general circulation.

In the first place, it is important to remember that whether the liver is a sugar producing or sugar destroying organ, all observers agree that normal blood *does* contain a very small, though fairly constant, quantity of glucose. According to Bernard, the amount of sugar in normal blood is 1 to 3 parts per 1000; according to Pavy, 0·6 to 1·0 or a little over 1·0, per 1000 (in animals); according to Seegen, 0·1 to 0·2 per cent. in man.

It is stated that in animals kept without food, and made to perform muscular work, only traces of glycogen are found in the liver and muscles, yet the arterial blood still contains the usual quantity of sugar.

Many years ago, Claude Bernard discovered that the liver of animals fed entirely on flesh meat contained sugar, when examined soon after death. In animals fed on flesh diet, he also found that the blood of the portal vein was free from sugar, but that of the hepatic vein was rich in sugar. Lehmann has since obtained similar results.

Bernard afterwards discovered the substance in the liver which he named glycogen. He found that the blood of the hepatic vein and right side of the heart was comparatively rich in sugar, whilst arterial blood only contained a trace of sugar. He also found that there was a difference between arterial and venous blood; that arterial blood contained 0·3 parts per 1000 more sugar than venous blood. Bernard therefore concluded that sugar is formed in the liver from glycogen, and transmitted to the general circulation to be burnt up in the tissues.

These statements have been disputed by some observers. Pavy (4), by passing a catheter into the right side of the heart, obtained blood from the living animal. He states that blood obtained in this way contains only traces of sugar, whilst in the dead animal the blood of the right side of the heart is rich

in sugar; and that blood obtained during life from the right ventricle contains only 0·4 to 0·7 parts per 1000 of sugar, *i.e.* not more than the amount in the carotid blood; whilst blood from the right ventricle after death contains 5 to 9·4 parts per 1000. Hence, in the latter case, Pavy regards the excess of sugar in the blood obtained from the right side of the heart simply as the result of a post-mortem change. Ritter has obtained similar results.

M'Donnell (5), by means of a catheter, removed blood during life from the right side of the heart in twelve dogs, which had been fed for some weeks exclusively on meat diet. In seven of these he could not detect any sugar; in five, traces were present.

In order to determine whether sugar was present in the liver, Pavy removed pieces of this organ from animals immediately after they were killed. The pieces of liver were placed at once in a freezing mixture, broken up into fragments, and the pulp thrown into boiling water. A filtered decoction gave either no reaction or only a minimal reaction for sugar.

Ritter removed pieces of the liver from animals during life; the liver fragments were thrown into boiling water, but no reaction for sugar was obtained. Pieces of the liver removed a few minutes after death and treated in the same manner were found to contain sugar.

M'Donnell (5) obtained similar results. A portion of the liver removed immediately after death gave scarcely any indication of the presence of sugar, but a similar portion removed twenty minutes after death was found to contain 12·5 grs. of glucose.

M'Donnell (5) also made more conclusive experiments on the hedgehog. The animal was surrounded by ice until it became torpid. The application of cold was continued until the animal was frozen into a solid mass. When the liver was removed, it did not give the slightest reaction for sugar. The liver of a frog frozen slowly was found to contain no sugar; but if a frog was frozen rapidly, the animal struggled considerably, and the liver was found to contain a small amount of sugar.

Bernard in his last work stated that pieces of liver taken from the body during life and thrown into boiling water contained 0·23 to 0·24 per cent. of sugar. Pavy has criticised Bernard's results, and believes that too little water was used in the method employed for the estimation of sugar.

As already mentioned, Claude Bernard at first suggested that the sugar in the blood was destroyed in the lungs. Afterwards he modified this view, and came to the conclusion that blood sugar was destroyed in the capillaries of the general circulation. From eleven observations, Pavy found, however, that the average amount of sugar in arterial blood was 0·941 parts per 1000, in venous blood 0·938. But he thinks the excess in arterial blood is too slight for the difference to be reliable.

According to Pavy, the liver prevents the sugar absorbed by the portal circulation reaching the system. [A minute quantity does reach the general circulation, however, since the blood of the systemic circulation contains a very small quantity of sugar.] According to Pavy and many authorities, normal urine also contains a very minute trace of sugar. Pavy holds that if sugar were continually formed by the liver and passed into the general circulation, as Bernard asserted, it would be eliminated by the kidneys, and the urine of every person would contain sugar in quantity. He believes that the sugar in the blood and in the urine run parallel, and that any excess of sugar in the blood is eliminated in the urine.

Biedl and Kraus (6), however, have recently made intravenous injections of 200 to 300 grms. of grape sugar in four persons; by this proceeding they estimated that the percentage of sugar in the blood was raised to more than three times the normal amount, yet no glycosuria or polyuria followed.

F. Voit (7) has recorded a number of interesting facts with reference to sugar destruction in the system. He points out that grape sugar, which ferments easily, must be taken in large quantities before it appears in the urine in a healthy person, whilst sorbose, which does not ferment, is excreted in the urine after small doses. Cremer has shown that the sugars which ferment most easily pass into the urine with greatest difficulty in health, whilst those which do not ferment appear in the urine most readily. The sugars which do not ferment do not form glycogen, they pass into the blood in great quantity, and are, in part at least, excreted in the urine.

By the subcutaneous injection of sugar the changes produced in the alimentary canal are avoided. Voit has made subcutaneous injections in man, and introduced solutions of various kinds of sugar under the skin. If the solutions used were not too concentrated, and if the instruments were carefully sterilised,

no bad effects followed. Ten per cent. solutions of sugar were employed.

Of the monosaccharides, experiments were made with dextrose, lævulose, and galactose. These three substances did not appear in the urine, or only appeared in very small quantities after subcutaneous injection. They were therefore rapidly destroyed in the organism.

	Injected.	Found in Urine.
Dextrose	100·00 grms.	2·64
	60·00 „	Traces.
	11·24 „	...
Lævulose	10·94 „	0·99
	10·13 „	Traces.
Galactose	9·23 „	0·16
	9·58 „	Traces.

Dextrose and lævulose are therefore good glycogen-builders. With galactose there is a greater excretion (in proportion to amount injected).

Of the disaccharides—saccharose, lactose, and maltose were tried.

	Injected.	Found in Urine.
Saccharose	25·60 grms.	24·88
	10·81 „	10·71
	9·29 „	9·95
	1·27 „	1·23
Lactose	9·36 „	10·06
	9·05 „	9·42
	1·09 „	1·03
Maltose	8·79 „	...

After the subcutaneous injection of cane and milk sugar, the whole of these substances was found again in the urine, but when given by mouth large quantities of cane sugar must be taken before glycosuria occurs. In the intestine cane sugar is inverted and dextrose and lævulose are formed, but by subcutaneous injection this change is prevented. The cells of the organism have thus no power of decomposing cane sugar circulating in the blood, and the liver cannot form glycogen from it.

Lactose is excreted by the urine after subcutaneous injection; but when given by mouth it only appears in the urine after considerable quantities have been administered.

When given by the mouth, milk sugar is inverted in the intestines, but the cells of the organism are not able to decompose it when injected subcutaneously. This explains why lactosuria occurs in the puerperal state (see p. 88). Milk sugar passes directly into the circulation from the mammary gland, and is therefore just in the same condition as when injected subcutaneously. The inverting action of the alimentary canal is avoided, hence lactose appears in the urine.

Maltose does not appear in the urine when injected subcutaneously; it is apparently taken up by the cells of the organism, and also forms glycogen in the liver. By the action of certain ferments, maltose can be formed from glycogen, also blood serum has the power of destroying maltose.

4. Seegen ([8]) of Vienna has repeated many of the experiments of Pavy and Bernard, and has obtained results somewhat different. From his observations he concludes that sugar formation is a normal function of the liver. He found that portions of the liver (excised and thrown into boiling water) contained 0·4 to 0·5 per cent. of sugar. He also found that the blood of the hepatic vein contained 60 to 100 per cent. more sugar than that of the portal vein. Whatever the nature of the food, and even during starvation, the blood from the hepatic vein always contained much more sugar than that of the portal vein.

Recently Mosso ([9]) has made observations on the latter point; he concludes that the hepatic vein does contain more sugar than the portal vein, but that the difference is very much less than that stated by Seegen.

Seegen thinks that as much as 100 grms. of sugar may be passed into the circulation from the liver in the twenty-four hours, and he points out that by excision of the liver the amount of sugar in the blood is diminished.

Minkowski has shown that when the liver is excised in animals, the sugar in the blood disappears after some hours.

By ligaturing the vascular connections of the liver, and thus excluding it from the circulation, Bock and Hoffmann found that sugar disappeared from the blood. Seegen observed a great diminution of the sugar in the blood in three similar experiments.

Tangl and V. Harley ([10]) have shown that by diminishing the blood supply to the liver in animals, by ligaturing the three intestinal arteries, the amount of sugar in blood taken from the carotid artery was diminished.

Kaufmann ([11]) also found that the blood sugar was diminished by ligaturing the vessels of the liver.

Seegen believes that albumin and fat are the materials from which the liver forms sugar, and bases his conclusions on a number of experiments and observations.

5. Pavy, in the Croonian lecture of 1894 ([12]), points out that the multiplication of the yeast plant in Pasteur's fluid—ammonium tartrate, 1 part; cane sugar, 10 parts; ash of yeast, 1 part; water, 100 parts—clearly demonstrates that sugar is used in the construction of proteid material. According to Pavy, a carbohydrate may also be prepared from egg albumin, by a cleavage of proteid material. Pavy believes that proteid matter has a glucoside constitution, and that proof has been afforded that carbohydrates can be incorporated to form proteids, and that it is also possible to dissociate the carbohydrate again.

From his experiments he concluded that—

(1) Not only can carbohydrate material be hydrated by ferment and chemical action, but when in these conditions of increased hydration, they can be transmuted by dehydration, under the influence of protoplasmic action, to substances having more complex molecules, *i.e.* amyloses. (2) In both the vegetable and animal kingdom, carbohydrates take part in the synthesis of proteids. (3) Carbohydrates are transformed into fat under the influence of protoplasmic action.

Recently ([13]) a nucleo-albumin has been separated from various organs—the pancreas, liver, thymus, muscles, thyroid, and spleen. This nucleo-albumin has been shown to be of a glucoside nature, and by special treatment a carbohydrate has been separated from it, which has been proved to be a sugar—pentose (Blumenthal).

6. Pavy, in his Croonian lecture of 1894, has restated his old views respecting sugar formation, and has put forth a new theory with reference to sugar destruction.

Briefly stated, the following are his conclusions:—

(1) The liver at death is not more saccharine than other organs of the body; (2) the blood flowing from the liver is not more saccharine than that flowing to it, but the contrary; (3) there is no evidence of destruction of sugar in the systemic capillaries.

After a meal of fat, the cells of the villi of the intestines become charged with fat globules, which pass into the lacteals.

A similar condition is met with after carbohydrate food. Oats contain only 5 per cent. of fat, yet after a meal of oats the lacteals in the rabbit were as fully distended with milky chyle as in the dog after a meal of fat. Hence Pavy believes that the carbohydrates of food are converted into fat by the protoplasm of the cells of the intestinal villi.

He thinks that glycogen is formed in the liver from the carbohydrates of the food which have escaped synthesis by the cells of the intestinal villi. There *are thus two lines of defence*, the intestinal villi and the liver. Even in health both lines of defence may be passed, and then the urine contains sugar; this happens if too much carbohydrate food is taken.

Pavy has shown that from the liver, when treated with alcohol, dried, and powdered (in a special manner, which he describes), a substance can be produced which may be kept indefinitely in a bottle. When this powder is treated with water, and placed in an incubator for two or three hours, an active production of sugar takes place. He holds, therefore, that sugar formation is not due to vital action, but to the presence of a ferment.

The latter statement and many of Pavy's results have been criticised by Noël Paton ([14]). He points out that in rats a diet of fat causes the epithelium cells of the intestinal villi to be loaded with fat particles, but on a diet of starch or sugar the cells are free from fat globules.

Noël Paton concludes that "the early changes in the excised liver are simply a continuation of the vital processes of the organ—the katabolic side of metabolism being exaggerated, the anabolic side in abeyance." In his last article he records the results of a number of experiments, from which he comes to the conclusion that "the whole weight of evidence seems to be against the view that an active amylolytic zymen develops in the liver immediately after death, while no material argument has been adduced in opposition to the view that the conversion of glycogen to glucose is simply due to katabolic changes in the liver substance."

Pavy ([15]) has replied to the criticism of Paton, but even an outline of the discussion would occupy too much space here, and the reader is referred to the original articles.

* * *

It has only been possible to refer to some of the chief

views with respect to sugar formation and the hepatic functions in the above summary.

The two apparently opposite views with regard to the liver functions are not, perhaps, so irreconcilable as appears at first sight. Most observers admit that the liver acts to some extent as a sugar absorbing or sugar converting organ, transforming carbohydrates obtained from the portal circulation into glycogen. Whether the liver be a sugar forming or sugar absorbing organ, it is allowed by all that a small percentage of sugar *is* present in the blood. If the function of the liver and the intestinal villi be to prevent sugar entering the general circulation, there can be no doubt that this action is not complete, and that sugar *does* find its way into the general circulation.

Those who hold Bernard's view would say that this small percentage of sugar is paid into the circulation by the liver. Those who hold Pavy's view will probably admit that a small quantity of sugar is allowed to leak into the circulation. After all, whichever way the action of the liver is described, there is no difference of opinion as to the final result, so far as the blood is concerned, *i.e.* a small amount of sugar is present.

The diminution of sugar in the blood after excision of the liver, or after exclusion of that organ from the circulation, appears certainly to be in favour of the view that the liver is a sugar forming organ. Then again, if the liver be an organ which absorbs sugar, and which prevents sugar reaching the circulation, how is it that no glycosuria occurs when the liver is seriously diseased, and the liver cells destroyed to such a great extent as in cases of cancer, acute yellow atrophy, and other serious hepatic affections ?

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CHAPTER IV

EXPERIMENTAL DIABETES AND GLYCOSURIA.

We have seen in the previous chapter that the glycogenic functions of the liver, sugar formation in the system, and sugar destruction, etc., are all still vexed questions.

The theories which have been put forward to explain diabetes mellitus are exceedingly numerous, and the views are even more varied than those with reference to the glycogenic functions of the liver and sugar formation.

The riddle has not yet been solved, and probably the day is far distant when a satisfactory answer will be given. Nevertheless, many important facts have been ascertained, and experiments on animals have furnished much interesting information.

Only the more important results of experimental work can be referred to, however, in a book devoted to the clinical side of the subject.

Claude Bernard (1) found, many years ago, that *puncture of the floor of the fourth ventricle* in a very limited space produced glycosuria in animals. The point of puncture was situated between the deep origins of the vagus and auditory nerves, *i.e.* about the region of the vasomotor centre. When this experiment is performed on a well-fed rabbit, its urine in the course of one or two hours becomes increased in quantity, and contains a considerable amount of sugar. A little later the quantity of sugar reaches its maximum. It then diminishes, and in the course of a day or two the urine becomes normal again. The better the rabbit is fed, the more glycogen its liver contains, and the greater the amount of sugar in the urine. If the animal be starved before the puncture of the fourth ventricle, so that little or no glycogen is present in the liver, then the urine will contain little or no sugar. Hence it is assumed by many physiologists that, when the fourth ventricle is punctured, the

glycogen in the liver is suddenly converted into sugar, and passed into the general circulation—the liver is suddenly "emptied of its glycogen." Hyperglycæmia is the result, and as a consequence glycosuria occurs.

Claude Bernard found that, after puncture of the fourth ventricle, diabetes continued, even though the vagi were divided. Galvanisation of the peripheral ends of the divided vagi did not modify the glycogenesis, but galvanisation of the central ends gave rise to an increased formation of sugar.

The liver is supplied with nerves from the hepatic plexus, which accompany the hepatic artery and portal vein, and which are distributed to various parts of the organ. This plexus is an extension of the great solar plexus. The right (posterior) vagus sends the greater part of its fibres to the solar plexus; and the splanchnic nerves (major and minor) end in it, on both sides of the body. The left (anterior) vagus forms only slight connections with the solar plexus, but sends off a very distinct branch directly to the hepatic plexus. The liver, therefore, has nervous connections with the central nervous system by the vagi, and is also connected with the splanchnic nerves.

The nature of the influence or impulses started by puncture of the floor of the fourth ventricle, and the paths by which they reach the liver, are not definitely known. Since the "diabetic centre" is close to, or almost identical with, the vasomotor centre in the floor of the fourth ventricle, it is possible that the changes in the liver are vasomotor in nature; but there is no direct evidence in support of this view. Section of the splanchnic nerves, the channel by which the vaso-constrictor impulses pass to the liver, does not produce diabetes. It seems more probable that the nervous events produced in the medulla by puncture of the floor of the fourth ventricle are able to bring about changes in the hepatic cells. The path by which the nerve impulses pass is not well defined. They do not travel by the vagus, for puncture is effective after division of both vagi. They probably make their way to the liver by the sympathetic system, passing into the sympathetic chain in the upper thoracic region. If it be true, as stated, that the puncture fails when both splanchnic nerves are divided, the impulses probably travel along those nerves.

Pavy (2) found that division of the medulla gives rise to glycosuria when the circulation is kept up artificially; but

division of the spinal cord below the origin of the phrenic nerves does not produce glycosuria. Also, when the cord is divided high up in the spinal canal, between the second and third cervical vertebræ (artificial respiration being maintained), no sugar is found in the urine.

In operating on the brain, Pavy found that many complications arose, but when these were least, there was no sugar in the urine after division of the crura cerebri just in front of the pons.

Although no diabetic effect was observed after division of the cord and vagi together, yet after division of everything belonging to the nervous system in the neck, as by decapitation, the urine became in a very short time strongly saccharine (artificial respiration being performed).

Eckhard ([3]) has shown that mechanical injury of the vermiform process of the cerebellum produces glycosuria.

Schiff ([4]) has found that diabetes can be produced by injury of the nervous system at various parts. In addition to puncture of the floor of the fourth ventricle, he found that injury to the pons also gave rise to diabetes; but here the puncture of a needle was not sufficient; a broad instrument was necessary, or the needle had to be moved about in the wound right and left. Schiff also produced diabetes by division of the spinal cord at various levels; by division of the cord before and behind the origin of the brachial nerves; in frogs and rabbits, by division of the posterior columns. Also after complete division of the spinal cord in the rat, at the level of the last cervical or first two dorsal vertebræ, diabetes was produced, if sinking of the bodily temperature was prevented.

Pavy found that division of the carotid sympathetic in the neck did not give rise to glycosuria. But division of the sympathetic fibres accompanying the vertebral artery produced saccharine urine. Ligature of the two vertebrals and two carotid arteries did not occasion saccharine urine; nor did simply tearing through everything traversing the vertebral canal on either side of the neck; but, by combining the two operations, sugar rapidly appeared in the urine. Though division of the cervical sympathetic does not produce any effect, yet removal or injury of the superior cervical ganglion may cause marked glycosuria in a very short time.

Pavy states that the diabetes resulting from all these operations on the sympathetic is quite of a temporary character,

and is prevented by the injection of carbonate of soda (200 grs.) into the circulatory system, previous to the experiment.

Arthaud and Butte (5) believe that the changes producing diabetes occur in the district of distribution of the vagus, and regard hypersecretion of the liver parenchyma as the most probable cause.

In order to produce permanent irritation of the vagus, they injected lycopodium powder, or a solution of croton-oil in ether and alcohol, into the cervical part of the nerve. By experiments on both vagi death occurred too rapidly. Therefore the right vagus only was injected.

In a series of experiments in which the above mentioned injections were made either into the uninjured nerve, or, after section, into the peripheral end of the same, the following changes were noted:—Wasting, polyuria, polydipsia, polyphagia, glycosuria (not constant, but sometimes marked), albuminuria, and azoturia. Neuritis produced in the central end of the divided vagus was followed by slight glycosuria and temporary azoturia.

In their further researches the authors produced neuritis in both vagi by the injection of powders. One vagus was injected some weeks after the other. After the injection into one vagus, polyuria and slight albuminuria were observed. After the injection into the other vagus, gastric disturbances, thirst, wasting, and glycosuria were noted.

The authors conclude that, through centrifugal vagus irritation in animals, the various clinical forms of human diabetes can be simulated.

Pavy discovered that, after ligaturing the portal vein and allowing the blood of the hepatic artery only to reach the liver, the contents of the circulatory system became highly charged with sugar. No sugar was found in the urine, but this was probably owing to the accumulation of blood to such a great extent in the portal system that the supply to the kidney was insufficient to permit the secretion of urine.

Pavy found that the injection of defibrinated arterial or oxygenated blood into the portal system induced marked glycosuria, but the injection of defibrinated venous blood did not give this result. He also produced glycosuria by causing dogs to breathe oxygen or carbonic oxide instead of air, but this result was not obtained in all cases. Pavy believes that blood

containing an excess of oxygen or blood containing carbon monoxide acts upon the amyloid substance of the organism, and leads to its abnormal transformation into sugar.

Schiff asserted, years ago, that Bernard's puncture produced dilatation of the small vessels of the intestine and liver—a paralytic hyperæmia of the organs, and he suggested that in the hyperæmic state a ferment probably developed which acted upon the amyloid substance of the liver and gave rise to glycosuria.

Pavy believes that, owing to a vasomotor paralysis produced by a lesion of the nervous system, an imperfectly de-arterialised blood finds its way into the portal vein, and this determines the escape of sugar from the liver. But hyperæmia of the liver alone is not sufficient to cause glycosuria. Division of all the nerves going to the liver, which might be expected to produce great hyperæmia, is not followed by glycosuria.

Pavy thinks the above explanation is probably true for natural diabetes. He believes that diabetes is produced by a loss of power in the vasomotor centres, or by a lesion of some part of the cerebro-spinal system which leads to an inhibitory influence being exerted upon these centres.

In the last Croonian lecture, and in his recent work on the Physiology of the Carbohydrates, Pavy ([6]) points out that in diabetes the two lines of defence—the villi of intestine and the liver—are inadequate to accomplish their function of synthesising the carbohydrates, and thus carbohydrates reached the general circulation in excessive quantity, and appear in the urine as sugar. A diabetic person has not the protoplasmic power sufficient to dispose of the carbohydrates in his diet by synthesis to proteids, by transmutation into fat, and by dehydration into glycogen. Pavy believes that this power is influenced by the state of the blood vessels, which again is determined by the condition of the nervous system. A hyper-oxygenated state of the blood favours the passage of carbohydrate matter into glucose, and is capable of producing saccharine urine. Dilatation of the hepatic arterioles permits the blood to pass too rapidly through the capillaries, so that the blood in the veins is not sufficiently de-arterialised. Under such circumstances, the passage of carbohydrates into glucose is favoured.

Pavy thinks that the whole history of diabetes goes to prove that it is frequently due primarily to changes in the nervous system. But in many severe cases there is some other abnor-

mality; the most rigid diet does not check the glycosuria. Also complete absention from all food does not suffice altogether to prevent the appearance of sugar in the urine. The tissues therefore must produce sugar, and since they consist mainly of proteid matter, which has a glucoside constitution, Pavy thinks it is only necessary to suppose the existence of a ferment action to explain the pathogenesis.

Extirpation of the cœliac plexus.—The cœliac plexus has been regarded by some writers as the seat of the lesion in diabetes. This plexus has been extirpated by several observers, but the results have varied somewhat. The following are those obtained by Lustig and Peiper.

After the removal of the cœliac plexus from dogs and rabbits, Lustig (7) observed the following symptoms:—The digestive system was not affected; there was nothing abnormal as regards the appetite; the fæces had their usual appearance; a temporary glycosuria occurred frequently; there was no atrophy of the pancreas; acetonuria was a constant result, and it continued until the death of the animal. Other symptoms were—increasing emaciation, sinking of the temperature below normal, and slowing of respiration; after a time albumin appeared in the urine. The animals died in most cases, some survived; but in the rest, after one or more weeks, death by coma occurred.

Lustig regards the occurrence of acetone in the urine as a marked symptom of the extirpation of the cœliac plexus.

Peiper (8) gives the results of experiments on fifteen rabbits. Eleven animals survived at least three or four weeks; the other four died partly in consequence of the ether narcosis, partly from hæmorrhage and peritonitis. In the animals which survived, great emaciation followed the operation, without the occurrence of any other marked symptom. Diarrhœa did not occur in any case. There were no signs of hyperæmia of the abdominal organs at the post-mortem examination. Diabetes insipidus was not observed. Glycosuria occurred frequently soon after the operation. In one case, in which, however, an extensive resection of the splanchnic nerves was undertaken, the sugar in the urine amounted at various times to 2, 3, and 4 per cent. Atrophy of the pancreas did not occur in any case. Acetone (as tested by the methods of Lieben and Reynolds) was only discovered a few times. Albuminuria was found only in two cases.

Four rabbits, which had lived two to four months, were killed, but no special changes were found at the autopsy. Seven rabbits showed symptoms of marked marasmus.

Thus the experiments of Peiper are opposed to the view that diabetes insipidus depends upon a derangement of the cœliac plexus. They also are opposed to the view that diarrhœa or diabetes mellitus is produced by extirpation of the plexus. Acetonuria and albuminuria are not characteristic symptoms after extirpation of the plexus.

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CHAPTER V.

PHLORIDZIN DIABETES.

In 1886, v. Mering (1) discovered that the administration of phloridzin produced diabetes in dogs.

Phloridzin (phlorhizine or phloorhizine) is a substance met with in the bark of the trunk and root of apple, pear, plum, and cherry trees. Its chemical formula is given as $C_{21}H_{24}O_{10} + 2H_2O$. It consists of fine silky needles which are very soluble in water at 50° C., but dissolve only in 1000 parts of cold water. Dilute acids decompose it on boiling into phlorose and phloretin.

$$\underset{\text{(phloridzin)}}{C_{21}H_{24}O_{10}} + H_2O = \underset{\text{(phloretin)}}{C_{15}H_{14}O_5} + \underset{\text{(phlorose)}}{C_6H_{12}O_6}$$

Phlorose is a form of sugar which reduces copper solutions. By boiling with caustic potash, phloretin is converted into phloretin acid, $C_9H_{10}O_3$, and phloroglucin, $C_6H_6O_3$.

Given internally or hypodermically, phloridzin produces glycosuria, but the hypodermic method is the more powerful. For hypodermic injection phloridzin may be dissolved in a weak solution of sodium carbonate, or suspended in olive-oil; or it may be given in mucilage of gum-arabic. The latter form is said to be the best (Coolen [2]).

After the administration of phloridzin, the quantity of urine is increased, the specific gravity is raised, and sugar is present. The form of sugar is glucose. It reduces Fehling's solution, ferments with yeast, and behaves like glucose on examination with the polariscope. Phloridzin does not give rise to a permanent diabetes. When the drug is discontinued, the glycosuria and other symptoms disappear. If the drug be continued, the animal loses weight, and by its prolonged administration death is caused. Occasionally, after the drug has been given for a long time, acetone and β-oxybutyric acid have been found in the urine, and symptoms like those of diabetic coma have been observed.

v. Mering has also produced a temporary diabetes in the human subject, in three cases, by the administration of phloridzin. The amount of sugar in the urine was considerable. In one case 1 grm. of phloridzin was given night and morning for a month, and the average daily excretion of sugar was 97 grms. The glycosuria disappeared the day after the phloridzin was discontinued, and no bad effects or disturbance of the general condition were observed.

The sugar excretion after the administration of phloridzin is not dependent on the nature of the food. When dogs were fed on an exclusively nitrogenous diet, glycosuria was still produced by phloridzin. When large quantities of amylaceous food were given, the sugar excretion was not greater than when the animal was fed only on nitrogenous food. After starvation for eighteen days, when it may be assumed that all the glycogen had disappeared from the liver and muscle, phloridzin still produced glycosuria; also glycosuria was produced even after the liver had been removed in geese and frogs (v. Mering).

According to v. Mering, Minkowski, and others, in phloridzin diabetes there is no excess of sugar in the blood, whilst in ordinary diabetes in man the blood sugar is generally much increased in quantity. Levene (3), however, has found the amount of sugar in the blood often diminished, but in some cases increased. Coolen states that in rabbits rendered diabetic by the hypodermic injection of large quantities of phloridzin, he has detected an increase of sugar in the blood (*i.e.* there is a hyperglycæmia, just as occurs in ordinary diabetes in man). Pavy (4) has recently criticised the methods of analysis employed by v. Mering and Levene. He finds that in cats rendered diabetic by phloridzin the amount of sugar in the blood is increased. There is, then, a considerable difference of opinion with regard to the condition of the blood in this form of diabetes.

Minkowski (5) has shown that phloridzin diabetes is not caused by any special action of the drug on the pancreas. It can be produced in those animals in which diabetes does not follow pancreas extirpation. Minkowski is of opinion that this drug acts on the kidneys in some way, and thereby produces diabetes. He found that extirpation of the kidney in animals suffering from pancreatic diabetes caused an increase of the sugar in the blood, whilst kidney extirpation in animals suffering from phloridzin diabetes did not materially affect the amount

of sugar in the blood. Also, in the diabetes produced in animals by pancreas extirpation, phloridzin increased the amount of sugar in the urine; hence we may assume that phloridzin diabetes is not the result of the action of the drug on the pancreas. Levene states that the venous blood of the kidney contains more sugar in some cases than the arterial blood.

Of the decomposition products of phloridzin, only phloretin produces diabetes; phlorose, phloretin acid, and phloro-glucin have no effect.

v. Mering concludes, from the results of a number of experiments, that the sugar which is excreted after phloridzin administration is formed from the albumin of the body.

Rosenfeld (6) has shown that, under certain conditions, phloridzin produces fatty liver as well as glycosuria, and he records the results of a number of careful experiments on dogs. The dogs were kept without food for five days; then on the sixth and seventh days 10 grms. of phloridzin were given. The animals were killed on the eighth day, forty-eight hours after the first dose of phloridzin. Pathologically, fatty liver was found, and microscopical examination showed that the condition was one of fatty infiltration and not fatty degeneration, also that the fat was situated chiefly around the central veins of the lobules.

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CHAPTER VI.

EXPERIMENTAL PANCREATIC DIABETES.

THE theory that lesions of the pancreas play some part in the causation of diabetes mellitus is by no means a recent one. In the year 1788, Thomas Cawley (1) found, on making the post-mortem examination in a case of diabetes, that the pancreas was full of calculi; its right extremity was very hard, and "appeared to be scirrhous." On looking over the literature of the subject, it is interesting to note that, since the days of Cawley, various physicians have, from time to time, called attention to the connection between diabetes and lesions of the pancreas. Thus Chopart in 1821, and Recklinghausen in 1864, especially drew attention to the pancreatic lesions in diabetes; Rokitansky found pathological changes of various kinds in the pancreas, in thirteen out of thirty cases of diabetes; also Lancereaux, Baumel, Cantani, and many others, have pointed out the importance of these pancreatic lesions. Baumel (2) in 1882 went so far as to attribute diabetes to the absence of diastatic pancreatic ferment in the alimentary canal, and recommended the use of pancreatic preparations in the treatment of the disease. Many years ago, Lancereaux especially insisted that diabetes with wasting is associated with pathological changes in the pancreas.

But it was not until 1889 that Minkowski, v. Mering, and de Dominicis showed, by experiments on animals, that pancreatic lesions may give rise to diabetes.

With respect to the relation of pancreatic lesions to diabetes mellitus, both pathological anatomy and experiments on animals furnish important evidence. Apart from all theoretical considerations, there are two facts of great interest:—

1. Total extirpation of the pancreas gives rise to diabetes mellitus in dogs and many other animals.

2. The records of pathological examination show that the

pancreas is diseased in a considerable proportion of cases of diabetes mellitus in man.

In this section only the experimental evidence will be considered; the pathological evidence will be discussed in the section devoted to etiology and etiological relations.

The older experimenters did not succeed in producing diabetes by operations on the pancreas. Claude Bernard obstructed the pancreatic duct by injecting various substances, but failed to produce diabetes thereby. Heidenhain and Finkler obtained similar results; Arnozan, Vaillard, and others ligatured the pancreatic duct in rabbits, but did not produce diabetes.

In 1889, however, Minkowski and v. Mering ([3]) in Germany, and de Dominicis in Italy, succeeded in producing permanent diabetes mellitus, resembling that which occurs in man, by total extirpation of the pancreas in dogs. The papers recording these results were published about the same time, but to the two German experimenters belongs the honour of proving that *total* extirpation of the pancreas *invariably* produces diabetes; they also showed that if a small portion of the pancreas be left behind at the time of the operation, diabetes will not occur, even though this portion be separated from the duodenum, and the pancreatic duct be ligatured.

Some experimenters have found sugar in the urine in the majority of cases after extirpation of the pancreas, but not in all cases. Thus de Dominicis ([4]) produced glycosuria in twenty-one out of thirty-four cases; Renzi and Reale ([5]) in 75 per cent. of the cases. De Dominicis found that the other symptoms, such as polyphagia, polydipsia, polyuria, emaciation, falling off of the hair, etc., invariably followed extirpation of the pancreas, but that glycosuria was absent in over one-third of the cases (thirteen out of thirty-four cases). When pancreas extirpation has not been followed by diabetes, it appears probable, however, that a small portion of the gland has been accidentally left behind, and that this has prevented the appearance of sugar in the urine.

The statement of Minkowski and v. Mering, that *complete* removal of the pancreas is *invariably* followed by diabetes mellitus, has since been confirmed by Hédon, Lépine, Lancereaux, Thiroloix, Gley, Vaughan Harley, and others.

In 1893, Minkowski published a long article, giving a very

full account of his brilliant and numerous experiments on pancreatic diabetes; from this and from his previous articles most of the following details are taken ([6]).

(*a*) *Effects of pancreas extirpation in various animals.*—In dogs and cats, diabetes mellitus of a most severe form was invariably produced by total removal of the pancreas. In rabbits, owing to the anatomical position of the gland, total extirpation was scarcely possible. In pigs, total extirpation also produced diabetes. Minkowski failed to produce diabetes in frogs by this experiment, but Aldehoff has been successful.

(*b*) *Sugar excretion after total extirpation.*—In dogs, as a rule, the day after the operation the urine contains only 1 per cent. of sugar, on the second day 4 to 6 per cent., and on the third day 8 to 10 per cent., which is the highest sugar excretion. If no food be given, the sugar excretion gradually diminishes, but does not disappear, even after seven days' starvation. If the animals be placed on a free diet, the sugar excretions remain very high, and show great variations, according to the nature of the diet. The sugar excretion has a definite relation to the urea excretion, on the average 2·8 to 1, when carbohydrates are excluded from the diet.

The result of pancreas extirpation in dogs was to produce not a temporary glycosuria, but a genuine permanent diabetes, corresponding to the most severe form of the disease in man. The sugar excreted in the urine was grape sugar. The dogs were abnormally voracious, and suffered from great thirst. If allowed to drink as much water as they desired, polyuria occurred. In spite of the large amount of food which they took, they soon became thin and feeble. The amount of sugar in the blood was considerably increased.

In course of time, when the dogs became emaciated, the quantity of sugar in the urine diminished. Shortly before death it became very small, and occasionally disappeared completely, just as sometimes occurs in cases of diabetes in man.

(*c*) *Partial extirpation.*—Diabetes does not occur after partial extirpation of the pancreas. Minkowski found that when one-quarter or one-fifth of the gland was left behind, diabetes did not develop. Even when the pancreatic duct was ligatured, and the remaining piece of the pancreas had no connection with the duodenum, still it was sufficient to prevent glycosuria. In these cases, after large quantities of carbohydrates (500 to 1000 grms.

of bread and 100 to 200 grms. of cane sugar), sugar did not appear in the urine, as a rule.

Vaughan Harley (7) states that if one-sixteenth part of the gland be left behind, even though it may have no excretory duct opening into the intestine, it is sufficient te prevent glycosuria. Minkowski (8), however, points out that it is not possible to say exactly what the size of the remaining pancreas fragment must be to prevent the occurrence of diabetes, since much depends on the condition of the nutrition and blood supply of the fragment. In some cases a slight or temporary glycosuria was produced by partial extirpation, the sugar disappearing when the animal was fed on nitrogenous food only.

(*d*) *Transplantation of pieces of pancreas under the skin of the abdomen.*—Minkowski has shown the relation of the pancreas to diabetes by the most striking experiment of transplanting a piece of the gland. He has succeeded (in dogs) in transplanting a portion of the pancreas, and grafting it under the skin of the abdominal wall external to the abdominal cavity. If the transplanted portion of pancreas (or graft) does not necrose, but maintains its nutrition, then diabetes will not occur when the whole of the remaining intra-abdominal part of the gland is removed. But if the transplanted portion of pancreas—*i.e.* the graft under the skin of the abdomen—be subsequently removed, then diabetes occurs. Hence a portion of pancreas grafted under the skin of the abdomen is sufficient to prevent the occurrence of diabetes when the whole of the gland is removed from the interior of the abdomen, but, on the removal of this graft, diabetes in its most severe form follows. The disease is thus finally produced by an extraperitoneal operation of very short duration—a few minutes only—in which all secondary influences can be excluded. Minkowski's results with respect to these graft experiments have been confirmed by Hédon, Thiroloix, Gley, and Lancereaux.

In Hédon's experiments (9), the descending portion of the pancreas of the dog was grafted under the skin of the abdomen, care being taken not to destroy a vascular connection (in order that the nutrition of the grafted piece might be maintained), until adhesions had formed between the pancreas graft and the subcutaneous tissue. The grafted piece of gland communicated, therefore, with the abdominal cavity by slender vessels only. These were ligatured at a later date, without destroying the

vitality of the graft. In dogs having pancreas grafts, as just described, removal of the whole of the pancreas remaining in the abdomen did *not* produce glycosuria. But when the extra-abdominal pancreatic graft was subsequently removed, very intense glycosuria developed, and persisted up to the death of the animal.

(*e*) *The effects of various articles of food, etc., on sugar excretion in pancreatic diabetes.*—In the pancreatic diabetes of dogs the amount of sugar in the blood is considerably increased, and the glycogen of the organs disappears early. The whole of the grape sugar given in the food is excreted in the urine. Minkowski thinks this would not occur if another organ besides the pancreas could bring about the destruction of sugar.

After pancreas extirpation, ordinary starch passes away unchanged in the fæces. Soluble starch and dextrin produce an increased excretion of grape sugar; feeding with bread also increases the sugar in the urine. After feeding with maltose, the sugar excretion is increased, but grape sugar only appears in the urine With regard to the lævorotatory carbohydrates, Minkowski has shown (1) that for the most part they are burnt up in the organism; (2) in part they are changed into grape sugar, and excreted as such; (3) after the administration of large quantities of lævulose, a portion passes off unchanged in the urine; but when the animal is fed with inulin, lævulose is not found in the urine. After feeding with cane sugar, neither this body nor lævulose are found in the urine, but the grape sugar is considerably increased. When lactose is given, the sugar in the urine is increased, but only *grape* sugar is excreted. Subcutaneous injection of freshly prepared pancreas extract, and also feeding with fresh pancreas, has no influence on the sugar excretion (Minkowski). The use of jambul gave negative results.

(*f*) *Glycogen in the organism in pancreatic diabetes.*—v. Mering and Minkowski have shown that after pancreas extirpation the glycogen rapidly diminished in the liver, until only traces of it were left, and yet in these cases the amount of sugar in the blood was abnormally high. But in animals in which a portion of the pancreas was left in the abdomen, and in which, therefore, the intensity of the diabetes was slight, a considerable amount of glycogen was found in the liver.

After extirpation of the pancreas, Abelmann has shown that

absorption of fat from the intestines ceased entirely, and only about half of the albuminous material was absorbed.

Acetone, aceto-acetic acid, and oxybutyric acid, were sometimes met with in the urine, but they were not always present. The glycogen in pus cells, and in the white blood corpuscles in cases of pancreatic diabetes, was found to be increased. Complications, such as peritonitis, necrosis of the duodenum, abscesses, etc., prevented the excretion of sugar, just as sometimes occurs in diabetes in man. Possibly by the influence of pathogenic micro-organisms the sugar of the blood is destroyed.

(*g*) *The cause of diabetes after complete removal of the pancreas.*—(1) In the first place, diabetes following extirpation of the pancreas is not due to absence of pancreatic juice in the intestine, nor to the diminished elimination of certain substances formed in the pancreas. As above mentioned, the older experimenters failed to produce diabetes by ligature and obstruction of the pancreatic duct. More recently, Hédon has obtained the same negative results. Then, as already mentioned, Minkowski and v. Mering have shown that if a small portion of pancreas be left behind in the abdomen, no diabetes follows, even when the pancreatic duct is ligatured, and when the portion of pancreas remaining has no connections with the duodenum. When a small portion of the *tail* of the gland is left behind, diabetes does not occur. Further, the fact that diabetes can be prevented by a pancreas graft under the skin of the abdominal wall, when the whole of the gland is removed from within the abdomen, is conclusive evidence that it is not the absence of pancreatic juice from the intestinal canal which is accountable for the development of the disease. (2) Neither is diabetes after pancreas extirpation the result of lesion of the solar plexus of the abdominal sympathetic nerves. As Minkowski and v. Mering point out, the solar plexus would be injured as much by partial extirpation (when only a fragment of the gland is left behind) as by total extirpation, and yet in the former case diabetes does *not* occur. Then, again, the fact that an extra-abdominal pancreas graft can prevent the occurrence of diabetes, when the whole of the gland is removed from the abdominal cavity, shows that the injury of the solar plexus is not responsible for diabetes after pancreas extirpation. Further, Peiper ([10]) and Lustig ([11]), by removal of the cœliac plexus, were not able to produce true diabetes (see p. 78). (3) Neither is pancreatic diabetes due to an increased

flow of arterial blood to the liver, owing to the ligature of the vessels supplying the pancreas on removal of the gland. Though Arthaud and Butte ([12]) have produced glycosuria by ligature of all the branches of the cœliac axis, with the exception of the hepatic artery, their results have not been confirmed by others; and the effects of partial extirpation of the pancreas and of subcutaneous pancreas grafting, as above described, are opposed to this view. One would expect the supply of arterial blood to the liver to be increased practically to the same extent in partial pancreas extirpation (when only a fragment is left behind) as in total extirpation, yet diabetes occurs in the latter case, but not in the former. Again, the arterial supply to the liver would be the same in an animal from which the pancreas had been totally removed, as in the case of an animal in which all the gland had been removed from the abdomen, but a pancreatic graft left under the skin of the abdominal wall. Yet diabetes occurs in the former case, but not in the latter. (4) Pancreatic diabetes is not due to a renal disturbance, such as is supposed by some to be the cause of phloridzin diabetes, since removal of the kidneys produces an increase of the sugar in the blood, whilst it does not affect the amount of sugar in the blood in phloridzin diabetes. (5) Minkowski's remarkable experiments, and especially the fact that a subcutaneous graft of pancreas will prevent pancreatic diabetes from occurring when the whole of the gland is removed from the abdominal cavity, all point to a special or specific function of the pancreas in preventing diabetes. A "something" is formed in the pancreas which passes into the circulation, and brings about sugar destruction, or prevents the accumulation of sugar in the blood (Minkowski).

By many this "something" is regarded as an internal secretion. Lépine believes that in the normal condition the pancreas forms a sugar destroying ferment—the glycolytic ferment—which is absorbed by the pancreatic lymphatics and veins, and, passing into the general circulation, prevents the accumulation of sugar in the blood. According to Lépine, the absence of this ferment from the blood is the cause of diabetes when the pancreas is removed completely.

Lépine and Barral ([13]) have shown that in blood withdrawn from the body, and kept for some time at the body temperature, the sugar pretty rapidly disappears. This loss of sugar they believe to be due to the presence of a ferment

in the blood—the glycolytic ferment, and they regard the pancreas as one source of this ferment. The loss of sugar during a given time, and under certain conditions, is taken as the indication of the glycolytic power of the blood, and they have shown that in the pancreatic diabetes of dogs this glycolytic power is diminished. The loss of sugar is less, in a certain time and under certain conditions, in the blood taken from dogs suffering from pancreatic diabetes than in the case of healthy dogs; it is also less in the blood of diabetic patients than in healthy persons.

According to Lépine ([14]), the pancreatic cells perform their functions in two directions. From the inner portions of the cell, pancreatic juice is poured into the branches of the excretory duct. From the outer portion of the cell, the base, or the part in relation to the vessels, the glycolytic ferment is poured out into the venous blood and lymphatics, *i.e.* an internal secretion occurs. According to Lépine, the pancreas is not the only source of the glycolytic ferment, since the blood possesses a certain glycolytic power after the removal of this gland.

The experiments above mentioned, in which a graft of pancreatic tissue in the abdominal wall prevented the occurrence of diabetes, when the whole of the pancreas was removed from within the abdomen, certainly seem to indicate that some substance or "internal secretion" passes from the gland tissue into the circulation, and in some way prevents the occurrence of diabetes. But Lépine's views respecting the so-called glycolytic ferment have been much criticised.

Arthus ([15]) has made a number of experiments on the subject, and concludes that the glycolytic ferment does not exist in the circulating blood, but is formed outside the body, and that the glycolysis or sugar destruction observed is a cadaveric phenomenon as in the coagulation of the blood.

Kraus ([16]) has shown that the so-called glycolytic power of blood, obtained by venesection, varies in different individuals, but the same variations are found in diabetic patients. Seegen ([17]) thinks that the disappearance of sugar from the blood removed from the body is a post-mortem change. He found that if chloroform be added to the blood, and its protoplasm thereby killed, the same disappearance of sugar occurs, and that sugar added to the blood undergoing putrefactive changes gradually disappears. He also found that if blood be heated to a tem-

perature sufficient to destroy any enzymes present, and if sugar then be added, in time it disappears totally or partially; and he therefore concludes that there is no definite evidence of a glycolytic ferment in the blood. Kaufmann ([18]) and Chauveau have made a series of analyses of the arterial and venous blood in healthy persons and in cases of diabetes, but they have never found any difference between the normal sugar destruction and that in diabetes.

Minkowski ([19]) has also recorded an experiment in which pancreatic diabetes of a severe form was produced in a dog, and yet the blood lost a greater percentage of sugar in one hour, after withdrawal from the body, than the highest limit observed in the case of normal blood, *i.e.* the so-called glycolytic power was not at all diminished. Minkowski thinks that it is not possible at present to give a satisfactory explanation of the exact manner in which extirpation of the pancreas produces diabetes. Nevertheless the graft experiments so often referred to show that the pancreas has a specific function, even if only a small fragment of the gland be present, in preventing the occurrence of diabetes.

Baldi ([20]) has performed experiments on dogs, in order to ascertain the changes produced in the blood during its passage through the pancreas. Blood, to which grape sugar had been added, was passed through the vessels of the gland *in situ*. The amount of sugar was found to be less in the blood of the pancreatic veins than in the blood sent to the pancreas, also the blood of the pancreatic veins contained a little less sugar than the carotid blood. Baldi concludes that the living pancreas parenchyma, and not a ferment, causes the destruction of sugar in the blood.

Marcus ([21]) has shown that in frogs extirpation of the liver checks the sugar excretion after removal of the pancreas. By extirpating the liver, the source of the formation of sugar is removed, and hence diabetes cannot occur in these cases.

Hédon ([22]) found that puncture of the floor of the fourth ventricle in animals rendered diabetic by extirpation of the pancreas, considerably increased the glycosuria—to the extent of 30 to 40 per cent., sometimes more. Hence puncture of the floor of the fourth ventricle does not produce diabetes by its action on the pancreas.

Thiroloix ([23]) has produced slow atrophy and destruction of the pancreas in animals by injecting foreign substances into the pancreatic excretory duct. The results were as follows:—(1) The animals wasted; (2) then they recovered weight; (3) when the pancreas had become markedly atrophied and sclerosed, glycosuria occurred, if the diet consisted of amylaceous and saccharine material, but ceased when the diet was nitrogenous; (4) when the atrophy of the pancreas had become so great that the gland was practically destroyed, diabetes developed, and sugar was then present in the urine, whatever the nature of the food. From the results of a number of experiments, Thiroloix concludes that in the normal condition the pancreas produces a substance which is carried by the portal vein to the liver, and the action of this substance on the liver cells transforms sugar into glycogen, and fixes it in the cells. When the pancreas is completely destroyed, the liver produces sugar largely, and glycosuria follows.

(*h*) *Pancreatic diabetes and the nervous system.*—Kaufmann ([24, 25, and 26]), during the last four years, has performed a large number of experiments on animals with respect to the relation between the pancreas, the nervous system, and the liver in the control of sugar formation. From these experiments he concludes that the pancreas, by its internal secretion, plays the part of inhibitor of sugar formation in the liver, indirectly by means of the central nervous mechanism of the latter, and directly by its influence on the liver cells.

Section of all the nerves to the liver, in an animal having the pancreas still active, is followed either by hypoglycæmia, or the amount of sugar in the blood remains normal. But removal of the pancreas in a dog in which all the nerves to the liver have been divided, is followed by hyperglycæmia. Hence the internal secretion of the pancreas must have a direct action on the liver by means of the blood—an action hindering sugar formation. Further, Kaufmann has shown that in animals which have no excess of sugar in the blood, if the nerves of the liver and pancreas be completely destroyed, puncture of the fourth ventricle does not produce its usual effect of hyperglycæmia and glycosuria. But if hyperglycæmia and glycosuria be present, the nerves of the liver and pancreas being destroyed, or the nerves and the liver being destroyed and the pancreas removed, puncture of the fourth ventricle always greatly increases the hyperglycæmia and

glycosuria. Hence Kaufmann concludes that puncture of the fourth ventricle acts not only on the liver and pancreas, but also on the general histolytic work of the various tissues of the organism; and that the histolysis is regulated both by the pancreatic products thrown into the blood, and also by the nervous system. The internal pancreatic secretion has an inhibitory action, by means of the blood, on the tissue changes, and on sugar formation in the liver.

From Kaufmann's experiments, it appears, therefore, that the internal secretion of the pancreas has an inhibitory action on sugar formation—

(1) Indirectly, through the central nervous system and hepatic nerves.

(2) Directly, through the blood, which carries the internal secretion of the pancreas to the liver cells.

(3) By its influence on the tissues of the body.

It has been shown that the pancreatic internal secretion is also under the control of the central nervous system.

In addition to the above-described experimental proceedings, glycosuria may be produced in animals in numerous other ways; but it has only been possible to refer to those which are of chief interest to the practitioner of medicine.

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CHAPTER VII.

GLYCOSURIA FROM VARIOUS CAUSES.

Alimentary Glycosuria.

In health, according to some authors, the urine contains a minute trace of sugar, but it is so small (if present) that it is not detected by the usual clinical method of testing, and for practical purposes the urine may be considered to be free from sugar. It has been demonstrated, however, by a number of observers that when a *very large quantity* of saccharine food is taken, a small amount of sugar is found in the urine even in health.

Moritz (1) found sugar in the urine in five out of eleven healthy persons, after a meal very rich in saccharine materials; two to four hours after food 0·1 to 0·25 per cent. of sugar was present; but the glycosuria soon disappeared.

The sugar found in the urine is said to be the same as that taken in excess—glucose producing glycosuria; lactose, lactosuria; lævulose, lævulosuria; saccharose, saccharosuria.

According to von Noorden (2), the amounts of the various forms of sugar which must be taken before the sugar is found in the urine are as follows:—

Milk sugar, over 120 grms.
Cane sugar, „ 150 to 200 grms.
Fruit sugar, about 200 grms.
Grape sugar, „ 180 to 250 grms.

These figures represent, therefore, the amounts of the various forms of sugar required to produce alimentary glycosuria in healthy persons. They indicate the average quantities only, and naturally they vary somewhat in different individuals. To produce this alimentary glycosuria the sugar should be given all at one dose, early in the morning, when the stomach is empty, and the urine should be examined every hour for sugar.

The occurrence of alimentary glycosuria depends not only on the quantity of glucose taken, but also on the rapidity of absorption. For example, in a case examined by Strümpell (3), 150 grms. of glucose given all at once on an empty stomach caused distinct glycosuria, but when the same quantity was divided into three portions, and taken separately in the course of an hour, the urine remained free from sugar.

The sugar appears in the urine from three-quarters to one hour after the administration of the glucose, and the excretion thereof continues one to three hours.

The total amount of the various forms of sugar excreted is as follows :—

2·8 per cent. of the cane sugar taken, 1 per cent. of the grape sugar, 0·8 per cent. of the milk sugar.

The power of assimilation for *starch* in healthy persons appears to be unlimited ; probably so much time is required for its absorption and digestion, that over-saturation of the blood with carbohydrates does not occur. Those persons whose urine contains sugar after a diet containing large quantities of starch, have a low and abnormal assimilation limit, and the condition approaches diabetes.

In healthy persons, then, slight glycosuria can only be produced by very great excess of sugar in the diet, and not by excess of starch ; in mild forms of diabetes, starchy food as well as saccharine food produces glycosuria ; in the most severe forms, glycosuria is present even when the diet consists of nitrogenous materials only.

By an excess of carbohydrates in the food, the glycogen stored in the liver and muscles is increased, but the storing space is apparently not unlimited. When there is an excess of carbohydrates absorbed day by day, the limit of the storing capacity of the liver and muscles seems to be reached, and the excess of carbohydrates is transformed into fat, which is deposited in the connective tissue in various parts of the body. When the excess of carbohydrates cannot be disposed of in either of these ways, because the glycogen depôt is too limited, or the quantity of carbohydrates too great permanently or temporarily, there is an excess of sugar in the blood, and glycosuria results.

A number of observations have been made during the last ten years, with reference to power of sugar assimilation in various

diseased states, in order to ascertain whether in these conditions glycosuria can be produced with smaller quantities of sugar than in health; but in a few conditions only has this power been found diminished. In most diseases, 150 to 200 grms. of grape sugar can be taken without glycosuria being produced (v. Noorden); but larger doses — as in health — produced glycosuria.

Lanz (4) has found, however, that the power of assimilation of grape sugar is diminished during pregnancy. To thirty pregnant women he administered 100 grms. each of pure grape sugar, and in nineteen cases he was able to detect sugar in the urine. (As already stated, normally, 180 to 250 grms. of grape sugar can be assimilated.)

According to Kraus and Ludwig (5), Chvostek (6) and v. Noorden, there is a diminished power of sugar assimilation in Graves' disease, *i.e.* alimentary glycosuria is more easily produced than in health. A similar condition was found by Strümpell in cases of neurasthenia, or traumatic neurosis. In other diseases of the brain, spinal cord, nerves, and muscles, no diminished power of sugar destruction has been detected.

In some cases of cirrhosis of the liver glycosuria has been produced more readily than in health, but in most cases, as well as in other forms of liver disease, there has been no diminished power of sugar destruction. This is somewhat remarkable, since in many of these diseases the liver tissue is destroyed to a great extent.

v. Jaksch has shown that in phosphorus poisoning, however, when the symptoms are far advanced, and when the protoplasm of the muscles and liver cells is markedly affected, alimentary glycosuria is produced more readily than in health.

In diseases of the heart, lungs, and blood, in arterio-sclerosis and marasmus, the power of sugar destruction does not appear to be altered. In many, but not in all, cases of chronic alcoholism, or, more correctly, cases of habitual drinkers of large quantities of beer, Strümpell found that glycosuria could be readily induced by 100, 75, or even 50 grms. of grape sugar. The same condition the author discovered in some persons after they had taken an excessive quantity of beer (1½ to 2 litres) very rapidly. Alimentary glycosuria does not occur in all great beer drinkers, however, and much depends upon individual peculiarity.

Puerperal Glycosuria.

It has long been known that a substance occurs in the urine in the puerperal state, which reduces Fehling's solution like grape sugar. Blot ([7]) drew attention to this fact many years ago. He concluded that a physiological glycosuria existed in women during labour, in women during lactation, and in almost 50 per cent. of women during pregnancy. No diabetic symptoms are present in this physiological glycosuria. After delivery, and on the cessation of lactation, the sugar disappears. The observations of Blot were disputed at first, but have now been abundantly confirmed. Matthews Duncan ([8]) stated that in the Edinburgh Maternity he found a slight amount of sugar in the urine of every woman during lactation.

Ney ([9]) examined the urine of 148 women during lactation, and found sugar present in 77 per cent.

M'Cann and Turner ([10]) have investigated one hundred cases, in order to decide whether sugar is always present in the urine of nursing women at some period of lactation. The following are the results of their observations:—

1. That sugar is present in the urine of women during lactation.

2. That sugar is present at some period in every case.

3. That in the majority of cases the largest amount occurs on the fourth and fifth days of the puerperium.

4. That the quantity depends on (*a*) the condition of the breasts, (*b*) the quantity and quality of the milk, and (*c*) the sucking of the child. In one hundred cases the average quantity found was 0·35 per cent., *i.e.* 1½ grs. per ounce.

5. That when lactation is diminished or suppressed the amount of sugar diminishes or disappears.

6. That when the production and exhaustion of the milk are equal, the amount of sugar is very small.

Kaltenbach ([11]) has demonstrated that the form of sugar in puerperal glycosuria is lactose. He bases this conclusion on the inability of the sugar to ferment directly, on its rotatory power, on the fact that it is transformed directly into fermentable sugar by boiling with sulphuric acid, and on the mucic acid reaction. (The other reactions given by lactose in the urine are pointed out on p. 32.)

The presence of lactose in the urine appears to be connected

with engorgement of the breast. The lactose in the urine is abundant in women whose children have been born dead or have died during the period of lactation; it is also abundant when, from mastitis, clefts of the nipples, or other causes, the child cannot be applied to the breast, and engorgement of the gland occurs.

Sinclair ([12]) states that he has never failed to find sugar in the urine, when the breasts have been engorged from any cause during the period of functional activity. He believes that the sugar in the urine is due to absorption from the engorged breasts; and he has met with a large number of cases in which sugar has appeared in the urine, on the occurrence of still birth, or when the child has been suddenly weaned. (See also p. 58.)

In cases of abscess of the breast, I have often found that the urine gives a slight reduction of Fehling's solution, but no indication of sugar by the fermentation test; also filtration through animal charcoal does not remove the reducing body, which in all probability is lactose.

Glycosuria produced by Poisons and Chemical Substances.

Numerous drugs have been stated to be capable of producing glycosuria, but it is probable that very frequently the substance in the urine which has reduced Fehling's solution has not been sugar, but some other reducing body—often glycuronic acid. When the urine reduces Fehling's solution after the administration of any drug, it is always necessary to try some confirmatory test before deciding that the reducing substance is sugar.

The following are the drugs and chemical substances which have been said to sometimes produce glycosuria in man or animals:—Curare, orthonitro-phenylpropiolic acid, carbon monoxide (in eleven out of sixteen cases observed by Frerichs ([13]) —the sugar disappearing in two to four days), amyl nitrite (by injection in dogs), and methyldelphinin. The following substances are said to occasionally produce glycosuria, when taken or inhaled in very large quantities:—Opium, morphia, chloral hydrate, prussic acid, mineral acids, coal gas (in one out of four cases—Frerichs), poisonous doses of mercury, arsenic, and phosphorus. Strychnia poisoning is stated to have produced

glycosuria in frogs, but Frerichs has failed to detect sugar in the urine in a well-marked case of strychnia poisoning in man.

According to Jacoby (14), caffeine, theobromin, benzoate of caffeine and soda, diuretin, and caffeine sulphonic acid, give rise to glycosuria with diuresis in rabbits, when the animals are fed on roots, carrots, and turnips. Ether and chloroform narcosis have been stated to occasionally give rise to slight glycosuria, but in cases examined by Frerichs no sugar was detected. I have examined the urine of a number of surgical patients, after chloroform narcosis, without ever being able to obtain even the slightest reduction of Fehling's solution.

I have recently examined the urine in three cases of opium poisoning, with the following results. In a case which terminated fatally in less than twelve hours, I was unable to obtain any evidence of sugar in the urine drawn off from the bladder immediately after death. In another case the urine reduced Fehling's solution slightly, gave the characteristic yellow crystals when the phenylhydrazin test for sugar was applied, and also a distinct reaction for sugar with the fermentation test. In a third case of opium poisoning, the urine gave no reaction for sugar when the fermentation test was employed.

It was pointed out by Leconte (15), in 1851, that the prolonged administration of small doses of uranium salts caused glycosuria in animals. Chittenden, Lambert, Woroschilsky, and others, have published the results of observations on the physiological action of these salts, and the subject has been recently reviewed by Cartier (16). In large doses, nitrate of uranium is an irritant poison, but small doses act as a diuretic. The specific gravity of the urine is increased, and albuminuria and glycosuria are produced: other symptoms are loss of appetite, thirst, general torpor, paresis of the posterior limbs, paralysis, and emaciation. Finally, the animals become comatose, and death occurs. Cartier points out that the chief changes found pathologically are in the liver and kidneys. Small doses cause simply hepatic congestion. After larger doses (in rabbits), hyaline masses have been found in the interior of the liver cells, and the nuclei have been found pushed to the side of the cell; at some parts the cells are necrotic. The hyaline masses do not contain glycogen. The changes in the kidney have varied from congestion up to necrosis. The chief lesion

has been found in the convoluted tubes where necrosis of the epithelium has been observed.

Pavy ([17]) has shown that phosphoric acid, injected into the jugular vein of animals, produces glycosuria.

It is stated that the intravenous injections of large quantities of a 1 per cent. sodium chloride solution, or of solutions of carbonate, sulphate, acetate, and succinate of soda, have produced glycosuria in animals.

Claude Bernard's diabetic puncture of the fourth ventricle is said to be unsuccessful in producing glycosuria, if sodium carbonate be previously injected into the blood, and the glycosuria which is produced by lesions of the sympathetic nerves can also be arrested by the injection of sodium carbonate.

In animals suffering from phosphorus or arsenical poisoning, Bernard's puncture is said to have only very slight effect.

Harley ([18]) produced glycosuria by injecting ether, chloroform, ammonia, alcohol, and methylated spirits into the portal vein.

Clinical Glycosuria.

In a number of varied diseased conditions, a small quantity of sugar is occasionally met with in the urine, though polyuria or other diabetic symptoms are absent. But it is well to remember, in enumerating these conditions, that in all of them glycosuria is much more frequently absent than present, and that when detected it is temporary, and continues usually for a few hours or days only.

Glycosuria is sometimes present in cases of *brain lesions*, and *injury* to the head is an occasional cause. It will be pointed out in the section on etiology that true diabetes sometimes follows, and is apparently excited by, a blow on the head. These cases are very rare, but cases of temporary glycosuria after an injury to the head are not very infrequent.

Higgin and Ogden ([19]) have carefully examined the urine in 212 cases of injury to the head, and have found sugar present in twenty. In cases of scalp wounds and minor head injuries, glycosuria was met with in 5·95 per cent.; in cases of scalp wounds with exposure of bone, glycosuria was present in 9·3 per cent.; in cases of concussion, in 2·5 per cent.; in fractures of the vault of the skull, in 20·8 per cent.; in fracture of the base, in 23·8 per cent.

From the examination of these 212 cases, the authors draw the following conclusions :—

1. That sugar may appear in the urine as early as six hours after a head injury, and disappear within twenty-four; the average time for its appearance being eight to twelve hours; the average time for the disappearance being from the fifth to the ninth day.

2. That a small proportion of cases exhibit a permanent glycosuria from the date of the injury to the head.

3. That acetone and diacetic acid are rarely, if ever, found in such cases, excepting where the condition becomes a permanent glycosuria, and even then probably only after a number of months or years.

Brain lesion, such as cerebral hæmorrhage, meningitis, cerebral aneurysm, brain tumours, tumours of the pituitary body, as well as neuralgia, sciatica, and Graves' disease, have all been occasionally associated with glycosuria. Occasionally, though very rarely, glycosuria has been found in cases of tetanus, paralysis agitans, epilepsy, and atheroma of arteries about the floor of the fourth ventricle; but the glycosuria is usually temporary. A few cases of locomotor ataxia, associated with glycosuria, or much more rarely with true diabetes, have also been recorded.

Glycosuria is occasionally associated with mental diseases. Bond ([20]) has carefully examined the urine of 355 cases of mental disease, but has only found sugar present in 5·35 per cent. Only two suffered from true diabetes; the rest were cases of simple glycosuria. In the majority of the cases in which glycosuria was present, the patient suffered from melancholia. Maniacal patients, epileptics, and congenital cases were apparently exempt.

Naunyn ([21]) has drawn attention to the occasional association of glycosuria, or mild forms of diabetes, with general paralysis of the insane.

Glycosuria has been met with, though very rarely, after the following febrile affections :—Typhoid, scarlet fever, malaria, diphtheria, cholera, anthrax. It has been observed occasionally, though very rarely, in gallstone colic; and several instances of glycosuria associated with appendicitis have been recorded.

In most of the above-mentioned cases the glycosuria is temporary, and persists only for a few hours or days; occasionally it is permanent, and all the symptoms of diabetes may develop.

In other cases the glycosuria disappears for a time; but may afterwards reappear, and occasionally true diabetes may ultimately develop. Loeb has recently recorded cases in which this has occurred (see p. 166).

v. Noorden found that in four out of fourteen obese individuals, temporary glycosuria was produced by the administration of only 100 grms. of grape-sugar, *i.e.* there was a diminished power of sugar destruction in the system. Of these four persons, two became diabetic some years later; in the other two cases, the lapse of time is still too short to allow any very definite opinion to be given with regard to the probability of diabetes developing.

The association of glycosuria with the above-mentioned affections is usually exceedingly rare. Whilst a slight glycosuria is not very uncommon in the ailments of stout and wealthy elderly persons seen in private practice, it is rare amongst the poor and badly-nourished patients of large hospitals.

In addition to the diseases mentioned, I have recently met with the following affections associated with glycosuria:—

Cerebral hæmorrhage and fractured skull (recorded on p. 294).

Two cases in which there was marked double optic neuritis, with severe headache. Other indications of brain lesion were absent; the sugar disappeared from the urine in the course of some days, and gradual improvement took place.

One case of chronic lead-poisoning, with double wrist-drop.

A case of ataxia, of sudden onset, accompanied by diplopia and paresis of both external recti. The optic discs were normal, no other nervous symptoms were present, and in the course of a few weeks the glycosuria and nervous symptoms disappeared.

Two cases of hemiplegia.

One case of optic atrophy.

One case of chronic parenchymatous nephritis, with enlarged liver.

A case of fracture of the tibia. On admission to the Hospital, sugar was present in the urine in large quantity, but disappeared in a few days. There were no other indications of diabetes.

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CHAPTER VIII.

ETIOLOGY AND ETIOLOGICAL RELATIONS.

A. Etiology.

1. *General relations.—Sex.*—Diabetes mellitus is a disease which is more common in males than females. In the early period of life, however, the liability of the two sexes is about equal. Afterwards, especially after 30, males are affected more frequently than females. Thus, in 100 cases of diabetes at the Manchester Royal Infirmary, the proportion was as follows:—

Males	62 cases.
Females	38 ,,

	Under the age of 30.	*Over* 30.
Males . .	18 cases.	44 cases.
Females . .	19 ,,	19 ,,

Age.—The following table shows the number of patients at various ages in 100 consecutive cases of diabetes. At the time of admission to the Hospital the majority were suffering from a severe form of the disease.

One Hundred Cases of Diabetes (chiefly Hospital Patients).

Age.	Years.						Total.
	10–20.	20–30.	30–40.	40–50.	50–60.	60–70.	
Males	6	12	14	18	9	3	62 Males.
Females	6	13	8	3	3	5	38 Females.
Total . .	12	25	22	21	12	8	100

In private practice the proportion of cases at various ages is somewhat different to that given in the above table. Thus

Karl Grube (1) of Neuenahr—a spa much frequented by diabetic patients—found the highest percentage of cases between the ages of 50 and 60.

The following table, which I have prepared from the published records of several authors, shows that there is considerable difference with regard to the age of the patients in various series of cases. Probably the difference is due to the fact that in private consulting practice a large number of cases of diabetes of the milder form, in well-to-do elderly people, are met with, whilst these cases are much more rare amongst the poor and hard-working classes that chiefly supply the diabetic hospital patients; or, at least, if these mild forms do occur in elderly people amongst the poor, they more rarely come under treatment.

Percentage of Cases of Diabetes at various Ages.

	Under 10 yrs.	10–20.	20–30.	30–40.	40–50.	50–60.	60–70.	70–80.	Over 80.
Grube	...	1·7	2·8	11·2	23·1	39·5	18·1	3·4	...
Seegen	0·5	3	16	16	24	30	10	0·5	...
Pavy	0·58	4·19	7·13	16·4	24·92	30·73	13·37	2·49	·07
Frerichs	1	7	10	18	25	26	11	1	...
Manchester Royal Infirmary	...	12	25	22	21	12	8	...	...

The mortality (per million living), as given in the Report of the Registrar-General, is greatest between the ages of 65 and 75; whilst, amongst hospital patients in Manchester, the table given above shows that 68 per cent. are between the ages of 20 and 50 when they first come under treatment.

The table on page 97 is taken from the "Supplement to the Fifty-fifth Annual Report of the Registrar-General" (Part I., 1895, p. cxi.).

Death from diabetes is very rare in extreme old age. In young persons and children the disease is rare, as shown by the following table. Recently two patients each aged 12 years, and one patient aged 11, were admitted to the Manchester Royal Infirmary, suffering from diabetes mellitus. Bell (2) has recorded a fatal case of diabetes mellitus in a child æt. 3 months.

Mortality from Diabetes Mellitus per million living.

Years.		All Ages.	0-	5-	10-	15-	20-	25-	35-	45-	55-	65-	Upwards.
1861-70	Persons. . . .	30	3	5	9	17	19	32	42	59	95	117	74
1871-80		38	1	4	10	19	25	37	51	72	132	171	113
1881-90		57	4	7	15	24	30	46	64	107	217	293	238
1861-70	Males	41	3	5	10	22	24	44	55	83	136	180	120
1871-80		50	1	4	10	24	34	48	68	96	181	247	172
1881-90		69	5	7	14	26	35	58	78	134	282	397	314
1861-70	Females . . .	20	2	4	8	13	14	22	30	37	58	62	38
1871-80		27	2	4	10	14	18	27	35	50	87	106	67
1881-90		45	3	6	15	22	26	35	51	82	161	206	180

Wegeli (3) gives the following table with reference to the ages of 102 cases of diabetes mellitus in children:—

Under 1 year . . .	3
1–5 years	26
5–10 „	31
10–16 „	42
	102

In children and young people the disease often runs a very rapid course though occasionally there are exceptions to this general rule. In elderly persons the disease is frequently associated with gout and obesity; it is then generally of a mild form, and often runs a very chronic course.

2. *Geographical distribution, racial influence, and rarity of the disease.*—In most countries diabetes is a rare disease. A medical man engaged in a busy general private practice in England only occasionally meets with a well-marked case. In hospital practice more cases are collected, and here the disease can be best studied. At the Manchester Royal Infirmary, during the twenty years 1875–1895, the number of *medical in-patients* was 27,721, and of these only 272 suffered from diabetes, not quite 1 per cent. (= 0·9 per cent.).

The death-rate from diabetes in England, per million living, in the ten years 1881–1890 was 57. In Manchester the census of 1891 gave the population as 505,368; in Salford,

198,717. The number of deaths from diabetes in the same year was 29 in Manchester, and 8 in Salford—total, 37.

Osler (4) states that the disease is more rare in America (United States) than in Europe. The last census for the United States gave a mortality of 2·8 per 100,000, whilst in European countries the mortality is from 5 to 9 per 100,000. Among 35,000 patients treated at the Johns Hopkins Hospital, Baltimore, there were only ten cases of diabetes mellitus.

The following table, prepared by Ebstein (5), shows the proportion of cases of diabetes treated in various University clinics in Germany :—

Year.	Berlin.[1]	Bonn.	Breslau.	Göttingen.	Greifswald.	Halle.	Kiel.	Königsberg.	Marburg.	Total No. of Diabetic Cases.	Total No. of all Cases treated.	
1887–88	18	8	4	7	...	5	2	4	1	49	54,494	In the Medical Polikliniks
1888–89	15	4	8	10	1	5	2	5	3	53	39,973	
1889–90	Vacat.	11	5	7	1	8	...	6	1	39	41,470	
Total	33	23	17	24	2	18	4	15	5	141	135,937	
1887–88	Vacat.	2	2	11	4	6	10	15	1	51	7,919	and In the Medical Clinics
1888–89	12	1	5	10	...	4	8	9	4	53	11,965	
1889–90	13	2	2	10	1	3	2	20	2	55	14,346	
Total	25	5	9	31	5	13	20	44	7	159	34,230	

Of the Prussian Universities.

[1] In the Medical Clinic of the Berlin Charité Hospital there were in the

Year 1874,	amongst 3268	medical cases,	9	diabetic patients,	1 : 363.
,, 1875,	,, 3076	,,	7	,,	1 : 439.
,, 1888-89,	,, 3605	,,	12	,,	1 : 300.
,, 1889-90,	,, 5239	,,	13	,,	1 : 402.

Ebstein also mentions that, in the Eppendorff Hamburg Hospital, amongst 7710 medical cases there were only four cases of diabetes, *i.e.* one in 1927.

The disease is therefore met with more frequently in the Manchester Royal Infirmary than in German hospitals.

In India, Ceylon, South Italy, and Malta, diabetes is much more common than in most other countries.

Bose (6) has pointed out that of the various races of India it is the Hindus who chiefly suffer. Amongst 250 cases which he has collected, only two were Mohammedans, seventeen were Europeans, and 231 Hindus. All the 250 cases were males.

Bose points out that in India the disease is chiefly one of middle life, but it also occurs, though rarely, at an early age. He believes that the disease is increasing greatly.

Sen (7) also has shown that in Lower Bengal the Hindus suffer more than other races; he gives the following table of the mortality from diabetes in Calcutta:—

	1876–80.			1881–85.			1886–90.		
	Male.	Female.	Total.	Male.	Female.	Total.	Male.	Female.	Total.
Hindus . .	98	13	111	142	17	159	167	36	203
Mohammedans	3	...	3	2	1	3	3	...	3
Non-Asiatics	...	...	...	...	...	...	3	2	5

The following table shows the proportion of races amongst the inhabitants of Calcutta (Sen):—

	Hindus.		Mohammedans.		Christians.		Other Religions.	
	Male.	Female.	Male.	Female.	Male.	Female.	Male.	Female.
1881. . .	168,107	98,538	75,731	33,722	11,581	10,484	2,359	1,149
1891. . .	272,432	156,330	125,591	63,635	13,690	12,716	3,326	1,681

Total—1881, 401,671; 1891, 649,401.

The following table shows the mortality from diabetes in Calcutta per 100,000 deaths, from 1876–1890 (Sen):—

1876 . . .	263	1881 . . .	215	1886 . . .	384
1877 . . .	173	1882 . . .	291	1887 . . .	382
1878 . . .	107	1883 . . .	263	1888 . . .	445
1879 . . .	190	1884 . . .	276	1889 . . .	325
1880 . . .	196	1885 . . .	314	1890 . . .	379

In Sweden, East Prussia, and the middle Rhine provinces, diabetes is said to be more common than in other parts of the German Empire (v. Noorden). According to Strümpell, in Germany the disease is most common in Würtemberg and Thüringen. Seegen (8) states that a large proportion of the diabetic patients who visit Carlsbad come from Frankfurt-am-Main and Thüringen. He points out that his diabetic patients from Thüringen were mostly poor, hard-working people, and that

a large proportion of the patients from Frankfurt were Israelites. Twenty-five per cent. of his cases were Israelites. Making allowance for the frequency of the visits of wealthy Jews to Carlsbad and other spas, he thinks that 10 per cent. would indicate fairly the proportion of Israelites amongst his diabetic patients. Seegen attributes this frequency of the disease amongst the Israelites to a less stable condition of the Hebrew nervous system.

Other writers have drawn attention to the frequency of the disease in the Hebrew race. Frerichs states that of his 400 cases 102 were Jews.

But amongst the wealthy Jews it is probable that the conditions of life play an important part in the causation of the disease, as well as racial peculiarity. Purdy states that the Israelites generally suffer from a mild form of the disease, and that the patients have usually been great eaters.

At the Manchester Royal Infirmary a considerable number of very *poor* Russian, Polish, and German Jews are admitted as in-patients, but, as far as one can judge, diabetes certainly does not appear to be more common amongst these *poor* Jewish patients than amongst the British patients.

Wallach (9), however, has clearly demonstrated the greater frequency of the disease amongst the Jews in Frankfurt. During nineteen years, 1872–1890, there were 171 deaths from diabetes in Frankfurt. The proportion of deaths from diabetes to the number of deaths from all causes was six times greater amongst the Jews than amongst the rest of the inhabitants. Carefully prepared tables show that the mortality from diabetes per 1000 was greater at all ages amongst the Jews than amongst the rest of the inhabitants of Frankfurt:—

Age.	Deaths from Diabetes per 1000 amongst the Jews.	Deaths from Diabetes per 1000 amongst people of other Faiths.	General mortality from Diabetes per 1000 Inhabitants.
0–14 years	0·02	0·005	0·007
14–19 ,, ...	...	0·007	0·005
19–29 ,, ...	0·11	0·03	0·04
29–39 ,, ...	0·04	0·02	0·02
39–49 ,, ...	0·19	0·09	0·10
49–59 ,, ...	1·01	0·20	0·38
59–69 ,, ...	2·40	0·69	0·92
69–79 ,, ...	2·86	0·54	0·94
79–89 ,, ...	2·52	0·31	0·75
89–99 ,, ...	...	...	...

Purdy ([10]) draws attention to the remarkable fact that the mortality reports of the census for 1880 in the United States of America do not furnish a single death from diabetes in either the Indian or Chinese population of the country. Indians are spare eaters, and subsist almost exclusively on nitrogenous food. With regard to the Chinese, the explanation is by no means easy, but the fact is interesting; diabetes does occur in China, however. The apparent exemption may be due to race peculiarity. Diabetes is said to be rare in Japan.

From a careful study of the mortality from diabetes in various regions of the United States, Purdy ([11]) concludes that it is highest in the regions where there is "the lowest range of temperature, in conjunction with the higher altitudes, and *vice versâ*."

Dickinson ([12]) concludes that diabetes is more common in the colder counties of England. He also thinks that the statistics show that the disease is more prevalent in agricultural than in urban districts.

Purdy has shown that in the United States the relative mortality of diabetes in rural and urban populations is chiefly determined by temperature; in the colder regions the mortality being decidedly higher in the country, whilst in the warmer regions it is higher in the cities.

Henniker, in the Forty-eighth Annual Report of Registrar-General (1885), draws attention (at pages xix.–xxi.) to the difference in the mortality from diabetes in various localities of England. He thinks there is an inverse relation between the prevalence of diabetes and the rainfall; that where the rainfall is least, as in eastern counties, the mortality is greatest.

The mean annual mortality from diabetes per million, from 1874 to 1883, was forty-two in England and Wales, thirty-one in Scotland, twenty-five in Ireland. In Scotland and Ireland the rainfall is much in excess of that of England. Of the various English counties, the death-rate per million living from diabetes during 1885–86 was highest in Norfolk; Berkshire came next, and then followed Suffolk, Derbyshire, Sussex, Rutland, whilst London and Lancashire came low down on the list.

3. *Is diabetes mellitus becoming more prevalent?*—An inspection of the reports of the Registrar-General for the last forty-five years shows that the number of deaths registered as due to diabetes, and therefore the mortality per million living, has steadily increased.

Deaths from Diabetes Mellitus per million living (in England).

1850	24	1873	35
1851	23	1874	37
1852	21	1875	39
1853	23	1876	37
1854	24	1877	41
1855	24	1878	42
1856	23	1879	41
1857	25	1880	41
1858	27	1881	47
1859	25	1882	47
1860	27	1883	51
1861	27	1884	54
1862	29	1885	55
1863	27	1886	59
1864	32	1887	62
1865	32	1888	62
1866	32	1889	60
1867	32	1890	65
1868	31	1891	66
1869	34	1892	68
1870	33	1893	70
1871	35	1894	68
1872	33	1895	75

No doubt the increase of the number of deaths registered as diabetes mellitus is due in some degree to the improved training of the medical man of the present day; cases are not so frequently overlooked at the present time as they were many years ago. But the increase is much too great and too constant to be explained in this way. Thus, in 1873 the death-rate was 35 per million, in 1895 it was 75 per million. The sugar tests *usually* employed at the present time are much the same as those of twenty years ago, and it cannot be maintained that medical men are now twice as careful in diagnosis and urine testing as they were then.

It is interesting to note that several Registrar-Generals have drawn attention to this increasing death-rate from diabetes.

Dr. Tatham, in the report for the ten years 1881–1890, especially draws attention to the increase. As he points out, the mortality has already become considerable, and is increasing year by year.

Thus for the ten years 1871–1880 it was 38 per million living, whilst in 1881–1890 it had risen to 57 per million. This increased mortality has been noticed in other countries also. Thus Purdy gives the following figures with respect to the United States:—

Rates of Deaths from Diabetes in the United States.

Year.	Ratio.
1850	72 to 100,000 deaths.
1860	98 „ „
1870	170 „ „
1880	191 „ „

Purdy attributes this remarkable increase to more extravagant and luxurious living.

Lépine ([13]) has pointed out that in Paris during the last thirty years the mortality has increased six fold—from 2–3 per 100,000 to 13 per 100,000 inhabitants.

In Denmark, Caroë ([14]) has shown that the same increase has occurred. Thus, from 1860–69 the death-rate from diabetes in Copenhagen and the towns of Denmark was 2 per 100,000; whilst in 1890–94 it had risen to 8 per 100,000 inhabitants.

Diabetes Mellitus amongst the In-patients at the Manchester Royal Infirmary, 1875–95.

	Total No. of Medical In-patients.	No. of Cases of Diabetes Mellitus amongst Medical Cases.
1875–76	981	8
1876–77	1003	6
1877–78	1277	10
1878–79	1280	9
1879–80	1351	22
1880–81	1433	26
1881–82	1428	13
1882–83	1519	19
1883–84	1543	10
1884–85	1658	16
1885–86	1474	17
1886–87	1448	14
1887–88	1477	11
1888–89	1511	17
1889–90	1525	16
1890–91	1528	11
1892	1376	12
1893	1374	18
1894	1286	5
1895	1249	12

There is no definite increase to be noted, however, in the proportion of cases of diabetes amongst the medical patients at the Manchester Royal Infirmary. This is shown by the table on p. 103. Perhaps the table is not quite a reliable indication of the frequency of the disease during the various years. During the years 1875–80 Sir William Roberts was physician to the hospital, and his great interest in urinary diseases no doubt caused some increase in the number of diabetic patients who sought relief at the Manchester Infirmary at that time. During the last ten years, however, the figures may be taken as a fairly reliable indication of the frequency of the disease.

During the ten years 1875–85 there were, therefore, 139 cases of diabetes mellitus amongst 13,483 medical in-patients; during the ten years 1885–95 there were 133 cases amongst 14,238 medical in-patients.

4. *Social position.*—v. Noorden thinks that the poorer classes of society suffer less from the disease. Frerichs found that only sixty out of his 400 cases belonged to the poorer classes. v. Noorden thinks that riches, culture, and good social position increase the liability to the disease ten fold. Diabetes has been thought to be more common amongst persons whose occupation demands much mental work and is associated with mental worry and irritation. It has been stated that it is more prevalent amongst learned men, musicians, poets, schoolmasters, merchants, and politicians. Also it is stated to be frequently met with amongst stout, wealthy, indolent persons.

In spite of these statements, however, it must be remembered that the disease, often in its most severe form, is met with amongst poor, hard-working people; whilst amongst the wealthy and better educated classes many of the cases are examples of the mild form of the disease.

5. *Heredity.*—The influence of heredity in the causation of the disease has been variously estimated. As above stated, it appears probable that certain races are a little more prone to suffer from the disease, as, for example, the Jews and Hindus.

Sometimes there is a distinct family history of diabetes. Several members of the same family, children of the same parents, occasionally suffer from the disease; sometimes an uncle or an aunt of the diabetic patient has been similarly affected; occasionally, but very rarely, the father or mother have been diabetic. But this family history of diabetes is not common.

In the first 100 cases of diabetes in which I took careful notes with respect to the family history, I found that evidence of heredity could be obtained in thirteen only. Most of these cases were hospital patients, and therefore 13 per cent. will probably be a minimum estimate of evidence of heredity.

The following were the instances amongst 100 consecutive cases in which a family history of the disease could be obtained:—

Case 1.—Female, æt. 20: two sisters also suffer from a severe form of diabetes.

Cases 2, 3, 4.—In each case a brother of the patient has died from diabetes.

Case 5.—A brother of the patient is said to have suffered from diabetes, and to have recovered.

Cases 6, 7, 8.—In each case an uncle of the patient had suffered from the disease.

Case 9.—Patient's aunt had suffered from diabetes.

Case 10.—The patient's mother is said to have suffered from diabetes many years ago, but to have recovered; her urine is now free from sugar.

Case 11.—Patient's mother is said to have suffered from glycosuria.

Case 12.—Patient's grandfather died of diabetes.

Case 13.—Patient's father and uncle died of diabetes.

In twenty-eight cases of diabetes in children, collected by Wegeli ([15]), there was a family history of the disease in eight. In seven of these cases a brother or sister had suffered from diabetes.

Often there is a history of phthisis or mental disease in the family of a diabetic patient, and in the mild form of the disease not infrequently a family history of gout or obesity is obtained.

6. *The possibility of infection.*—Schmitz ([16]) in 1890 drew attention to this subject. He recorded twenty-six instances amongst 2320 cases of diabetes, in which apparently healthy persons, living in intimate association with diabetics, had developed the disease. Most cases were instances of married females, who had become diabetic after nursing a diabetic husband. In these cases there were no indications of hereditary predisposition; there was no family relationship between the patients; no excess of sugar had been taken in the food; and the patients had not suffered from gout. Hence Schmitz raised the question of the possibility of the transmission of the disease.

This view seems very improbable, however, and has been much disputed. Nevertheless the association is interesting, and seems to point to some common cause, at least in some of the cases, as it is scarcely likely that all are mere coincidences. It is well known that the nursing of a patient during a long illness, and the anxiety connected therewith, have occasionally been the exciting causes of diabetes. Now, if a patient be suffering from diabetes, and be nursed by his wife, and if the anxiety and strain should bring on diabetes in the wife, then we should have the occurrence of the disease in two persons living together. If to these cases we add those due to accidental coincidence, an explanation may perhaps be offered for the facts above mentioned. I have never met with any instances of people living together who have both suffered from the disease, but I have recently been somewhat surprised to find that three diabetic patients at the Manchester Royal Infirmary all came from one small suburb of Manchester—Didsbury. One patient was a child, æt. 11, who died of diabetes after an illness of six weeks only. The other was a girl, æt. 12, and the third was a young adult female. Considering the rarity of diabetes, the occurrence of three cases in this small suburb is somewhat remarkable.

Oppler and Külz [17] have recently given a critical review of the cases of supposed infection hitherto published, and have recorded ten additional examples, taken from 900 cases of diabetes seen by the late Professor Külz.

Besides the ten (duplicate) cases they record, they have also found sixty-seven cases reported in medical literature. The numerical relation between diabetic married couples and other diabetic cases is shown in the following table, giving the results of the observations of several authors:—

Betz	1 married couple amongst	31	diabetic patients.
Hertzka	1 „	86	„
Lecorché	6 „	114	„
Schmitz	26 „	2320	„
Seegen	3 „	938	„
Külz	10 „	900	„
Total	47 married couples amongst	4389	diabetic patients.

or 1 : 93⅜, or 1·08 per cent.

Since the proportion of cases is so small, and since the influence of heredity and other predisposing causes cannot be

excluded with certainty, Oppler and Külz do not think there is sufficient evidence for accepting the view that diabetes is contagious.

Senator ([18]) states that amongst 770 cases of diabetes that have come under his observation, there have been nine instances of man and wife suffering from the disease. This proportion—1·19 per cent.—corresponds pretty closely with the statistics of Oppler and Külz.

But Senator points out that when all the cases are excluded in which there is a family history of the disease, or a history of any of the well-known etiological antecedents, the cases remaining (of diabetes in man and wife) are so few that it seems probable that the occurrence is accidental, or that both man and wife have been subjected to the same antecedents.

7. *External Injury.*—In the section devoted to glycosuria, it has been pointed out that after injuries to the head a small quantity of sugar is sometimes found in the urine for a short time. But, long ago, attention was drawn by Goolden ([19]) and Fischer ([20]) to the fact that true diabetes occasionally follows an external injury. When we consider how many people suffer from the effects of external injury, and in what a very small proportion of cases diabetes follows, it is quite evident that there must be some other factor beside trauma in the causation of the disease in these cases. Moreover, in a series of cases of diabetes a history of trauma is obtained only in a small proportion. Nevertheless, cases are occasionally met with in which there appears to be little doubt that the injury has been the exciting cause, or at least an important factor in the causation of the disease. The following is an example of diabetes following and apparently due to an injury to the head ([21]):—

M. A. R., æt. 18 (under the care of Dr. Steell at the Manchester Infirmary). The patient was a strong, healthy, stout girl up to the time of an accident seven months before admission. On going downstairs she suddenly slipped and fell down thirteen steps, the top of her head coming violently in contact with a door at the bottom of the steps. She was stunned by the fall, but did not lose consciousness. A dish which she had in her hand at the time was broken in the fall, and her face was cut by the broken porcelain just below the right eye. She received a deep cut on the flexor surface of the right forearm just below the elbow. She had great pain in the head for many hours, and very frequently suffered from severe

headache afterwards. Two weeks after the accident she first noticed thirst, which was soon followed by wasting. On admission, the patient was emaciated; knee-jerks absent; urine acid, 1045, no albumin; large amount of sugar present (23 grs. to the ounce); marked brownish-red coloration with Fe_2Cl_6. During the time the patient was in the hospital the amount of urine at first varied from 80 to 90 oz. daily, afterwards from 56 to 68 oz. daily, with increase of sugar to 33 grs. per ounce. The disease terminated fatally about eighteen months later.

I have met with a few other cases in which diabetes has followed an injury to the head or some other part of the body, but in these cases the connection of the disease with the injury has been less evident than in the case recorded above. In 100 consecutive cases of diabetes mellitus in which I made careful inquiries, a history of external injury was obtained in six only. In two of these six cases the connection between the injury and the causation of the disease seemed doubtful. Ebstein obtained a history of external injury in six cases out of 116 diabetic patients.

The earlier the diabetic symptoms follow the accident, and the greater the probability that there were no diabetic symptoms previously, the more likely it is that diabetes is due to the accident. Ebstein ([22]) has recently collected fifty cases of traumatic diabetes from his own clinic and from literature. From a review of the cases, he concludes that individual predisposition is an important factor. Occupation, age, and sex appear to be of no importance. Injuries to the head appear to be followed by diabetes more frequently than injuries to other parts. In *one-half of the fifty* cases of traumatic diabetes collected by Ebstein the head was the seat of injury. In other cases, injuries to the neck, liver, region of kidney, pubes, etc., have been followed by the disease.

From the fact that only an exceedingly small proportion of injured persons become diabetic, we must conclude that there exists some peculiarity in the nature of the injury, or some peculiarity in the individual, in cases of traumatic diabetes. The second view is the more probable.

Ebstein and Asher ([23]) have reported cases of traumatic neurosis which has been followed by diabetes.

8. *Mental Emotions.*—It has long been known that diabetes sometimes follows, and appears to be caused by, mental emotions,

such as fright, anxiety, mental worry, etc. These antecedents will be discussed later, in the section on the Relation of Diabetes to Affections of the Nervous System, p. 122.

9. *Obesity.*—It is well known that diabetes frequently occurs in the obese. Frerichs states that one-seventh of diabetics suffer from obesity (59 in 400). Women at the climacteric period, especially when they are stout, are liable to suffer from diabetes (Frerichs). In hospital practice, obesity is rarely connected with diabetes, but the association is much more common in private practice. Seegen points out that often obesity is present first; and generally diabetes does not develop for years after the obesity has become marked. In these cases the development of diabetes is slow; the disease generally commences between the age of 40 and 60, and it is almost always of a mild form; sugar usually disappears from the urine after a rigid diet, and the prognosis is favourable. But in another group of cases obesity occurs in young individuals, at an age when obesity is rare; it develops rapidly and to a marked extent, and then symptoms of diabetes in its severe form appear. In many of these cases there is a predisposition to diabetes in consequence of heredity or brain affection. In cases of the first group, obesity predisposes to diabetes. In cases of the second group, there seems to be a more intimate connection, and the obesity appears to be a forerunner of the diabetes, but the exact relation has not been determined (Seegen [24]).

The following case is an example of the latter variety:—

Mary A. L., æt. 29, in-patient at the Manchester Royal Infirmary (under the care of Dr. Leech). As a girl she was exceedingly fat, and was known in the country district where she lived as "fat Polly." She had influenza two years before admission to the hospital, and states that she has "never been well since." Ten months before coming under observation she began to suffer from thirst and diuresis. She has lost flesh and become weak. Weight previous to onset of diabetes, 200 lb. Present weight, 15th October 1893, 107½ lb. She is suffering from a severe form of diabetes. Urine 1038, large quantity of sugar present; marked reaction with perchloride of iron.

10. *Gout.*—Diabetes and gout are frequently associated. Grube ([25]), of Neuenahr, found that sixteen out of 177 diabetic patients suffered from gout, and twenty-three had gouty parents. But it is to be remembered that treatment by the Neuenahr mineral waters is especially recommended for the mild forms of diabetes

occurring in gouty patients, and this fact probably accounts, in part, for the frequency of the association of gout and diabetes in Grube's cases. In the diabetic cases at the Manchester Royal Infirmary (mostly poor patients suffering from a severe form of the disease), there is very seldom any association of the two affections.

v. Noorden ([26]) points out that gout and diabetes may be associated in three ways—

(1) Patients who are gouty in middle life may suffer from glycosuria at a later period.

(2) Gout and glycosuria may alternate.

(3) Gout and glycosuria may be present together.

In the cases in which the two diseases are associated, the diabetes is usually of a mild form, the general condition is good, and the prognosis is favourable. But if diabetes is present first, and gouty symptoms develop later, the prognosis is more unfavourable.

11. *Alcoholism.*—It has already been pointed out that in great beer drinkers alimentary glycosuria can often be produced more readily (*i.e.* with a smaller amount of glucose) than in healthy persons. In Manchester a history of alcoholism is not infrequently obtained from diabetic patients. In 100 consecutive cases of diabetes mellitus I obtained a history of very great alcoholic excess in seventeen. All of the seventeen patients were males, and the form of alcohol was generally English beer, of which enormous quantities had been taken daily for long periods.

Strümpell ([27]) points out that he has frequently met with diabetes in persons who have been great beer drinkers. Often these were cases of "diabetes with obesity." Frequently they were mild forms of the disease, but sometimes severe forms, complicated with gangrene and tuberculosis of the lungs, and often they have been complicated with other results of alcoholism—alcoholic neuritis, chronic nephritis, etc. Strongly in favour of the view of a "beer diabetes" are the results of Strümpell's observations on alimentary glycosuria in great beer drinkers. No sharp line can be drawn between alimentary glycosuria and diabetes. At first, as a result of excessive beer drinking, the sugar destroying function of the system is weakened, and alimentary glycosuria occurs; later, the sugar destroying function is lost, and permanent diabetes follows.

Strümpell believes that it is excessive beer drinking, rather than simple alcoholism, which is the cause of certain cases of diabetes.

12. *Influenza.*—During the last six years influenza appears to have been the exciting cause in a considerable number of cases of diabetes. But when we consider how many persons have suffered from influenza during the recent epidemics, how very seldom diabetes has followed, and how rarely diabetes can be traced to a previous attack of influenza, it is quite evident that there is always some other factor in the causation of the disease. Nevertheless, in a few cases, an attack of influenza does appear to have had some influence as an exciting cause.

In 100 cases of diabetes, in which I have taken careful notes on the previous history, I find that in six influenza appears to have played some part as an exciting cause.

In two of these cases the symptoms of diabetes first appeared whilst the patient was suffering from an attack of influenza, and continued from that date. In two the diabetic symptoms first appeared a few days after an attack of influenza. In two cases there was a considerable interval of time between the attack of influenza and the onset of diabetic symptoms; but in both cases the patients declared that they "were never well after the influenza"; the influenza attacks were followed by a low state of health, and finally diabetes developed. In one case a patient had suffered from diabetes, but the symptoms had subsided; an attack of influenza was followed, however, by a return of the diabetic symptoms, which persisted.

13. *Acute infectious diseases.*—Symptoms of diabetes are sometimes first noticed soon after an attack of one of the specific fevers, such as typhoid fever, scarlet fever, cholera, diphtheria, etc.; and occasionally diabetes follows an acute illness such as acute rheumatism, acute tonsillitis. I have met with one instance in which the diabetic symptoms first appeared when the patient was recovering from an attack of pleurisy; in another case they first appeared as the patient was recovering from an attack of pneumonia.

Probably, in some instances, the association of the two diseases is accidental. Certainly there must be some other factor in the causation besides the previous febrile affection; though it is very probable that an acute illness may act occasionally as an exciting cause. We know that in acute

diseases secondary changes often occur in the heart, lungs, kidneys, and other organs, and it is possible that occasionally the pancreas may be affected and diabetes produced.

14. *Exposure to cold and wet.* — Occasionally diabetic symptoms have been attributed by the patient to exposure to cold and wet. Sometimes diabetic symptoms have first been noticed when the patient has been suffering from, or just recovering from, an attack of nasal catarrh and bronchitis.

In three cases out of 100 in Manchester, the diabetic symptoms first developed whilst the patients were suffering from a severe cold.

15. *Drinking of cold fluids.*—A number of cases are on record, in which apparently healthy persons have developed diabetic symptoms directly after drinking large quantities of cold fluid, or after taking ices, when the body has been very hot and covered with perspiration.

In one instance which I have met with, the symptoms were first noticed after drinking a large quantity of cold water one very hot summer's day. Diabetic symptoms were definitely stated to have been absent previously. In two cases the thirst was said to have commenced suddenly whilst the patients were drinking beer. Peiper ([28]) reports the case of a person who, whilst very hot at a ball, drank a very large quantity of cold water, and immediately diabetic symptoms developed.

16. *Malaria.*—The relation between malaria and diabetes is disputed. Some authors regard malaria as an occasional exciting cause of diabetes, but by others this relationship is denied. Cantani ([29]) is not inclined to attach any importance to malaria as a cause of diabetes, except perhaps in so far as it increases the vulnerability of the organism generally, and diminishes its resisting power. In 218 of his cases, only thirteen had suffered from malaria—a percentage which is very small considering the frequency of malaria in Italy.

17. *Lightning stroke.*—Hermanides ([30]) reports a case in which a man, after being struck by lightning, suffered from severe headache. One year later diabetes developed, and two years later hemianopsia was detected. The disease terminated fatally. Post-mortem examination showed that the dura mater over the hemispheres was markedly thickened in many places, and adherent to the pia. The latter was turbid and adherent to the brain cortex, most markedly in the region of the right parietal lobe.

18. *Syphilis.*—Several cases have been recorded, by Ord ([31]) and others, in which glycosuria has been found in patients presenting the ordinary general symptoms of constitutional syphilis. A few cases are also on record, in which true diabetes has been met with in syphilitic patients, and has very probably been due to a syphilitic lesion.

Feinberg ([32]) has reported three cases of diabetes, and one of glycosuria, which were apparently of syphilitic origin. In all of these cases there were signs of syphilitic affection of the nervous system, and under anti-syphilitic treatment recovery occurred in one of the cases of diabetes, great improvement in the other two, but in the case of glycosuria no definite improvement followed. It is quite possible that syphilis may cause diabetes by producing a specific lesion of the brain, especially of the medulla. Syphilitic arterial disease, with secondary nervous lesions in the region of the fourth ventricle, or a gumma in this part, would be capable of producing diabetes. Also it is possible that syphilis may give rise to diabetes by causing disease of the blood vessels of the pancreas and secondary disease of the gland tissue.

Though syphilis may be an occasional cause of diabetes, there can be no doubt that such cases are exceedingly rare. In 100 cases of diabetes I obtained a history or indications of previous syphilis in six only, and in these cases there was no reason to regard syphilis as the cause—probably in all of the six cases the association with syphilis was accidental.

19. *Food.*—It has already been pointed out, that if a very large quantity of saccharine material be taken by a healthy person, a trace of sugar appears in the urine for a short time. But glycosuria cannot be produced by amylaceous food, however great the quantity taken. Diabetes has often been attributed to the excessive use of saccharine or amylaceous food. I have never met with any case, however, in which I could satisfy myself that there was any reason for attributing the disease to excess of carbohydrate food, or to a special form of diet.

Cantani ([33]) thought that the excessive consumption of farinaceous and saccharine food predisposes to diabetes. Amongst his Italian patients he seldom met with a diabetic who had not taken excess of these articles of food. In the 210 cases which came under his observation, generally the patient's diet had consisted chiefly of farinaceous and saccharine food, and but little

albumin. Many of his wealthy patients had eaten flesh meat only once or twice a week, his poor patients only once or twice a year.

In Thüringen diabetes is more frequent than in other parts of Germany, and Cantani points out that the people of that district live chiefly on farinaceous food.

In Ceylon, where diabetes is so common, a large quantity of saccharine food is taken. But the Chinese rarely suffer from diabetes, and yet their diet consists chiefly of farinaceous food.

20. *Diabetes and pregnancy.*—It has been pointed out on p. 88 that during the puerperal state lactose is present in the urine. Apart from this condition of physiological lactosuria, there appears to be occasionally some connection between pregnancy and the onset of true diabetes. Matthews Duncan ([34]) has studied this association, and has collected twenty-two cases from his own practice, and from medical literature. He draws the following conclusions with respect to the connection between diabetes and pregnancy:—

(1) Diabetes may come on during pregnancy.

(2) Diabetes may occur only during pregnancy, being absent at other times.

(3) Diabetes may cease with the termination of pregnancy, recurring some time afterwards.

(4) Diabetes may come on soon after parturition.

(5) Diabetes may not return in a pregnancy occurring after its cure.

(6) Pregnancy may occur during diabetes.

(7) Pregnancy and parturition may be, apparently, unaffected in its healthy progress by diabetes.

(8) Pregnancy is very liable to be interrupted in its course, and probably always by the death of the fœtus.

Amongst the cases of diabetes which have come under my observation, the following have been associated with the puerperal state:—The symptoms first developed in one case just after confinement; in another case after a miscarriage, the fifth which had occurred; in another case after a fourth miscarriage; in another case the patient had had a miscarriage, after which she had never been well, and soon symptoms of diabetes developed. In three cases the diabetic symptoms developed directly after the patient had suffered from an abscess of the breast. In one case the child would not suckle, and three

months later diabetic symptoms appeared. It is possible that in some of these cases, pregnancy, the puerperal state, or the condition of the breast, may have been exciting causes of the disease.

21. *Climacteric diabetes.*—It has been thought by some writers that the climacteric period favours the occurrence of diabetes in women.

Tait ([35]) believes that there is a climacteric glycosuria which ends in recovery.

Imlach ([36]) reports an interesting and apparently well-marked case of diabetes in which pyosalpinx was present. Removal of the diseased uterine appendages was followed by disappearance of the diabetic symptoms, which did not return, even when ordinary diet was taken.

22. *Sexual excess.*—Occasionally the diabetic symptoms first appear in previously healthy men not long after marriage, and the question of the part played by sexual excess as an exciting cause has been sometimes raised by the patients. It has not yet been clearly shown, however, that sexual excess acts as an exciting cause.

B. On the Relation between Diabetes Mellitus and Diabetes Insipidus.

Experiments on animals have shown that there is a close relation between polyuria, and polyuria with glycosuria. Clinically, also, there appears to be a close relation between diabetes mellitus and diabetes insipidus in a few rare cases. With regard to the etiology, it is well known that both forms of diabetes are often connected with altered conditions of the nervous system. Gross lesions are only found in a few cases, but there are frequently indications of some minute or functional changes in the nervous system in each affection. Also diabetes mellitus and diabetes insipidus occasionally occur in near blood relatives. Senator ([37]) has recorded a case of diabetes insipidus occurring in a person whose mother died of diabetes mellitus. Another indication of the relationship of the two diseases is the occasional transition of one disease into the other, or the alternation of the diseases in the same patient. The transition of diabetes mellitus into diabetes insipidus is the more common. This is a favourable change, and sometimes complete recovery finally

occurs. Senator has recorded two cases of diabetes mellitus in which the sugar disappeared and was replaced by albumin; then the albuminuria disappeared, and polyuria remained. Finally, the patients recovered completely. He also reports a case of diabetes insipidus in which glycosuria occurred; the patient became wasted, and the disease terminated fatally. Westphal ([38]) has recorded the alternation of diabetes mellitus and diabetes insipidus in the same patient.

All these facts indicate that occasionally the two diseases are closely related.

C. Relation between Diabetes Mellitus and Diseases of the Liver.

From the results of physiological experiments, one would expect that there would be some clear relationship between diabetes and pathological changes in the liver. If the function of the liver be to prevent sugar entering the general circulation, as Pavy believes, then one would expect that in serious hepatic diseases this function would not be performed, and that diabetes would follow. But from clinical experience and pathology we know that extensive destruction of the liver parenchyma may occur, in cases of cancer and cirrhosis of that organ, in phosphorus poisoning and other diseases, without any sugar appearing in the urine. Glycosuria is very rare, even in advanced diseases of the liver. Frerichs has recorded a case of cirrhosis of the liver, in which subsequent post-mortem examination showed that there was almost complete degeneration of the liver parenchyma, yet no glycosuria occurred, even after a large quantity of sugar had been taken by the mouth. Again, in nineteen cases of phosphorus poisoning, large quantities of sugar (200 grms.) were given by Frerichs, but in seventeen of the cases no glycosuria was produced; in two cases only did a small quantity of sugar appear in the urine. Frerichs also found that there was no sugar or glycogen in the liver in phosphorus poisoning when fatty degeneration of that organ had occurred.

No definite or constant pathological change is met with in the liver in diabetes, though this organ is sometimes diseased. In the cases which have come under my observation pathologically, apart from hypertrophy, there have been generally no definite naked eye changes in the liver. In a few cases,

however, changes were present. In one case there was cirrhosis with fatty infiltration, and the liver was much enlarged; but during life the diabetic symptoms were only slight. In another case cirrhosis was present, but the patient had been a great beer drinker. In one case *multiple abscesses of the liver* and recent purulent cerebro-spinal meningitis were found post mortem. The following are the notes of the case:—

J. R. came under my care on 28th September 1890. History of an attack of vertigo and vomiting in February 1890. Five weeks later he began to be troubled with thirst and polyuria. He had been unemployed for eleven months, had lost a large sum of money, and been subject to great mental anxiety before the onset of diabetes. He had obtained employment, however, at a bleaching works about one month before he first noticed diabetic symptoms. A brother died of diabetes.

When first seen the patient was considerably wasted. He suffered from thirst and polyuria. Urine 1032, acid; contained 5·17 per cent. of sugar; no albumin. Knee-jerks absent. Commencing cataract in each eye. Bowels regular. Heart, lungs, liver, and spleen normal. Four months later the amount of sugar varied from 2500 to 4800 grs. daily, and the amount of urine from 90 to 130 oz. From 21st January 1891 until 24th February the temperature was normal. At the latter date the evening temperature was 102° F.

25*th February.*—Patient complained of pain in the epigastrium. Urine contained for the first time a trace of albumin, and also gave for the first time a dark reddish-brown coloration with Fe_2Cl_6. Bowels constipated. For the next three days the evening temperature was between 102° and 102·8°; then for four days the evening temperature was between 99° and 100°.

4*th March.*—Evening temperature 102°; pulse 96; respirations 25.

5*th March.*—Morning temperature 99·6°; evening 103·2°.

6*th March.*—Morning temperature 101·2°; evening 100·2°. Patient complained of pain in the right hypochondriac region. Edge of liver felt about one inch and a half below the ribs. No jaundice; no rigors. Patient became very restless and semi-conscious, but he could be roused to answer questions. Knee-jerks absent; calf muscles tender; no paralysis; no anæsthesia. Death at 2 A.M. on 7th March. Shortly before death the pulse was 224; respirations 72. No discharge from ears or symptoms of suppurative otitis media during the patient's illness.

Necropsy (abstract).—Peritoneum, pericardium, heart and aorta normal. Lungs: adhesions at right apex; small patch of broncho-pneumonia in left lower lobe and another at right apex. Left apex puckered; contained several small calcareous nodules and cicatrices. The kidneys were enlarged, each weighed 11 oz. Suprarenals: medulla deeply con-

gested; two small yellowish nodules, each about the size of a pea, in the medulla of the right suprarenal. Spleen slightly enlarged, very soft, almost semifluid, congested; weight 11 oz. Pancreas: weight 2½ oz., somewhat small, firm to the touch. Liver: weight 5 lb., capsule normal; on the under surface of the right lobe a few small irregular yellowish patches, each about the size of a pea. On section, scattered throughout the right lobe irregularly, but most numerous in the outer half of the lobe, were a number of small points of suppuration, varying in size from a pea to a marble. About the middle of the outer half of the right lobe the points of suppuration were clustered together so as to form a large, irregularly-shaped abscess, about 4 in. in the transverse and 2–3 in. in vertical diameter. The pus could be easily washed away from the points of suppuration, leaving cavities bounded by a distinct limiting wall. In only a few places was there any zone of congestion around the abscesses. The pus was of a greyish-yellow colour. Under the microscope, pus cells and a few scattered granules of bile pigment were seen. The gall bladder contained a small amount of pale orange-coloured bile. The mucous membrane was congested, but no ulceration could be detected. There was no obstruction of the cystic duct, common bile duct, or hepatic duct. A number of the large bile ducts were traced into the liver substance with a probe and slit open, but no obstruction was met with; the ducts were not dilated. They did not contain any pus. No thrombosis in the portal vein, nor in any of its larger branches. Stomach: no ulceration. Rectum: no ulceration, nor any other abnormality detected. Bladder contained a large amount of urine. Prostate normal. Spinal dura mater normal to the naked eye. Anterior surface of the spinal cord and arachnoid normal. Arachnoid of posterior surface of a yellowish turbid appearance in the dorsal region. Only slight turbidity in the cervical and lumbar regions. Vessels on the posterior aspect of the cord much distended. Only slightly distended on the anterior aspect. On section, the cord presented a normal appearance.

Skull cap, dura mater, and blood sinuses normal.

Brain.—Membranes of each cortex presented a turbid, yellowish-white appearance. Distinct suppuration along the course of the large vessels, and at the sulci of the convolutions. At the anterior end of the first left frontal convolution was a hæmorrhage about the size of a halfpenny. It was irregular in shape, situated between the arachnoid and the cortex, and passed down between the convolutions, but did not enter the brain substance. The membranes at the upper surface of the cerebellum presented the same appearance as those of the cortex cerebri. Membranes of the base of the brain, pons, and under surface of cerebellum of normal appearance. The lateral ventricles contained a small amount of turbid fluid. In the posterior horn of the left lateral ventricle was a small

amount of pus. Vessels of velum interpositum and choroidal plexuses much distended. In the fourth ventricle nothing abnormal detected.

On section, basal ganglia, pons, medulla, and cerebellum normal to the naked eye.

Microscopical examination of the medulla and cord reveal purulent meningitis, but no other changes. Microscopically the pancreas was normal.

Pathological diagnosis.—Diabetes mellitus; multiple abscesses in the liver, spinal and cerebral meningitis.

It is difficult to say what was the relation of the liver abscesses to the diabetes. A similar case is published by Frerichs ([39]), and two are mentioned by Saundby ([40]).

Condition of the liver in a series of consecutive cases of diabetes mellitus.—In discussing the relation of diabetes to liver diseases, it will be well to consider next the conditions of this organ in a series of consecutive cases. Taking for this purpose the records of the Pathological Institute of Vienna, we meet with the following results in 122 cases of diabetes (recorded by Seegen).

During the professorship of Rokitansky thirty cases were examined:—

In 15 the liver was enlarged, firm, and hyperæmic.
„ 2 „ small and anæmic.
„ 1 medullary cancer of the liver was present.
„ 1 tuberculosis „ „

During the professorship of Kundrat ninety-two cases were examined:—

In 9 the liver was fatty.
„ 7 parenchymatous degeneration was present.
„ 8 there was fatty infiltration of the liver.
„ 4 the liver was atrophic.
„ 4 „ cirrhotic.
„ 5 „ congested.
„ 2 tuberculosis of the liver was present.
„ 1 gall stones were present.
„ 1 a fistula was present between the gall bladder and colon.

In the last twenty cases of diabetes in which I have seen or made the autopsy, the condition of the liver has been as follows:—

Liver enlarged in	11 cases.
Normal in size in	5 „
Diminished in size in . . .	4 „

In 1 case multiple abscesses were present.
„ there was marked alcoholic cirrhosis.
„ „ cirrhosis and fatty infiltration.
„ the liver was congested and fatty.

In the rest, beyond variation in size, the only other change detected was congestion, which was often present.

From the above lists it will be seen that no constant macroscopic pathological changes are met with in the liver in diabetes. Also, microscopically, no definite or constant change has been detected.

The most common abnormalities, as shown by the results given above, are enlargement, hyperæmia, fatty infiltration and degeneration, and cirrhosis. Recently attention has been drawn by a number of authors to the association of a peculiar, rare form of diabetes,—so-called "bronzed diabetes,"—with pigmentary hypertrophic cirrhosis of the liver (this variety is described on p. 308). Excluding the last pathological condition, it may be pointed out that the above mentioned changes are very often found unassociated with diabetes mellitus, and that none of them are sufficiently constant to be regarded as playing any part in the causation of the disease.

Glénard ([41]) states that he has found changes in the liver during life, by examination of the abdomen, in 60 per cent. of diabetic patients; in 34·5 per cent. hypertrophy was present. But it is well to remember that he practises at Vichy, which is visited by a large number of gouty and obese diabetic patients.

It has been pointed out on p. 110 that in some cases of diabetes there is a history of marked alcoholism, and that it appears probable that occasionally alcoholism plays a part as an exciting cause. Triboulet ([42]) regards diabetes in these cases as the result of a liver affection—a pre-cirrhotic change.

Glycogen in the liver of diabetic patients.—By means of a fine trocar, Ehrlich ([43]) removed a few liver cells, during life, from an alcoholic patient, four and a half to five and a half hours after a meal rich in amylaceous substances. Microscopically, glycogen was found in the cells in considerable quantity. In a case of diabetes, the liver cells, removed in the same way, were almost free from glycogen; only in a few isolated cells was glycogen found: but in another case of diabetes glycogen was present in the cells in considerable quantity.

Külz ([44]) estimated the amount of glycogen in the liver of

a diabetic patient, who had been restricted to a meat diet for a long time. The patient had taken his last meal thirty-four hours before death, and the autopsy was made twelve hours after death. He found that the total amount of glycogen present was 10 to 15 grms. The liver also contained a large quantity of sugar, which had been transformed from the glycogen. Hence the amount of glycogen during life must have been very considerable. v. Mering (45) found sugar and glycogen in abundance in the liver of two diabetic patients who died suddenly. In two other cases, in which sugar had disappeared from the urine eighteen and twenty hours respectively before death, neither glycogen nor sugar was found in the liver.

Whatever conclusions we might be inclined to draw from physiological experiments, with respect to the relation of the glycogenic or other functions of the liver to diabetes in man, it is clear, from a consideration of the above facts, that at present *pathological anatomy* alone does not furnish any clear evidence that diabetes is related to hepatic changes.

D. The Relation between Diabetes Mellitus and Affections of the Nervous System.

It is well known that diabetes sometimes immediately follows, and appears to be caused by, severe mental anxiety or shock. Long ago, Thomas Willis attributed the disease to "sadness or long sorrow"; Prout attributed it, among other causes, to mental anxiety or distress; and in medical literature many cases have been recorded which afford the strongest evidence of the importance of mental shock, anxiety, etc., in the causation of the disease. Seegen, Pavy, Frerichs, and Dickinson all regard changes in the nervous system as the most important factor in the causation of diabetes. Indications of gross lesion of the nervous system (brain or spinal cord) are comparatively rare; but numerous cases are on record in which the disease appears to have been due to some change in the nervous system, though it may not be referable to any definite anatomical lesion. The fact that diabetes and glycosuria can be produced experimentally by injuries to the nervous system—floor of the fourth ventricle and other parts—is also of great importance. Then again, it is interesting to note that diabetes sometimes appears quite suddenly, the patient being able to give the exact hour at which

the symptoms commenced (see p. 164); this sudden onset is very suggestive of a lesion of the nervous system.

Diabetes following mental disturbances.—Numerous cases have been recorded in which diabetes has followed fright, anger, or depressing mental emotions, mental over-strain, mental anxiety or worry owing to loss of money, loss of employment, etc., mental anxiety and overwork associated with the nursing of a sick relative, etc.

In 100 cases of diabetes (mostly patients at the Manchester Royal Infirmary), a careful inquiry into the history revealed the following facts with regard to mental disturbances:—

In eight cases the disease followed the mental anxiety, overwork, and loss of rest, etc., connected with the nursing of a sick relative—generally husband or wife—during a long and fatal illness.

In four cases the diabetic symptoms followed great mental worry and anxiety in connection with loss of money.

In two cases the disease followed mental anxiety from other causes.

In one case diabetes followed mental anxiety and worry connected with loss of employment for a long period.

In another case the disease followed great mental strain and overwork in connection with the preparation for the final B.A. examination of the London University. The patient, who had failed at the examination previously, decided to devote almost the whole of his time to reading (except that required for eating and sleeping). This he did for some months, until diabetes of a severe form developed.

In two cases the disease was attributed to fright.

The following are brief notes of one of these cases:—

Ellen B., æt. 20 (under the care of Dr. Steell at the Manchester Royal Infirmary), enjoyed good health until January 1892, when she suffered severely from mental anxiety and fright. She was left in charge of her sister's baby, but in order to attend, for a few minutes, to some household work, she placed the baby on the table, and went a few yards away. The child fell off the table, the head came in contact with the ground, and a scalp wound was produced. The patient was greatly frightened; at the time she feared the skull was fractured, and was in the greatest state of anxiety. A medical man was sent for at once, and stated that the patient Ellen B. was suffering

much more—owing to the mental shock—than the baby. In a short time the child recovered completely, but the mental distress and anxiety from which Ellen B. suffered were so great that she was *never able to do her usual work again.* Prior to the fright she had been in good health, and had followed her employment (that of a dressmaker) regularly. For many days after the accident she remained in a nervous and excited condition, and was never able to follow her employment again. Thirst and diuresis were noted four weeks after the fright. The urine was examined, and diabetes diagnosed. A severe form of the disease developed, and terminated fatally in about seventeen months. (For further notes, see p. 134.)

In eighteen out of 100 cases analysed, it appeared probable that mental disturbances played some part as an exciting cause, though no doubt there was generally some additional etiological factor.

Dickinson ([50]) reports a case similar to that of Ellen B. "A child fell from a third-floor window, and was smashed upon the pavement, to all appearance, hopelessly. But the accident was more fatal to its mother than itself. The child survived. The mother, who was abruptly made aware of the accident, never recovered from the shock. For three weeks she, to use her own words, could neither eat nor sleep. Within two months she became much emaciated, was consumed with thirst, and was passing water in great quantities, which incrusted upon and stiffened any garment it touched. She died of diabetes within ten months of the occurrence upon which it had succeeded."

Garrod ([51]) relates the following case:—"Two gentlemen fought a duel in Holland; after the first had fired he remained for some time in a state of suspense, from his adversary's pistol once or twice missing fire. He was uninjured, but, a day or so after, became diabetic."

Seegen ([52]) mentions the following cases:—Baron K., an officer, æt. 22, was present at a duel. One of the combatants, a friend of the patient, was killed on the spot. From that day Baron K., who had previously been a cheerful young man, became markedly unwell and depressed; he soon began to lose flesh; two months later it was found that he was suffering from diabetes of a severe form.

Seegen refers to another case, in which a previously healthy man received a violent mental shock; next day marked thirst

and diuresis commenced, and all the symptoms of diabetes followed.

In another case the symptoms followed a railway accident. Though the patient was uninjured, he was greatly agitated, and trembled for twenty-four hours. A few minutes after the accident he became very thirsty, and these symptoms continued for some weeks. He consulted a medical man, and a large amount of sugar was found in the urine.

Dickinson also cites the following case, communicated by Dr. Herman Weber:—A. C., a merchant, was for two months, in 1857, under constant excessive anxiety on account of business troubles. After many sleepless nights he became delirious, or rather insane,—for there was no pyrexia,—and almost suddenly began to pass urine very frequently and in large quantities. It was found to contain abundance of sugar. The daily quantity of urine varied from 7 to 9 pints, and the specific gravity from 1036 to 1044. His business passed safely through the crisis. Within three weeks the urine was free from sugar, and remained so, as ascertained by several annual examinations, until the year 1866. During the mercantile crisis of that year, A. C. again became restless, sleepless, and diabetic. After the crisis he again recovered completely, and remained well, with perhaps a single exception, up to 1870. At the outbreak of the Franco-Prussian war in this year, he became much excited, and died of apoplexy.

Pavy ([53]) relates the case of a gentleman who became diabetic under the influence of mental excitement, and ceased to be so when retirement from town and professional duties had enabled his mind to recover its equipoise.

Purdy ([54]) reports a fatal case due to over-anxiety in conducting extensive transactions on the produce exchange. The patient accumulated a large fortune at the expense of contracting diabetes, which proved fatal in less than twelve months. He also reports another case brought on by business worry; recovery occurred after a complete rest.

Frerichs ([55]) mentions a case in which the symptoms followed great loss of money. By removal from business excitement, and under treatment with opium, every trace of sugar disappeared in three weeks. Several months later, after a second business loss, diabetes again developed. In course of time the patient improved, but a third business misfortune caused the

disease to return. He also mentions the case of a man who became diabetic immediately after discovering that his wife had been unfaithful.

Roberts ([56]) states that in one of his patients the disease followed distress of mind, caused by an unjust suspicion of theft; in another, it followed the anxiety occasioned by the burning down of the patient's place of business; in a third, it was attributed to anxiety attendant on a Chancery suit.

Rayer ([57]) mentions a case of diabetes coming on after a violent fit of anger.

Diabetes and pathological changes in the nervous system.—Though there are so many points in favour of the connection of diabetes with some changes in the nervous system, it must be confessed that in a large number of cases pathological examination does not reveal any marked or definite abnormality in the brain or spinal cord. In a small portion of cases, however, changes have been met with, which are of great interest.

In discussing the relation of diabetes to pathological changes in the nervous system, it will be well to consider—(*a*) the condition of the brain in a series of consecutive cases of diabetes, and (*b*) the more important pathological changes which have been met with in the brain.

(*a*) *Condition of the nervous system in a series of consecutive cases of diabetes mellitus.*—Seegen ([58]) records the condition of the brain in 122 cases of diabetes mellitus, in which a post-mortem examination was made in the pathological department of the Allgemeine Krankenhaus, Vienna. Thirty examinations were made during the time Rokitansky was professor, and ninety-two during Kundrat's professorship.

In Rokitansky's thirty cases no changes of any importance were found. Cerebral œdema was present in three cases, œdema of the brain and chronic hydrocephalus in one case; in one case in which there was general tuberculosis, tubercular meningitis was present.

In fifty-four of Kundrat's ninety-two cases the brain was not quite normal. The following were the changes recorded:—

Slight General Changes.

	Cases.
Anæmia	5
Marked hyperæmia	8
Œdema of meninges	4

	Cases.
Œdema of the brain	10
„ of the brain and meninges	8
Atrophy of the brain (one case with hydrocephalus)	8
More Localised Lesions.	
Dilatation of the fourth ventricle with cerebral hyperæmia	3
Posterior horns of ventricle closed by a cicatrix; ependyma of septum granular	1
Cerebral hæmorrhages— (1) Intermeningeal hæmorrhage over frontal and temporal lobes, optic chiasma, pons, and into the ventricles; softening of gyrus fornicatus. (2) Hæmorrhages into the floor of fourth ventricle. (3) Hæmorrhages into lenticular nucleus breaking into ventricles (lateral and fourth). (4) Hæmorrhages into optic thalamus	4
Depression in the apex of the frontal lobe and at the top of the occipital lobes; cicatricial condition, with calcareous plates, in the arachnoid over the frontal lobes	1
Dura mater thick, and covered with purulent exudation at the vertex, corresponding to a necrotic patch in the skull; region of calamus scriptorius of fourth ventricle much depressed	1
Cysticercus the size of a cherry in the telachoroida, at the inferior and lower part of the fourth ventricle	1
Total,	54

In eleven only of the 122 diabetic cases, *i.e.* 9 per cent., was there any naked-eye change of much importance. In many of these, the significance of the changes with respect to the causation of the disease was very doubtful.

The spinal cord presented grey degeneration in the lateral and posterior columns in one of Kundrat's cases (how many were examined is not stated).

To consider the subject from another standpoint, in 485 cases of brain tumour—collected from literature—Bernardt ([59]) found that sugar was present in the urine in five cases only. In twenty-one cases of tumour of the medulla, sugar was found in the urine in one case only. In fifteen cases of tumour of the hypophysis, sugar was found in the urine twice; in ninety cases of cerebellar tumour, once; and in 124 cases of tumour of the cerebral hemispheres, once.

(*b*) *The more important changes which have been found in the nervous system.*—A number of cases have been recorded in medical literature in which well-marked and important changes have been met with in the nervous system, but the proportion of such cases, to those in which the nervous system presents no macroscopic or microscopic changes, is probably small.

The following is a tabulated group of thirty-four cases, collected from medical literature, in which definite changes of some importance have been found in the nervous system. In some of these possibly the association of diabetes mellitus with the nervous lesions has been accidental, but in many there can be little doubt that the lesions played a very important part in the causation of the disease:—

TUMOURS OF THE MEDULLA.

1. Cystic sarcoma, right half of medulla.	DOMPELING—*Nederl. Arch. v. Genees-en Natuurk.*, Utrecht, 1868 (quoted by Seegen, "Der Diabetes mellitus," Berlin, 1893, S. 208 and 425).
2. Tumour of each pyramid of the medulla close to the pons.	FRERICHS—"Ueber den Diabetes mellitus," Berlin, 1884, S. 202.
3. Tubercle of the medulla between the posterior border of the olivary body and the origin of the first cervical nerve.	DE JONGE—*Arch. f. Psychiat.*, Berlin, 1882, Bd. xiii. S. 663.

TUMOURS IN THE FLOOR OF THE FOURTH VENTRICLE.

4. Tumour in region of choroidal plexus of fourth ventricle.	RECKLINGHAUSEN — *Virchow's Archiv*, Bd. xxx.
5. Colloid tumour in fourth ventricle.	PERROTON—Thèse de Paris, 1859.
6. Two tumours of choroidal plexus.	LIONVILLE—"Verrons études sur les tumeurs du ventricle quarte," Thèse de Paris, 1874.
7. Tumour in fourth ventricle at the calamus scriptorius; glioma in floor of fourth ventricle.	REIMER—*Jahrb. f. Kinderh.*, 1876, s. 306.

OTHER CHANGES IN THE FLOOR OF THE FOURTH VENTRICLE.

8. Patch of softening, floor of fourth ventricle.	RICHARDSON — *Med. Times and Gaz.*, London, 1866.
9. Softening due to fatty degeneration, floor of fourth ventricle.	LUYS—*Gaz. méd. de Paris*, 1860, No. 24, p. 384.
10. Similar case.	LUYS—*Ibid.*
11. Cysticercus in fourth ventricle.	IVAN, MICHAEL—*Deutsches Arch. f. klin. Med.*, Leipzig, Bd. xliv.
12. Cysticercus in fourth ventricle.	Case under the care of Riess of Berlin, mentioned by OSLER, "Principles and Practice of Medicine," Edinburgh and London, 1895, 2nd edition, p. 320.
13. Disappearance of grey substance and of nerve cells from floor of fourth ventricle.	ZENKER—Quoted by Weichselbaum, *Wien. med. Wchnschr.*, 1881, No. 32.
14. Sclerosis in floor of fourth ventricle.	FRERICHS—*Loc. cit.*, s. 195.
15. Patches of disseminated sclerosis in the floor of the fourth ventricle; multiple sclerosis of cord and brain.	WEICHSELBAUM — *Wien. med. Wchnschr.*, 1881, No. 32.
16. Disseminated sclerosis, with lesion in the floor of the fourth ventricle.	EDWARDS—*Rev. de méd.*, Paris, 1886, p. 703.
17. Patch of disseminated sclerosis in floor of fourth ventricle.	RICHARDIERE—*Ibid.*, Paris, 1886, p. 623.
18. Cerebro-spinal meningitis; purulent fluid in fourth ventricle.	FRERICHS—*Loc. cit.*, S. 198.
19. Old and recent hæmorrhages in the floor of fourth ventricle and medulla.	FRERICHS—*Loc. cit.*, S. 203.
20. Hæmorrhage, floor of fourth ventricle.	DUTRAIT—Quoted by Weichselbaum, *loc. cit.*, 1881, No. 32.
21. Patch of sclerosis in floor of fourth ventricle, left side; connective tissue rich in nuclei; traversed by arteries with very thick walls.	THIROLOIX—*Gaz. de méd. et chir.*, 16th April 1892.

Lesion about the Base of the Brain.

22. Calcareous tumour compressing the under surface of pons; also abscess in posterior cerebral lobes.	Richardson — *Med. Times and Gaz.*, London, 8th March 1862.
23. Sarcoma of the pituitary body. (Two similar cases, coming under my observation in Manchester, are recorded on pp. 137–38.)	Rosenthal—"Klinik der Nervenkrankheiten," Stuttgart, 1875.
24. Tumour at the base of the brain, limited in front by the anterior frontal convolution, behind by the pons. Pia mater in the fourth ventricle thickened.	Grossmann—*Berl. klin. Wchnschr.*, 1879, No. 10.
25. Sclerosis of arteries of the base of the brain; old thrombus in the basilar artery, softening in the pons, left crus, and left cerebellar cortex.	Frerichs—*Loc. cit.*, S. 200.

Cerebellum.

26. Patch of softening in nucleus dentatus of left cerebellar hemisphere.	Mosler—*Deutsches Arch. f. klin. Med.*, Leipzig, Bd. xv. S. 229.
27. Cysticercus in cerebellum.	Frerichs—*Loc. cit.*, S. 193.

Changes in Cerebral Hemispheres.

28. Tumour, size of a hazel-nut, in the posterior part of the right temporal lobe.	Frerichs—*Loc. cit.*, S. 135.
29. Pachymeningitis in left occipital lobe, with calcareous tumour the size of a pea.	Frerichs—*Loc. cit.*

Lesions of the Spinal Cord.

30. Tumour compressing the spinal cord in the cervical region.	Shingleton Smith—*Brit. Med. Journ.*, London, 1883, vol. i. p. 657.
31. Hæmorrhage and softening in the spinal cord in the cervical and upper dorsal region.	Silver and Irvine—*Trans. Path. Soc. London*, vol. xxix.

32. Atrophy of the anterior horns of the upper part of the cord and lower part of the medulla (from the fifth cervical nerve up to the pyramidal crossing).	FRERICHS—*Loc. cit.*, S. 136.

VAGUS NERVE.

33. Calcareous tumour, the size of a hazel-nut, pressing on the right vagus nerve.	HARLEY—Quoted by Sir William Roberts, "Renal and Urinary Diseases," London, 1885, p. 279.
34. Tumour on the right vagus nerve, close to medulla.	FRERICHS—*Loc. cit.*, S. 91.

SUMMARY OF CASES TABULATED.

	Cases.
Tumours of the medulla oblongata	3
,, floor of the fourth ventricle	4
Other changes in the floor of the fourth ventricle	14
Lesions at the base of the brain	3
Tumour of the pituitary body	1
Lesions of cerebellum	2
,, cerebral hemispheres	2
,, the spinal cord	3
Tumour compressing the right vagus	2
	34

Microscopical changes.—Dickinson (60) has drawn attention to the presence of minute excavations, chiefly around the arteries, in the brains of diabetic patients. The importance of these changes was much discussed many years ago. In some cases of diabetes they have not been found by other observers. Then, again, perivascular excavations have been sometimes found in other diseases, and it is now generally believed that they have no relation to diabetes, but are due to the effects of hardening.

Frerichs (61) devoted much attention to the microscopical examination of the medulla in diabetes. He has described a marked dilatation of the fine vessels of the medulla, and this change he regards as the most important and constant in the nervous system in diabetes. Often the dilatation of the vessels is accompanied by small hæmorrhages, partly old and partly recent. To the dilatation of the perivascular spaces and thickening of the ependyma, Frerichs did not attach any importance, but he

has drawn attention to the great dilatation of a vein found, as a rule, just at the outer border of the vagus nucleus.

Apart from these vascular changes, no other constant or well-defined changes have been met with on microscopical examination of the medulla. The nerve cells of the vagus and other nuclei have not been found to present any abnormality.

Saundby ([62]) mentions that he has found the capillaries of the vagus nucleus in one case abnormally numerous and full of blood. In other cases examined, no changes could be detected in the medulla, basal ganglia, or cerebral cortex.

The two cases above referred to, in which tumours were found pressing on the vagus nerve, are interesting in connection with the experiments of Arthaud and Butte, on the production of diabetes by chronic irritation of the vagus nerve (see p. 66).

Slight changes in the posterior columns of the spinal cord have been found in a few cases, but they have probably been secondary in nature, and will be referred to under the complication of diabetes on p. 66.

The sympathetic nerves and ganglia.—From time to time changes in the abdominal sympathetic nerves and ganglia (chiefly in the cœliac plexus and the semilunar ganglia) have been described by various authors—by Klebs and Munk ([63]), Poniklo ([64]), Cavazzani ([65]), Lubrinoff ([66]), Saundby ([67]), Hale White ([68]), and others ([69]).

The changes have consisted chiefly of atrophy, sclerosis, or cell infiltration of the ganglia, of increased vascularity, and excess of connective tissue in the nerves; sometimes the ganglia have been greatly enlarged. But in other cases the histological examination of these nerves and ganglia has only yielded negative results. Then, again, marked changes, similar to those met with in diabetic patients, have been found in cases which had not presented any symptoms of diabetes during life.

As already mentioned, the cœliac plexus has been extirpated by Lustig and Peiper without producing a permanent diabetes.

Windle ([70]) has collected the results of the pathological examination of the sympathetic nerves and ganglia in seventeen cases; in eight of these the results were negative.

The relation of changes in the sympathetic nervous system to a number of pathological conditions has been carefully studied by Hale White, who has made histological examinations of the sympathetic ganglia in various diseases. Hale White has

examined the superior cervical ganglia of seven patients who died of diabetes, but no single condition was "ever present that is not found, and even more marked, in many patients who have never had glycosuria." He has also examined the semilunar ganglia. Sometimes the ganglia were well developed and healthy looking, and the changes found in the others were only such as are frequently observed when there have been no signs of diabetes during life. Hence he concluded that the ganglia in the cases he has examined showed no changes to which the disease could be attributed.

Diabetes and diseases of the nervous system.—In various well-defined diseases of the nervous system, glycosuria is occasionally met with, and sometimes, though very rarely, true diabetes; but the latter is generally of a mild form.

Thus diabetes has been met with occasionally, though very rarely, in association with disseminated sclerosis, locomotor ataxia ([71, 72, 73]), chronic anterior poliomyelitis, Graves' disease, etc. In Graves' disease, it has been already pointed out (see p. 87) that alimentary glycosuria is produced more readily than in healthy persons. Occasionally Graves' disease is complicated with glycosuria; much more rarely with true diabetes. A well-marked example of the latter association has recently been recorded by Bettmann ([74]). Occasionally diabetes is associated with symptoms pointing to a cerebral tumour or other gross cerebral lesion; but in such cases the diabetes is generally of a mild form.

Personal observations.—A number of cases of well-marked temporary glycosuria, associated with various nervous lesions, have come under my observation, but only a very few cases of true diabetes associated with evidences of gross lesion of the brain. In not more than 3 per cent. of cases of diabetes observed in Manchester, was there any evidence of gross lesion of the nervous system (*i.e.* excluding nervous complications due to the disease). The following are notes on an interesting case of diabetes associated with symptoms of gross lesion of the brain which came under my observation at the Manchester Royal Infirmary:—

Marked ataxia of sudden onset; paralysis of right internal rectus; tremor of right arm; onset of diabetes seven weeks after commencement of symptoms.—J. W., æt. 48, was admitted under the care of Dr. Steell on 7th May 1890. Patient was quite well until 26th April 1890.

On the morning of that day, when going to his work, he suddenly became ataxic and fell to the ground. There was no loss of consciousness, no paralysis of limbs. He has been unable to walk or stand since, owing to ataxia. History of alcoholism; no syphilitic history. On admission, patient is unable to stand alone; when well supported, he is able to advance a few steps, and throws forward his right leg in a jerky, irregular manner. Marked ataxia. No paralysis of limbs; no rigidity; knee-jerks present; no ankle-clonus. Right palpebral fissure smaller than left; apparent ptosis of right eye; paralysis of right internal rectus; left pupil larger than the right. Slight nystagmus; slight tremor of the right arm even when the limb is supported, but this is more marked on voluntary movement. Optic discs normal. Old perforation of right tympanic membrane. Temperature normal. Urine 1015, acid, no albumin, no sugar, quantity normal.

12*th June.*—Amount of urine increased to 92 oz. daily.

15*th June.*—Urine pale, clear, 1024, acid, contains a large amount of sugar.

23*rd June.*—Great thirst, voracious appetite. In the first three weeks during which the diabetic symptoms were noted, the amount of urine varied from 160 to 190 oz.; and the sugar from 3200 to 4200 grs. daily. The excretion of urine and sugar were both diminished by restricted diet. A few months later several large carbuncles developed on the gluteal region, but in course of time these, and the paralysis of the right internal rectus, the ptosis and nystagmus, disappeared. The diabetic symptoms, the tremor of the right hand, and the ataxia persisted.

In two cases diabetes was associated with typical symptoms of acromegaly, and post-mortem examination revealed a tumour of the pituitary body. These cases will be described subsequently.

I have only met with a few cases in which post-mortem examination has revealed any naked-eye lesion of the brain or nervous system. In fourteen cases in which I have recently had the opportunity of making a careful examination of the brain post-mortem, the results have been as follows:—

In nine cases the medulla oblongata and other parts of the brain appeared normal to the naked eye.

In five cases naked eye changes were found.

In two of these cases a tumour (round-celled sarcoma) of the pituitary body was present, and during life there had been typical symptoms of acromegaly. In these two cases the medulla appeared normal.

In one case there was well-marked cerebro-spinal meningitis,

and multiple abscesses in the liver, but sections of the medulla showed no other change beyond the inflamed meninges (see p. 117).

In another case, a cyst about the size of a small pigeon's egg was found in the right lateral hemisphere of the cerebellum on its under surface, close to the pons and anterior part of the medulla. Clinically, the case had been one of severe diabetes, finally complicated by phthisis. Death occurred from coma. During life there were no indications of brain tumour or other cerebral lesion. The cyst had a thin smooth wall, and the cerebellum was excavated by it. There was no indication of any tumour growth in connection with the cyst. During life the cyst would probably have pressed upon the nerves arising from the right side of the pons and medulla.

In one case, described below, a minute hæmorrhagic patch could be detected by the naked eye in the left vagus nucleus after the medulla had been hardened in Müller's fluid.

Microscopical examination of the medulla.—In ten cases of diabetes mellitus I have made a microscopical examination of the medulla, especially in the region of Claude Bernard's "diabetic centre." In all of these cases the medulla was hardened in Müller's fluid and embedded in celloidin for section cutting. The sections were stained with aniline blue-black, logwood, and according to the methods of Pal or Weigert.

In the following case distinct changes were found in the vagus nucleus:—

E. B., æt. 20. The clinical history of this case is recorded on p. 122. The symptoms followed a severe fright, which apparently was the exciting cause of the disease.

On making a transverse section through the medulla (after hardening in Müller's fluid) at the region of auditory striæ, a small dark red patch like a small hæmorrhage, was seen, just in the region of the left vagus and glosso-pharyngeal nuclei. It extended one-eighth of an inch above and one-eighth of an inch below the point of section. Altogether, therefore, its antero-posterior extent was a quarter of an inch. In transverse section it appeared as a very small dark red point. In sections examined under a low power of the microscope, it was seen that the hæmorrhagic patch extended at some parts almost to the surface of the floor of the fourth ventricle, whilst at other parts it was some distance below it, and was situated near the centre of the left vagus nucleus. In some sections there were two hæmorrhagic

patches in the region of the vagus nucleus. In one section there were a number of minute hæmorrhagic patches, just around the vessels, in the region of the left vagus nucleus. Under a high power it was seen that the hæmorrhagic patch consisted of red blood corpuscles, and the

FIG. 6.—Hæmorrhagic patch (shaded) in vagus nucleus in the medulla; case E. B., under the care of Dr. Steell (low power of microscope).

margins of the patch were well defined and regular. In fact it appeared as if the blood corpuscles were contained in well-defined spaces or capillary vessels. The patch resembled a capillary angioma situated in

FIG. 7.—Another section from the medulla of the same case (low power of microscope).

the vagus nucleus, though distinct vessel walls could not be detected (see Figs. 6. 7, and 8).

The blood vessels of both vagus nuclei were dilated and full of red corpuscles. The perivascular spaces were also dilated, and in many places in the left vagus nucleus contained red blood corpuscles. The nerve

cells of the vagus and other nuclei in the medulla, the nerve fibre and other structures, were of normal appearance. The changes in the region of the vagus nucleus appeared to indicate a condition of localised in-

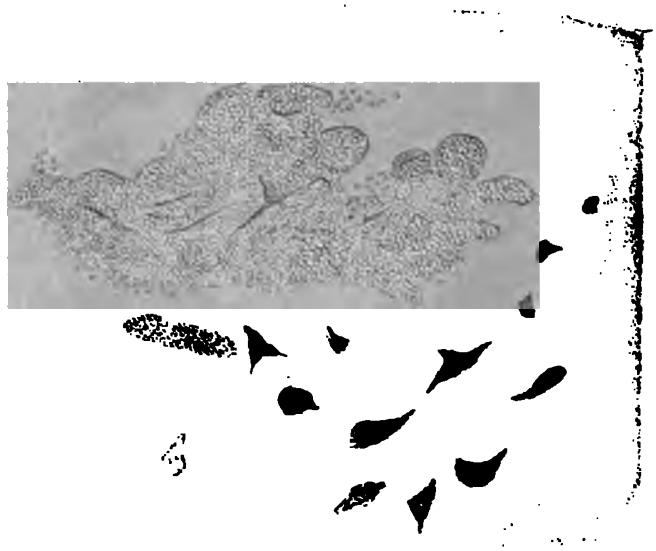

FIG. 8.—Hæmorrhagic patch in vagus nucleus of medulla; case E. B. (high power of microscope, Zeiss, D.).

creased vascularity, and may in some way have been connected with the causation of the disease.

In a second case, J. D., the clinical history of which is recorded on p. 243, small hæmorrhagic patches, similar to those in the case just reported, only much smaller, were found in the vagus nuclei.

In a third case, M'M., the vessels of the vagus nuclei were dilated, and minute hæmorrhages, mostly perivascular, were found in one vagus nucleus. In two other cases the vessels of the vagus nuclei were dilated, but no hæmorrhages were found.

In four cases, sections of the medulla were normal. In one case inflammation of the meninges was discovered (case of cerebro-spinal meningitis, recorded on p. 117).

Diabetes and acromegaly.—Diabetes has been associated with symptoms of acromegaly in two cases in which I have made a pathological examination of the brain. In both cases a tumour of the pituitary body was present. The optic chiasma, and

afterwards the optic nerves, had been compressed by the tumour growth in each case. The following are the notes:—

1. *Acromegaly; double optic atrophy; diabetes mellitus; tumour of the pituitary body.*—Mary W., æt. 36. Seven years before the patient came under my observation, she had noticed that the hands were becoming large. She was seen by Dr. Hill Griffith on account of impaired vision three years later. At that time there was bi-temporal hemianopsia, and Dr. Griffith recognised the case as one of acromegaly. The hands and feet became very large, the lips prominent and thick; the nose became enlarged, and the features altered very much. The patient was troubled with frequent pain in the head, chiefly in the forehead, at the early part of the illness, but there was no vomiting. Her vision gradually became worse, and for two years before she came under my observation she had been quite blind. For nine months she had suffered from thirst and diuresis, and had been under the care of my friend Dr. E. Somers, who had found a large quantity of sugar in the urine. After the onset of diabetic symptoms there was considerable wasting.

During the last six days of her life the patient was under the care of Dr. Dreschfeld at the Manchester Royal Infirmary, where, as medical registrar, I had the opportunity of carefully examining her.

The hands and feet were still enlarged, in spite of considerable wasting, which had been produced by the diabetes. The jaw, nose, and lips were enlarged, and the typical symptoms of acromegaly were present. The patient was quite blind, and ophthalmoscopic examination revealed double optic atrophy (primary). There was no paralysis of facial or ocular muscles. The knee-jerks were absent. Examination of the chest and abdomen revealed nothing of importance. The urine had a specific gravity of 1040; it contained a large amount of sugar, but no albumin on admission (2nd May 1895). There was a marked brownish red reaction with perchloride of iron, and also a distinct reaction for acetone (Legal's test).

The daily quantity of urine was as follows:—

3rd May.—76 oz.

4th May.—164 oz.; total quantity of sugar excreted in twenty-four hours = 4960 grs.

5th May.—160 oz.

During the night of 6th May the patient became very restless. On 7th May the pulse was rapid, 140 per minute, and very feeble; the respirations deep, 32 per minute. The patient was semi-comatose. The urine contained a small amount of albumin; it gave a distinct brownish-red coloration with perchloride of iron, and contained numerous hyaline and granular casts. Casts were not present in the urine on 4th, 5th,

and 6th May. Death occurred with all the symptoms of diabetic coma on 7th May.

At the autopsy there were the characteristic changes in the limbs—enlargement of the hands, feet, etc., but no abnormalities of importance were detected in the thorax or abdomen. The pancreas weighed 2 oz., and was normal macroscopically and microscopically. On examination of the brain, a tumour of the pituitary body about the size of a pigeon's egg was found. The under surface of the growth was smooth, and the sphenoid bone was not invaded by it. The optic chiasma and optic nerves were embedded in the growth. Microscopically, the tumour was a round-celled sarcoma. The medulla and other parts of the brain were normal.

2. *Acromegaly; double optic atrophy; diabetes mellitus; tumour of the pituitary body.*—A. H., æt. 23, was admitted under the care of Dr. Ross to the Manchester Infirmary on 16th November 1890.[1] History of headache and gradual enlargement of the hands and feet —symptoms of acromegaly. Temporal hemianopsia of the right field of vision; in the left field, vision entirely lost, with the exception of a very small area near, but a little to the temporal side of, the centre of the field. Urine 1035, no albumin, no sugar, loaded with urates. After remaining in the hospital for several weeks, the specific gravity of the urine rose to 1045, and it was found to contain sugar by Fehling's test, by the phenylhydrazin test, and also by fermentation. The amount of sugar at first was 14 grs. to the ounce; the amount of urine was then normal. The sugar gradually increased. The patient left the hospital for several months, and then returned on account of an abscess which had developed in the left breast. She was admitted on the surgical side under the care of Mr. Southam. The patient complained of thirst, and on examination of the urine a large amount of sugar was found. The abscess was opened and treated antiseptically, and the patient put on diabetic diet. The thirst, however, increased, and five days later the patient died of diabetic coma. The temperature remained practically normal. At the post-mortem examination a round-celled sarcoma of the pituitary body was found, which pressed on the optic chiasma. The left optic nerve was embedded in the growth. The rest of the brain was normal. The thyroid was a little enlarged, and contained a colloid cyst. There were changes in the pancreas, which will be afterwards described (see p. 146). Liver enlarged, weight 5 lb. 2 oz.; signs of fatty degeneration.

Glycosuria has been observed in other cases of acromegaly which have been recorded in medical literature; sometimes

[1] This patient's symptoms were the subject of a clinical lecture published by Dr. Ross in the *International Clinics*, vol. i. p. 1.

polyuria has been present also, and in some cases the symptoms have been those of well-marked diabetes, as in the first case just reported.

Thus sugar was found in the urine in six out of twenty-one recently reported cases of acromegaly; in the other fifteen the urine was free from sugar. In four of the cases in which glycosuria was present the symptoms were those of true diabetes. In two of the six cases a tumour of the pituitary body was found at the autopsy, just as in the two cases recorded above; the other four patients were still alive when the cases were reported. It is worthy of note, that in both of the cases recorded above, diabetes only came on at a late period of the disease, and probably some of the fifteen cases just mentioned, in which the urine was free from sugar, would develop glycosuria before death. In a case of acromegaly with diabetes, which has been recently reported by Hansemann ([75]), post-mortem examination revealed considerable increase in the connective tissue of the pancreas; a tumour of the pituitary body was also present. Out of ninety-seven cases of acromegaly which Hansemann has collected from medical literature, diabetes or glycosuria was present in twelve.

The association of diabetes with acromegaly does not appear to be constant, however, even at a later period of the disease.

* * *

From a consideration of the facts recorded in this section, we may draw the following conclusions respecting the relation of diabetes to affections of the nervous system:—

1. Emotional disturbances (mental anxiety, worry, shock, or fright) are antecedents, and apparently play some part as exciting causes in certain cases of diabetes. In 16 per cent. of the cases at the Manchester Royal Infirmary, a history of such emotional disturbances was obtained.

2. On post-mortem examination, in the majority of cases of diabetes, to the naked eye the nervous system is either normal, or presents only slight and unimportant changes.

3. In a minority of cases, definite macroscopic changes, of diverse nature, are found; they are most commonly localised in the floor of the fourth ventricle or in the medulla; in all probability they have played an important part in the causation of the disease.

4. In case of tumour of the pituitary body, sometimes there

have been symptoms of diabetes, often associated with those of acromegaly, during life.

5. Microscopically, the small vessels of the medulla are dilated in many cases of diabetes, especially in the region of the vagus nuclei; in other cases they are normal. The nerve cells and other structures in the medulla appear normal, or at least do not present any definite or constant change. Occasionally minute hæmorrhagic patches are found in the vagus nucleus.

In spite of the negative result of microscopical examination of the nerve cells and other structures of the medulla in the majority of cases, it is still quite possible that diabetes is often dependent on some minute or functional changes in this region. The microscopical examination of the medulla in other diseases teaches us that very slight changes in the nerve cells may be productive of most serious symptoms. In bulbar paralysis, for example, if the disease does not run a very chronic course, often the changes in the medulla are slight. During recent years a number of cases of bulbar paralysis and of ophthalmoplegia have been recorded, which have terminated fatally, and in which careful microscopical examination of the medulla, pons, etc., has failed to reveal any pathological changes; and yet there can be little doubt that disease has been present in these parts. (I have examined two such cases myself during the last four years.) Hence it is quite possible that some slight functional change in the nerve cells of the nuclei of the medulla may be the cause, or may play some important part in the causation, of certain cases of diabetes.

E. Relation between Diabetes Mellitus and Lesions of the Pancreas.

Changes in the pancreas in diabetes have been described, from time to time, by various physicians and pathologists, ever since Thomas Cawley ([76]), in 1788, recorded a case of diabetes in which the pancreas was atrophied and contained calculi. Thus attention has been called to the importance of pancreatic lesions in diabetes by Chopart, Bright, Recklinghausen, Frerichs, Silver, Munk, Mackenzie, Taylor, Bond, Windle, Duffey, and many others. Lancereaux, many years ago, put forward the view that diabetes with wasting is particularly associated with pancreatic lesions.

Baumel ([77]), in 1882, recorded cases of diabetes with pancreatic changes, and went so far as to attribute all forms of diabetes to the absence of diastatic pancreatic ferment in the intestine.

But the importance of these pancreatic changes was not fully recognised until 1889, when Minkowski and v. Mering ([78]) showed, by experiments on animals, that permanent diabetes mellitus could be produced by complete removal of the pancreas. (These experiments have been already discussed, see p. 74.) Since that time many cases of diabetes associated with pancreatic changes have been recorded (by Lépine, Williamson ([79]), Vaughan Harley ([80]), Hoppe-Seyler ([81]), Fleiner, Hansemann, and many others).

There can be no doubt, however, that whilst in some cases of diabetes the pancreas presents marked changes, in other cases no pathological changes can be detected by our present methods of macroscopical and microscopical examinations. Some writers refer all cases of diabetes to disease of the pancreas; some refer only diabetes with wasting to pancreatic affections ([82]); whilst others believe that there is no connection between diabetes and pancreatic lesions ([83]). Hence some caution is necessary before coming to a definite conclusion, and, in the following pages, evidence for and against the pancreatic theory of diabetes will be put forward.

1. *Frequency and nature of pancreatic lesions in diabetes mellitus.*—In looking over old post-mortem reports of cases of diabetes, very frequently one finds that there is no mention of the condition of the pancreas. Before the publication of the results of the experiments of Minkowski and v. Mering on pancreatic diabetes, frequently the state of the pancreas was overlooked in the post-mortem examinations of diabetic subjects. Rokitansky, however, found naked-eye changes in the pancreas in thirteen out of thirty cases of diabetes.

During the last seven years much attention has been paid to the macroscopical and microscopical condition of the pancreas in diabetes, and many cases have been recorded in which pathological changes have been found, but few in which the pancreas has been normal—microscopically, as well as macroscopically.

Lépine ([84]) has pointed out that the pancreas may appear normal to the naked eye, but may present distinct changes on microscopical examination. Lemoine and Lannois ([85]) have de-

scribed a peri-acinous sclerosis of vascular origin, which can only be recognised on microscopical examination—though the importance of these changes has been disputed.

Hence, in order to form a reliable estimate of the proportion of cases in which the gland is diseased, and the proportion of cases in which it is normal, and also of the nature and frequency of the various pathological changes, it is necessary to examine the pancreas, in a series of consecutive cases, microscopically, as well as macroscopically. The following are brief notes of the condition of the pancreas in twenty-three consecutive cases of diabetes mellitus. In twenty-two cases I have examined the pancreas microscopically, as well as macroscopically. A few of these were my own cases, but for the opportunity of making the pathological examination in the others, I am indebted to the kindness of Drs. Leech, Dreschfeld, Steell, Harris, and Wilkinson (of the Manchester Infirmary), to the late Dr. Ross, and to my friends Dr. Mackenzie and Mr. Milner:—

Case 1.—*Diabetes mellitus; history of alcoholism; marked cirrhosis of the pancreas, with small calculi.*—Thomas L., æt. 45.

Previous history.—Patient enjoyed fairly good health until the summer of 1890. In April 1890 he lost his employment (that of a door porter at a music hall), and was unable to obtain employment again until December 1890. During this period he had much mental worry, and was not able to obtain sufficient food. In September 1890 he began to lose flesh, and in November of the same year he began to be troubled with great thirst and diuresis, together with increased appetite. By January 1891 the patient had become much weaker, and the thirst and diuresis had increased. The patient's weight was 11 st. 8 lb. in April 1890; in January 1891, 8 st. 7½ lb. From the age of 29, until five weeks before admission, the patient had taken large quantities of alcohol (8 to 10 pints of beer) daily. There is no history of injury to the head or back. At the age of 19 he suffered from gonorrhœa, but no history of syphilis could be obtained. His wife has had one miscarriage. He has been fond of sweet food. There is no family history of diabetes.

Present state.—Patient complains of great thirst and diuresis. There is marked wasting; the skin is harsh, dry, and scaly; the temperature is normal. The *urine* is clear, sp. gr. 1037, acid, contains a large amount of sugar, but not a trace of albumin; there is no deposit. It has not, however, the pale straw colour of diabetic urine, but has a slight *reddish or pink tinge.* With perchloride of iron no brown-red coloration produced. The bowels are not constipated. Distinct signs of phthisis

present. Heart normal; pulse 84. Respirations 18. Hepatic and splenic dulness normal. Knee-jerks absent.

During the time the patient was in the hospital (22nd to 27th April), the amount of urine varied from 82 to 176 oz. daily; the specific gravity from 1035 to 1038; the amount of sugar from 27 to 36 grs. to the ounce, or from 2664 to 4752 grs. daily. Death from coma, 27th April.

Autopsy (Abstract). – Body wasted. Pericardium normal. Heart soft and flabby; valves normal.

Lungs.—In the uppermost lobe of the right lung was a large phthisical cavity, surrounded by nodules of caseous pneumonia. The lung tissue was also studded with miliary tubercles.

Brain.—Meninges normal. Slight thickening of the choroidal plexuses of the fourth ventricle; otherwise fourth ventricle, medulla, pons cerebellum, and cerebrum quite normal.

Liver.—Weight 3 lb. 10 oz.; capsule normal. On section, firm and somewhat congested; no evidence of cirrhosis.

Spleen congested, soft, and pulpy; weight 11 oz.

Stomach and intestines normal.

Kidneys slightly congested.

Bladder normal.

Pancreas very firm and hard; firmly adherent to, and very difficult to separate from, adjacent parts; the tail was adherent to the spleen. Weight $4\frac{1}{4}$ oz. On section it was pale, very firm, and cut with considerable difficulty. The pancreatic duct was dilated at several places, forming cyst-like dilatations (about the size of a small pea), which contained mucous fluid and small calculi. In one of these dilatations, about the centre of the pancreas, was an irregular oblong calculus, about the size of a small pea. At the tail extremity of the pancreas were several small cysts, containing calculi, each about the size of a pin's head. The calculi had a pale, yellowish colour, and were of the consistence of mortar. The pancreatic tissue (on section) was seen to be broken up into very small round or irregular masses, surrounded by broad tracts of fibrous tissue. After hardening in Müller's fluid, and then washing well in water, these changes in the pancreas were seen very clearly.

Microscopical Examination.—Sections of the pancreas, stained with logwood and eosin, showed most marked cirrhosis of the gland. In many parts, only a few small clusters of pancreatic cells could be seen, almost the whole of the field of the microscope being occupied with dense fibrous tissue. In other parts, there were well-stained small masses of pancreatic tissue, with one or two small ducts, in transverse or longitudinal sections. These masses of pancreatic tissue were separated and surrounded by a large amount of dense fibrous tissue; also fibrous bands were prolonged between the gland cells. In some parts of the

gland there were larger masses of pancreatic tissue, surrounded and infiltrated by dense fibrous tissue. Many of the pancreatic cells were broken down in these patches, and did not stain well with logwood. In many parts the dense fibrous tissue was well supplied by fine blood

FIG. 9.—Drawing of section of pancreas, showing marked cirrhosis, Case I. (Zeiss, D).

vessels. Microscopical examination showed that the condition was certainly one of marked cirrhosis, and not scirrhus (see Fig. 9). On microscopical examination, the liver appeared normal. After hardening in Müller's fluid, careful macroscopic examination of the medulla and pons failed to reveal any abnormality. Also on microscopical examina-

tion, sections of the medulla appeared quite normal, with the exception of very slight dilatation of the blood vessels at the posterior part, near the floor of the fourth ventricle.

In the case recorded, the urine had all the characteristics of diabetic urine, with the exception of the colour. Instead of the usual pale straw colour, it had a rose or pinkish tinge, and yet not a trace of albumin was present; there was no deposit of urates or other substances, and the urine was quite clear. Unfortunately, a thorough chemical examination was not made. Fichtner[1] records a similar case. In his case the urine became-rose coloured on standing.

CASE 2.—Mary H., æt. 34. Considerable wasting. History of thirst and diuresis for four weeks. Urine 1029; large amount of sugar present; acetone and diacetic acid present; trace of albumin. Death from coma on the second day after admission to the hospital.

Necropsy. — Pancreas small, weight 1¾ oz. The gland, especially at the head, was exceedingly firm and hard. Microscopical examination showed most extensive cirrhosis. There was no fatty degeneration of the pancreas. The brain was normal to the naked eye; microscopically, the medulla was normal.

CASE 3.[2]—Mary H., æt. 41. Duration of illness only about three months. Chief symptoms: epigastric pain, swelling of abdomen, ascites; ill-defined, resisting ridge felt in the epigastrium. Patient did not become very much emaciated. Urine not increased in quantity, sp. gr. 1047, acid, no albumin, large amount of sugar (20 grs. to the ounce), marked deep brown-red coloration with perchloride of iron (Gerhardt's reaction), also marked reaction for acetone (Legal's test). During the last few days of life, vomiting was frequent. Hæmatemesis and death from syncope.

Necropsy.—Peritoneal cavity contained a large quantity of bloody fluid; omental sac full of blood clot. The following is the condition which I found on dissection:—Pancreas densely infiltrated by tumour growth. At some parts the pancreatic duct contained a thick mortar-like material; three branched, irregular, friable white calculi, each a little larger than a pea, were found in the head of the gland. Near the middle of the gland were two larger calculi of similar colour and consistence, one about the size and shape of a date-stone, the other about ¾ in. long, and bent at a right angle at one end; a large

[1] *Deutsches Arch. f. klin. Med.*, Leipzig, Bd. xlv. S. 117.

[2] This case was reported by Dr. Dreschfeld in a paper in the *Med. Chron.*, Manchester, April 1895, p. 14.

number of smaller calculi were also present. Little or no normal pancreatic tissue could be detected. The growth extended from the pancreas in the most irregular manner into the surrounding parts at the posterior wall of the abdomen. On the serous surface of the posterior wall of the stomach was a diffuse mass of new growth, which extended towards the cardiac end of the organ. The growth was infiltrated with blood. The pancreatic tumour also extended from the spleen to the portal vein, which it compressed but did not infiltrate. Superficially the growth was very soft and vascular; the pylorus and duodenum were not invaded by it. The large omentum was much infiltrated with fat, and presented numerous secondary deposits. There were also secondary nodules in the gastro-hepatic omentum. The intestines were not implicated by the growth. The liver was small, and the surface smooth. There was no evidence of cirrhosis, but several small secondary deposits of new growth were found. The gall bladder was normal. The spleen was slightly enlarged. The kidneys were pale, but normal on section. On the serous surface of the uterus were several nodules of new growth. Microscopical examination showed that the growth was carcinoma, the firmer parts presenting the appearance of scirrhus.

Case 4.—O., æt. 67. Emaciated, but not to a great extent. Urine 1033, contained a large quantity of sugar. Severe thirst and diuresis.

Necropsy. — Pancreas hard and firm on section, weight 2 oz. Microscopical examination revealed distinct cirrhosis. In the interacinous connective tissue were many groups of fat cells (lipomatosis).

Case 5.—D., æt. 52. Much emaciated. Urine 1040; sugar varied from 20 to 26 grs. to the ounce. The daily quantity of urine varied from 140 to 170 oz. Arteries very atheromatous.

Necropsy.—Pancreas weighed 3 oz. It was very firm, and appeared cirrhotic. Microscopical examination revealed a moderate degree of cirrhosis, but no fatty degeneration. Brain normal. Extensive tuberculosis of both lungs. Arteries markedly atheromatous, in many parts calcified.

Case 6.—H., æt. 23. Acromegaly. Optic atrophy. Glycosuria without thirst. At a later date, thirst marked, diuresis. Patient well nourished. Death from coma. (For other notes, see p. 138.)

Necropsy.—Sarcoma of the pituitary body, involving the optic chiasma. Pancreas very large, infiltrated at many parts with fat; weight 7 oz. Microscopically, well-marked lipomatosis detected.

Case 7.—B., æt. about 35. Emaciated. Urine, sp. gr. 1040; daily quantity 80 to 150 oz.; large amount of sugar present.

Necropsy.—Pancreas much atrophied, exceedingly soft and flabby, weight 1¼ oz. Scattered throughout the gland (after hardening in Müller's fluid) were seen numerous small pale patches. Microscopical examination revealed fatty degeneration and fatty infiltration (lipomatosis) at these parts.

Case 8.[1]—J. C., æt. 46. Wasted markedly. Urine 100 to 136 oz. daily; sp. gr. 1035 to 1045; sugar 4000 to 5300 grs. daily. No reaction with perchloride of iron.

Necropsy.—Pancreas very small, weight not quite a quarter of an ounce. Pancreatic duct of normal size. All organs wasted. Heart only weighed 6 oz.; but the wasting of the pancreas was altogether out of proportion to that of the other organs. The pancreas was firm, and presented no other change beyond atrophy.

Fig. 10.—Actual size of atrophied pancreas in Case 8.[1]

Case 9.—J., æt. 65. Much emaciated. Urine, sp. gr. varied from 1028 to 1034; the daily quantity of urine from 74 to 104 oz.; the amount of sugar from 22 to 28 grs. to the ounce.

Necropsy.—Pancreas weighed 10 drms., and was atrophied and flabby. Microscopical examination revealed slight fatty degeneration with slight lipomatosis.

Case 10.—N., æt. 44. Very marked wasting. Urine, daily amount varied from 100 to 204 oz.; the sp. gr. was 1034 to 1035; a large amount of sugar present. Death from coma.

Necropsy.—The pancreas was markedly atrophied, and weighed 5½ drms. only; but, apart from the atrophy, microscopical examination did not reveal cirrhosis, fatty degeneration, or any other change.

Case 11.—W., æt. 19. The daily amount of urine varied from 70 to 90 oz.; the sp. gr. from 1035 to 1038; a large quantity of sugar was present. The disease ran a very rapid course, and death occurred from coma about fourteen weeks after the symptoms were first noticed.

Necropsy.—The pancreas was atrophied, and weighed 10 drms.; but microscopical examination did not reveal any other pathological change.

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[1] Case under the care of Dr. Harris. Described by him at a meeting of the Manchester Pathological Society. See *Brit. Med. Journ.*, London, 28th November 1896.

CASE 12.—Ellen B., æt. 20. Marked emaciation. Tuberculous lung disease. The diabetic symptoms came on soon after a severe fright. Urine, amount varied from 90 to 116 oz. daily; sp. gr. 1032 to 1036; sugar 28 to 30 grs. to the ounce.

Necropsy.—Pancreas weighed 11 drms. (but all the organs were very much wasted); microscopically it appeared normal.

CASE 13.—R., æt. 29. Marked wasting. Urine, daily amount varied from 100 to 150 oz.; sp. gr. 1030 to 1042; and the sugar from 20 to 36 grs. to the ounce.

Necropsy.—Pancreas weighed 1¼ oz.; macroscopically and microscopically it appeared normal.

CASE 14.—T., æt. 26. Duration of disease, nine months. Emaciation. Urine 90 to 120 oz. daily; sp. gr. 1035; sugar 30 to 38 grs. per ounce.

Necropsy.—Pancreas atrophic, weight 1½ oz.; microscopically normal.

CASE 15.—W., æt. 31. Marked history of alcoholism. Great emaciation. Death from coma. Urine 255 to 293 oz. daily; sp. gr. 1036; sugar 22 to 23 grs. to the ounce.

Necropsy.—Pancreas, weight 1½ oz. Macroscopically, normal. Microscopically, no cirrhosis, no fatty degeneration, or infiltration; in some places nuclei of cells stained badly with logwood, otherwise the sections appeared normal. Lungs presented early tubercular changes.

CASE 16.—B., æt. 52. History of alcoholism. Liver enlarged. At first urine 154 oz.; sp. gr. 1017; 10 grs. of sugar to the ounce. Afterwards the diabetic symptoms increased rapidly, the sp. gr. of the urine reached 1031, and the amount of sugar was 26 grs. to the ounce.

Necropsy.—Pancreas weighed 3½ oz. On microscopical examination the gland appeared normal. Marked cirrhosis of the liver; tuberculous disease of the lungs.

CASE 17.—M., æt. 46. Emaciated slightly. Urine, daily amount varied from 170 to 190 oz.; sp. gr. 1035; sugar 30 grs. to the ounce. Tuberculous disease of the lungs. Death from coma.

Necropsy.—Pancreas weighed 3 oz.; macroscopically and microscopically it appeared normal.

CASE 18.—F., æt. 21. Much emaciated. Urine, daily amount varied from 130 to 140 oz.; sp. gr. from 1030 to 1040; sugar 33 to 35 grs. to the ounce.

Necropsy.—Pancreas weighed 2½ oz.; macroscopically and microscopically it appeared normal.

CASE 19.—R., æt. 42. Great emaciation. Urine, amount varied from 90 to 130 oz. daily; sp. gr. 1032 to 1045; amount of sugar, 5 to 7 per cent.

Necropsy.—Pancreas weighed 2½ oz. On microscopical examination it appeared normal. Multiple abscesses in the right lobe of the liver. Cerebro-spinal meningitis (recent).

CASE 20.—R., æt. 35. Marked emaciation. Amount of urine varied from 117 to 125 oz. daily; the amount of sugar was about 30 grs. to the ounce. Tuberculous lung disease.

Necropsy.—Pancreas weighed 2½ oz.; macroscopically and microscopically it appeared normal.

CASE 21.—W., æt. 36. Bi-temporal hemianopsia, afterwards double optic atrophy. Acromegaly. At a later date, marked wasting. Symptoms of diabetes mellitus. Urine 160 oz.; sp. gr. 1032; sugar 31 grs. to the ounce; trace of albumin; marked brown-red coloration with perchloride of iron. Death from coma.

Necropsy.—Sarcoma of pituitary body, involving optic chiasma. Macroscopically, pancreas appeared normal, weight 2 oz. Microscopically it also appeared normal.

CASE 22.—M'M., æt. 19. Duration of symptoms five weeks only. Sudden onset from thirst. Marked wasting. Urine 180 oz.; sp. gr. 1032 to 1034; sugar 4400 to 4860 grs. daily.

Necropsy.—Pancreas weighed 1¾ oz., atrophied somewhat, but scarcely out of proportion to the general wasting of the body. Otherwise, macroscopically and microscopically, the gland appeared normal. Tubercular disease of the apex of the left lung.

CASE 23.—B., æt. 26. Admitted into hospital comatose. Diabetes then first discovered. Urine, strongly acid, 1025; large amount of sugar present. Marked brownish-red coloration with perchloride of iron. Good reaction for acetone (Legal's test). Patient emaciated.

Necropsy.—Pancreas weighed 2½ oz.; normal macroscopically and microscopically, except that a few scattered patches were seen in which the nuclei of the cells did not stain well.

Results.—Condition of the pancreas in twenty-three consecutive cases of diabetes mellitus:—

	Cases.
(1) Extensive changes:—	
Very marked cirrhosis	2
Cancer	1
(2) Fairly well-marked changes:—	
Cirrhosis	2
Lipomatosis	1
Atrophy, fatty degeneration, and infiltration	1
Very advanced atrophy, gland weighing less than ¼ oz.	1
(3) Slight changes:—	
Atrophy, with slight fatty degeneration	1
Atrophy (without any other changes) out of proportion to the general wasting	2
(4) Atrophy, but only in proportion to general wasting; no other change	4
(5) Pancreas normal, macroscopically and microscopically	8
Total	23

In twelve out of twenty-three cases, therefore, the pancreas was either normal, or only atrophied in proportion to the general wasting.

Some of the above cases were published by the writer ([86]) in a paper in *The Lancet*, 1894 (14th April), and soon afterwards an article appeared by Hansemann ([87]) of Berlin, in which the relation of the pancreas to diabetes is carefully discussed. A survey of the pathological reports of the Berlin Pathological Institute for ten years gave the following results:—

	Cases.
(1) Diabetes without pancreatic changes	8
(2) Diabetes without any information respecting the pancreas	6
(3) Diabetes with pancreatic affections	40
(4) Pancreatic disease without diabetes	19

As it is not stated that a microscopical examination was made in every case, these results probably refer to the macroscopical changes only. It is remarkable, that of the forty cases in which pancreatic changes were found, thirty-six presented simple atrophy; three cases presented fibrous induration; one was a case of pancreatic cyst.

Nature of pancreatic lesions in diabetes.—The above table of twenty-three cases along with the results of Hansemann,

shows the nature of the pancreatic changes. But in order to obtain further information on this point, I have collected and classified the results in 100 cases of diabetes, recorded in medical literature, in which the *pancreas was abnormal.*

In very few of the cases was a microscopical examination made, hence this table represents generally the *positive result* of macroscopical examination only.

ONE HUNDRED CASES OF PANCREATIC LESIONS IN DIABETES.

	No. of Cases.	
Atrophy of the pancreas (more or less marked)		39
Very marked atrophy, gland almost absent	3	
„ „ gland not recognised by naked eye	2	
Very marked atrophy, with cystic dilatation of duct	2	
„ „ „ and induration	1	
Calculi present, other conditions not stated	1	
Marked fatty degeneration	10	
„ „ „ with calculi	3	
Fatty degeneration, with increase of connective tissue	1	
Complete fatty degeneration and marked atrophy	1	
„ transformation of pancreas into a fatty mass	2	
Cystic disease	3	
Large pancreatic cysts	3	
Cyst of pancreas, with necrosis	1	
Transformation into a firm mass of fibrous tissue, pancreatic tissue being almost absent	10	
Marked cirrhosis	3	
Cirrhotic and cystic pancreas	1	
Calcified pancreas	1	
Peripancreatitis and pancreatitis hæmorrhagica	2	
Abscess	3	
Cancer	8	
	—	61
		100

Hansemann has given the following results from an analysis of seventy-two cases recorded in medical literature:—

	Cases.
Pancreatic calculus	14
Cancer with obstruction of the duct	5
Simple atrophy with interstitial inflammation	38
Other changes	15

The changes in the pancreas in diabetes are therefore varied in nature. Atrophy is the most common change, but it is probable that in some of those cases, at least, the atrophy may be really only a part of the general wasting. Marked atrophy of the pancreas has been observed, however, in diabetes when the general wasting has been absent or trifling (as in Case 11), and it has also been observed in stout diabetics.

Hansemann states that the atrophy of the pancreas in diabetes differs from atrophy of the pancreas which is simply a part of general wasting. In the former condition, the stroma of the gland is not atrophied as in the latter; and in the former the stroma has filled more or less the spaces left by the atrophy of the gland parenchyma, *i.e.* a kind of interstitial inflammation has taken place. He compares the condition to granular atrophy of the kidney. I have often been struck by this appearance of the atrophied pancreas in diabetes.

2. *Condition of the pancreas in a series of consecutive autopsies.*—In considering the relation of pancreatic lesions to diabetes, it is important to know what is the condition of the gland in a series of unselected autopsies on persons dying from various ailments. On this point Kasahara ([88]) has published the records of the pathological examination of the gland in eighty-three consecutive cases. The following table I have drawn up from his records:—

	Cases.	
Pancreas normal, or presenting only trifling changes		42
Increase of fat—		
Interstitial fat markedly increased	2	
Interstitial fat moderately increased	1	
Fatty metamorphosis (one case of diabetes)	6	
Marked localised fatty changes	1	
Partial fat necrosis	1	
Interstitial fat greatly increased	1	
Increase of connective tissue—		
In a marked degree	7	
In a moderate degree	3	
Slightly increased	9	
Increased locally	6	
Marked atrophy (both cases of diabetes)	2	
Cancer	1	
Marked turbidity of cells	1	
	—	41
		83

Kasahara points out that in these eighty-three unselected cases (of various diseases) met with in the post-mortem room, marked atrophy was found in two only, and both were diabetic patients. In no class of cases, accompanied by wasting, has he found such marked atrophy of the pancreas as that met with in some cases of diabetes.

3. *The condition of the urine in diseases of the pancreas.*— In discussing the relation of diabetes to disease of the pancreas, it is interesting to consider the subject from yet another standpoint. In a series of cases of definite pancreatic disease, what is the condition of the urine? Undoubtedly the urine will be found free from sugar in a large proportion of such cases.

Numerous cases of pancreatic disease are on record in which the urine did not contain sugar. But it is important to bear in mind the results of Minkowski's experiments on partial extirpation of the pancreas. If a small part of the pancreas be left behind (one-fifth even has sufficed), diabetes does not occur. Now, if this small piece of pancreas remaining in the abdomen is sufficient to prevent the occurrence of diabetes in animals, one would expect that in pancreatic affections in man, if the whole of the gland be not diseased, *i.e.* if a small piece should retain its function, that diabetes would not occur. Certainly, in a very large number of cases of pancreatic disease in man, a portion of the gland has remained unaffected. Thus, in ten cases of pancreatic disease (confirmed by autopsy) at the Manchester Royal Infirmary, the urine was free from sugar in every one. But post-mortem examination showed that in five of the cases only the head of the pancreas was affected, and the rest of the gland was normal. In the other five cases the post-mortem records state that the lesion was in the head of the pancreas, and no mention is made of the condition of the rest of the gland, so that we are not justified in concluding that the whole of the gland was affected; probably the rest of the gland was normal.

In many cases of pancreatic cyst, diabetes has been absent; but this is explained by the fact that there has been some normal gland tissue remaining.

On the other hand, there are on record some cases of extensive necrosis, and some cases of diffuse cancer infiltrating the whole of the pancreas, which have not been associated with

diabetes. With both of these conditions diabetes is sometimes associated, however.

4. *Conclusions.*—It is very improbable that all the varied pancreatic changes which have been recorded in diabetes are the *result* of the disease. It is scarcely credible that one disease—diabetes—should produce such a number of varied affections of the pancreas as cancer, cirrhosis, atrophy, abscess, etc. Then again, from the frequency of pancreatic lesions in diabetes, and from the fact that often the pancreas presents marked changes, whilst in the rest of the organs none of importance are detected, it is improbable that the lesions are *accidental.* Further, when we consider the remarkable results produced by extirpation of the pancreas, it appears very probable that, *in certain cases,* diabetes is *directly due* to pancreatic disease.

Whilst experiments on animals appear to have conclusively proved that total removal of the pancreas produces diabetes, there are two objections to the pancreatic theory of the origin of diabetes in man, as was pointed out by Minkowski himself. In the first place, pathological changes are not found in all cases of diabetes in man ; secondly, sugar is not found in all cases of disease of the pancreas. This second objection has just been discussed, and partly met. As regards the first objection, it was pointed out by Minkowski that the number of cases in which the pancreas had been carefully examined, microscopically as well as macroscopically, was comparatively small. But during the last five years great attention has been paid to the condition of the pancreas in diabetes, and there can now be no doubt that, microscopically as well as macroscopically, the pancreas not infrequently appears normal, as is shown in the records of the cases reported above. The proportion of cases in which the pancreas is diseased can only be correctly estimated by the examination of a series of *consecutive* cases, and the records of the twenty-three cases which I have described above, furnish, I believe, a fairly correct representation. From these records we see that in eight out of twenty-three cases the pancreas appeared normal, both microscopically and macroscopically; and in four other cases the only change was atrophy, which was scarcely out of proportion to the general wasting of the body. Hence, in twelve out of twenty-three cases diabetes was due to some other cause than pancreatic disease, or the pancreatic affection must have been one giving rise to changes which cannot be detected

microscopically or macroscopically, *i.e.* a functional disease. It may be pointed out, that not only the pancreas but also the brain, liver, and other organs are very often normal, or present changes only which are undoubtedly of a secondary nature. On the other hand, the importance of the pancreas is evident, when we bear in mind the results of experiments on animals, which show that *total* removal of the pancreas invariably produces diabetes, and that a small portion of pancreatic tissue, grafted under the skin of the abdominal wall, is sufficient to prevent diabetes, when the whole of the gland is removed from within the abdomen. Considering also the number of cases recorded in which marked pathological changes in the gland—often almost complete destruction—have been found at the post-mortem examination of diabetic patients, it appears exceedingly probable that the disease has been due to a pancreatic lesion when *extensive* changes have been found in that gland.

But it must be borne in mind that *partial* extirpation of the pancreas in animals is not followed by diabetes. A small portion of the gland left behind is sufficient to prevent the occurrence of glycosuria. Hence it is very questionable whether diabetes in man can be attributed to pancreatic disease when the gland presents only slight changes ([89]).

There is another point to consider with reference to the subject. The pancreas is a very vascular organ, and a slight lesion in the nervous system might produce vasomotor changes in the gland, and cause an excess of arterial blood to flow through it. This might lead to alteration in the internal secretion, and yet, post-mortem, no definite pathological changes might be detected.

In a considerable number of cases of diabetes—twelve out of the above twenty-three cases—it seems probable, therefore, that diabetes was either due to some other cause than pancreatic lesion, or to some functional or vasomotor change in the pancreas.

In two of the cases a tumour of the pituitary body was probably the cause of the disease.

In eight or nine of the twenty-three cases recorded above, it appears probable that the disease found in the pancreas was the cause of the diabetes—Cases 1, 2, 3, 4, 5, 7, 8, 9 (?), and 10.

That diabetes is produced in various ways seems very probable. Just as fever is produced in many ways, so it is

probable that glycosuria and the accompanying symptoms of diabetes mellitus are produced by several pathological conditions.

Lancereaux ([82]) recognises three varieties of diabetes—(1) Traumatic or spontaneous diabetes through lesion of the nervous system; (2) diabetes with wasting, or pancreatic diabetes; (3) diabetes with obesity, or constitutional diabetes. Diabetes with wasting, however, is not always associated with pancreatic disease. Lépine ([84]) has pointed out that the pancreas may be normal in diabetes with wasting, and he has found this gland diseased in diabetes with obesity. And in the cases recorded above, 18, 19, 20, 22, and 23, there was marked wasting, and yet the pancreas was of normal weight and appearance.

Hoppe-Seyler ([81]), Fleiner ([90]), and others have recorded cases of diabetes associated with pancreatic disease and arterio-sclerosis. In these cases it appeared probable that arterio-sclerosis of the pancreatic arteries was the cause of the affection of the pancreas, and therefore indirectly of the diabetes.

F. Relation between Diabetes Mellitus and Arterio-sclerosis.

Diabetes and arterio-sclerosis are both diseases most commonly met with after the age of 45. It is not surprising, therefore, that the two affections should be frequently associated in elderly people. But not infrequently diabetics under middle age present marked signs of arterial sclerosis, and it seems probable that in some cases there is an indirect connection between the two diseases.

Grube ([46]) of Neuenahr found arterio-sclerosis present in sixty-three out of 137 male patients, and in three out of forty female patients. But the majority of his patients were over the age of 45, and most of them suffered from the milder forms of the disease.

In a case of diabetes in a male æt. 52, with very advanced atheroma of the arteries, I had the opportunity of making an autopsy some time ago. Apart from the tubercular lung mischief (which had developed late in the disease), the most striking pathological condition was the very advanced atheroma of the arteries in almost all parts of the body. Many of the arteries were calcified, and many of their small branches ramifying in the muscles were markedly atheromatous and rigid. I have never seen a case which has presented more extensive atheroma

of the arteries on post-mortem examination. Definite symptoms of diabetes had been present during the last eleven months of life only, whilst the arterial changes were evidently of much longer standing. In this case it is by no means improbable (though not capable of proof) that the arterial disease was the starting-point of the diabetes, possibly through secondary changes in the pancreas, since cirrhosis of that organ was present.

Frerichs ([47]) drew attention to the frequency of arterial changes in chronic forms of diabetes, especially when associated with gout, and thought that probably some connection existed between diabetes and the arterial changes. Other writers (Perraro, Laache, Grube, Fleiner) also regard arterio-sclerosis as a cause of diabetes in certain cases.

It is conceivable that arterio-sclerosis may cause diabetes by producing changes in the pancreas or in the nervous system (medulla).

Hoppe-Seyler ([48]) records an instructive case of diabetes mellitus, in which post-mortem examination showed that the pancreas was transformed into a mass of adipose tissue. Microscopically, it was found to consist chiefly of fat, with small scattered islands of degenerated pancreatic tissue. There was atheroma of the aorta, and the cœliac, gastro-duodenal, and splenic arteries, especially the latter, were markedly calcified. Also the smallest branches of the splenic artery entering the pancreatic substance were thickened. Hoppe-Seyler attributes diabetes in this case to the pancreatic changes, and believes that these were produced by arterial sclerosis.

Fleiner ([49]) has also recorded a case of cirrhosis of the pancreas, apparently the result of marked arterio-sclerosis.

Arterio-sclerosis often produces cirrhosis of the kidney; myocarditis may follow arterio-sclerosis of the coronary arteries; also valvular lesions of the heart, and various cerebral affections may be produced by the same arterial changes. Hence it is quite conceivable that arterio-sclerosis may occasionally lead to cirrhosis, or other lesions of the pancreas.

When the changes produced in the pancreas by arterio-sclerosis only affect a portion of the gland, then the remaining normal gland tissue may be sufficient to prevent the occurrence of diabetes; but when the whole of the gland is affected, it is probable that diabetes will follow.

Fleiner thinks that a great number of the milder forms of

diabetes in elderly persons are probably indirectly due to arterio-sclerosis.

G. Diabetes of Endogenous Origin.

In many cases of diabetes, the most careful inquiry into the previous history of the patient fails to reveal indications of any external exciting cause. There is often no history of injury, mental shock or anxiety, over-work, alcoholism, syphilis, heredity, or any of the supposed exciting causes of the disease which have been already referred to. In 100 cases at the Manchester Royal Infirmary, there was no history of *any* of the so-called exciting causes in fifteen at least. It is quite possible, as has been pointed out by Strümpell and others, that some cases are entirely or almost entirely of endogenous origin, *i.e.* they are due to some developmental abnormality; and in most of the cases which appear to be due to the above-mentioned causes, it is probable that there is an endogenous in addition to the exogenous factor (or external exciting cause) in the production of the disease. In very many cases in which a history of some supposed exciting cause is given, it is difficult to say whether this has really played any part in the production of the disease. Sometimes the most careful examination of the brain, pancreas, liver, or other organs fails to reveal any pathological change, or any change to which importance can be attached, and there is also no history of any of the supposed exciting causes. Such cases show how very meagre is our knowledge respecting the origin of the disease, in spite of the enormous mass of literature which exists in relation to this subject.

Etiology of Diabetes.

In 100 consecutive cases of diabetes, I have made careful inquiries with respect to the usual etiological factors, with the following results:—

Heredity: other members of family affected .	in 13 cases.
History of marked mental worry, anxiety, mental shock	„ 10 „
Mental anxiety and over-work, etc., connected with the nursing of a sick relative for a long period	„ 8 „

Disease associated with acromegaly . .	in 2 cases.
„ followed overwork	„ 5 „
„ „ external injury . . .	„ 6 „
History of great alcoholic excess . . .	„ 17 „
Definite history of syphilis	„ 6 „
Disease followed soon after pregnancy, miscarriage, or abscess of breast . . .	„ 7 „
Disease developed directly after influenza .	„ 8 „
„ „ directly after an acute	
„ „ pleurisy	„ 2 „
„ „ directly after pneumonia .	„ 1 „
„ „ during an attack of nasal catarrh and bronchitis	„ 3 „
Patient exceedingly stout before diabetes developed	„ 4 „
Very sudden onset of thirst—exact time given	„ 9 „
No history of any definite exciting cause .	„ 15 „
„ „ gout obtained in any of the cases.	

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CHAPTER IX.

SYMPTOMATOLOGY.

The Appearance of the Patient.

There are two well-marked forms of diabetes, the severe and the mild, besides intermediate varieties; and the appearance of the patient generally differs in the two forms of the disease. In well-marked examples of the severe form the patients are very often under middle age; frequently they are young persons; they are thin, they have lost flesh, sometimes to a very great extent, and the skin is dry and harsh. The appearance of the face is sunk and wasted, and yet the facial expression differs from that of other diseases associated with great wasting, such as phthisis and malignant disease. In the severe forms of diabetes, the wrinkles of the face, about the mouth, are often well-marked; the naso-labial fold is deep or sharply defined, and it is frequently prolonged downwards, well round the angle of the mouth. Sometimes the face is pale; but there is rarely any marked anæmia, unless the disease be complicated with tuberculosis. In other cases, a very slight degree of congestion or cyanosis is observed about the tip of the nose, the cheeks, and the lips; and sometimes the conjunctivæ appear abnormally moist. Though the face is wasted, there is not the great anæmia of advanced phthisis. The lips are not anæmic, and the pink flush of the cheek and the refined delicate expression of the face, so common in phthisis, are absent in the diabetic; also the earthy cachetic appearance of the face of malignant disease is absent. Patients suffering from the severe form of diabetes often look older than their years, and the appearance of the face is frequently suggestive of nervousness, anxiety, or grief (1). The face in many cases of the severe form of diabetes may be briefly described as anxious or sad, *wasted*, but not *anæmic*, or not markedly anæmic. To define the facial

expression in diabetes of the severe type is difficult, yet I am inclined to think there is often something peculiar in the appearance of these cases. Whether this is so or not, on seeing the new cases admitted to the wards of the Manchester Royal Infirmary, the facial expression has on several occasions caused a diagnosis of diabetes to flash across my mind before any questions had been asked, and examination has proved the suspicion to be correct.

The facial appearance above described is not always observed, even in severe cases of diabetes; and in the mild forms of the disease the patient is often well nourished, sometimes very stout, and the facial expression is not in the least characteristic. In these cases, though the patient is still well nourished, or even stout, on inquiry we often find that there has nevertheless been considerable loss of flesh.

In the severe cases with wasting there is often very great loss of weight, and Saundby points out that there are often marked and sudden fluctuations in the weight.

In any case of marked wasting in a young person, or of great obesity, especially in an old person, an examination of the urine for sugar should never be omitted.

Hanot and others have described a rare form of diabetes, associated with pigmentation of the skin and hypertrophy of the liver. The pigmentation is most marked on the face, limbs, and genital organs. To this peculiar form Hanot has given the name of *diabète bronzé*. It is described on p. 308.

Onset of Diabetes.

The patient sometimes first seeks medical advice on account of loss of flesh, or of gradually increasing weakness. Pains in the legs, especially cramps in the calf muscles, are sometimes the earliest signs of the disease which attract attention. In many cases, increase in the quantity of urine is the first symptom the patient notices. He finds that he has to get up during the night to micturate, whilst previously he had always been able to sleep undisturbed. But in the majority of cases great thirst is the first symptom, and it is a curious fact that sometimes the thirst comes on very *suddenly*. The patient may be able to state the date on which the thirst commenced, often the time of the day, or the exact hour. (Nine out 100 cases, see p. 159.)

Thus a most intelligent patient stated that the thirst commenced on September the 24th, in the afternoon. Another diabetic stated that the thirst commenced suddenly one night at 12 o'clock, whilst he was engaged on night duty at his work. In a third case, it began suddenly in the evening, whilst the patient was working unusually late. In a fourth, it began suddenly between 8 and 9 o'clock in the morning. In two other cases, the thirst came on very suddenly after drinking a glass of beer.

A diabetic patient recently told me that he had been perfectly well until one evening when he took a great quantity of beer; he was carried to bed intoxicated, and next morning on awaking he experienced a most intense thirst, which he has never been able to quench since.

Another diabetic stated that he had gone to bed quite well one evening, but next morning the "legs had shrunk," the "flesh had shrunk," and he experienced an intense thirst, which he was quite certain had not been present the day previously. The thirst persisted ever afterwards, and the patient suffered from a very severe form of the disease.

Sometimes, especially in the mild forms of the disease, the patient first comes under treatment on account of some of the complications of diabetes, such as soft cataract, carbuncle, gangrene, irritation about the genitals, eczema of the vulva, or skin diseases of various kinds. Occasionally diabetic patients first seek advice on account of nervous depression, failure of health, loss of strength, and inability to perform their daily duties, the diuresis or thirst not having attracted their attention. These symptoms have often followed mental shock, or great anxiety, or occasionally some bodily injury (see p. 107). In the former cases, the state of nervous excitement or mental depression has persisted for some time, and, on examination of the urine, sugar has been detected.

One of my patients first consulted me on account of a soreness of the throat and a salty taste in the mouth. Two weeks previously, immediately after drinking half a glass of beer, he had experienced a salty taste in the mouth, and this had continued ever since, and the throat had become dry. On examination of the urine, I found he was suffering from a severe form of diabetes.

In certain cases the urine has contained sugar in small

quantities, or there has been a temporary glycosuria months or years previous to the onset of severe diabetic symptoms. Loeb (2) has recently drawn attention to this point. In one of his cases, the urine contained 5·3 per cent. of sugar, the specific gravity was 1038, and there was a history of thirst of only fourteen days' duration. But he happened to have examined the urine two years previously, whilst the patient was suffering from an attack of intercostal neuralgia. At that time 0·25 per cent. of sugar was present, but this had disappeared at the end of nine months. Hence, long before the well-marked symptoms of diabetes had developed, there was a diminished power of utilising carbohydrates in the system, and slight temporary glycosuria as a result. In a second case of diabetes, the urine contained 7·9 per cent. of sugar, and had a specific gravity of 1042. The patient stated definitely that symptoms of the disease had been present for four weeks only. But Loeb happened to have made an examination of the urine five months previously, and at that time had found traces of sugar present. In a third case of diabetes, the urine contained 4 per cent. of sugar. Loeb had found traces of sugar in the urine two years and a quarter previously. Several similar cases have come under my own observation.

On the other hand, it has also been clearly shown that diabetes in its severe form is *not* always preceded by slight glycosuria. Thus, Wallach (3) records a case of acute diabetes in which the urine of the patient happened to have been examined chemically a little more than five weeks before death. No sugar was present at that time; but after an attack of bronchial catarrh, diabetes developed suddenly, and terminated fatally five weeks after the urine had been examined.

The Urine.

Quantity.—An increase in the amount of urine passed is often the most obvious sign of diabetes; and diuresis, and especially the necessity for micturition during the night, are frequently the first symptoms which attract the patient's attention to the disease. The daily quantity of urine varies considerably, according to the severity of the case. The amount may be 100, 150, or 300 oz. in the twenty-four hours. It has been known to reach 640 oz., but in most cases the daily

quantity is between 100 and 300 oz. In many of the mild cases, in old stout persons, the increase is not great (60 to 100 oz.), and in the mildest cases (chronic glycosuria) the urine is often normal in quantity. Then again, in some of the severe cases with marked wasting, which have had a very rapid course, I have often found that the amount has not been more than 90 or 100 oz.

In most cases, but not in all, the night urine is less than the day urine (whilst the opposite condition is met with in granular kidney).

Generally the amount of urine increases with the percentage of sugar which it contains. The more sugar is excreted, the greater the quantity of urine, and *vice versâ*.

This is well shown by the following figures from a case in which the sugar and urine were very carefully estimated:—

Date.	Daily Amount of Urine.	Daily Amount of Sugar.	Remarks.
	Oz.	Grs.	
June 1	230	4600	Ordinary diet.
,, 2	240	4800	
,, 3	200	4200	
,, 4	150	2850	Very rigid nitrogenous and fatty diet.
,, 5	112	1792	
,, 6	150	1800	
,, 7	150	2400	
,, 8	159	1908	
,, 9	188	3384	Ordinary diet.
,, 10	258	5676	
,, 11	220	4840	
,, 12	220	4400	

But, as v. Noorden points out, there are exceptions to these general rules, and the amounts of sugar and urine do not always run parallel.

As the glycosuria increases, the amount of urine also increases, but at a slower pace; hence the urines which are greatest in quantity have generally the highest percentage of sugar. The urine may sometimes increase in quantity, however, without the amount of sugar increasing, and again the urine may diminish without a corresponding diminution of sugar taking place. As Külz points out, two patients may excrete the same amount of sugar, and very different quantities of urine.

The amount of urine is about equal to the quantity of fluid taken. It is reduced by a rigid diet of nitrogenous food; it is

also reduced by an intercurrent disease, as, for example, by any febrile affection; and it often diminishes just before a fatal termination. There is frequently a diminution of urine just before the onset of diabetic coma; and I have often noticed, when phthisis has developed as a complication, that towards the termination of life the whole clinical aspect of the illness has changed, the thirst has entirely disappeared, and the quantity of urine has become quite normal. The spontaneous diminution of thirst and diuresis, in an advanced case, is therefore by no means a favourable sign, though it is very pleasing to the patient. Apart from this final diminution, in some cases, from time to time, there is a temporary return of the urine to the normal quantity. Naturally, the amount of urine is less if diarrhœa be present.

The *colour* of the urine is very pale—generally light yellow or straw-coloured. Very often it has a slight pale *greenish-yellow* tint. This greenish tint I have never noticed in any other disease; it may be detected best by placing the urine glass on a sheet of white paper, and looking down from above; it is not always present, however, even in severe cases. Diabetic urine is bright and clear, and froths in the urine vessel more than normal urine.

When the quantity of urine excreted is not increased, or is only a little increased, then the colour and appearance may be those of normal urine. A normal colour generally indicates a mild form of the disease; also I have often observed a pale diabetic urine to become darker, almost normal in tint, as fatal coma has developed. In one case I noticed a slight pinkish tinge of the urine during coma, and yet it contained no blood pigment, and no deposit of urates (see p. 142).

When a mucous cloud is present in diabetic urine, it is frequently seen, not at the bottom, but at the *upper* part of the urine glass.

On standing, diabetic urine speedily becomes opalescent, owing to the rapid development of yeast spores and other fungi.

Sometimes cases of glycosuria are met with in which frequent micturition is a troublesome symptom, and yet, when the total twenty-four hours' urine is collected, it is found that it is not above normal; the frequent micturition being due to the irritation of the mucous membrane of the bladder by the saccharine urine.

The *odour*.—Diabetic urine has often a peculiar sweet or aromatic smell, and when coma occurs, or when this termination is threatening, generally the urine has a peculiar sweet or chloroform-like smell—a smell supposed to be due to acetone.

The *taste* of the urine was formerly frequently noted in diabetes. As Willis pointed out long ago, it is "wonderfully sweet, as it were imbued with honey or sugar."

The *reaction* is usually acid. It is often strongly acid, and the acidity increases at the onset of diabetic coma. When allowed to stand, diabetic urine remains acid for many days, and it may even increase in acidity, owing to the development of lactic acid by fermentation.

The *specific gravity* is increased. It generally ranges between 1030 and 1045 or 1050; sometimes it is even higher still. In any urine which is clear and *not high coloured*, if the specific gravity be over 1025, there is the strongest probability that sugar will be present. Whilst the specific gravity is raised if a large quantity of sugar be present, we cannot conclude, if it be low, that sugar will be absent. Urines are sometimes met with in which the specific gravity is low, and yet a small amount of sugar is present.

The specific gravity corresponds broadly to the amount of sugar present, and is higher the greater the percentage of sugar, and *vice versâ*; but to this general rule there are many exceptions. A high specific gravity must not be regarded as a *proof* of the presence of sugar, nor as an exact measure of the percentage of sugar, since it depends not only on sugar, but on the urea and other solids of the urine. A high-coloured urine has often a high specific gravity, though sugar is absent.

The *presence of sugar* is, of course, the most important change in the urine in diabetes. Sometimes before the patient has noticed any symptoms of the disease, he has been struck by the fact that flies have been attracted to his urine. This has been due to the sugar which it contained. In other cases the patient has noticed that if a drop of urine has fallen on his boot, or on to any adjacent object, and has been allowed to dry, a white salt-like deposit has been left.

The sugar present in diabetic urine is grape sugar (glucose, dextrose). The percentage varies according to the nature of the case, from 0·5 up to 8 or 12. The daily quantity of sugar excreted also varies. It is often 3000 to 4000 grs. in the

twenty-four hours, but may rise up to 12 or even 25 oz. It has been stated to have reached $2\frac{1}{2}$ lb. in the twenty-four hours. On the other hand, it may fall to 1 oz. daily.

Besides dextrose, lævulose and other forms of sugar are occasionally met with in the diabetic urine: but Seegen states that the presence of lævulose in the urine, with or without dextrose, is exceedingly rare; he has found it only once in 1000 cases.

To estimate the amount of sugar, the total quantity of urine for the twenty-four hours must be collected and mixed well, and then a sample submitted to examination.

The sugar increases, in the mild cases, after food, and diminishes during fasting; and hence during the night the sugar excretion is at its lowest. Külz has shown that in mild cases the sugar excretion reaches its highest level between two and three hours after a meal.

In very mild cases, sugar may be absent or greatly diminished in the urine which has collected in the bladder during the night, *i.e.* in the urine passed early before breakfast.

The sugar excretion is increased by starchy or saccharine food, and diminished by nitrogenous diet. Hence, in comparing the severity of two cases, or of the same case at different periods of the disease, it is of importance to know the exact diet, as a small amount of sugar, when the patient is on a nitrogenous diet, is of much graver import than a large amount when the patient is on a mixed diet.

The two well-marked types of diabetes, the *mild* and the *severe* forms, present points of difference with respect to sugar excretion.

In the *mild* cases, when carbohydrates are withdrawn from the diet, the sugar disappears in a few days, and only when carbohydrates are added again does sugar reappear in the urine. In some cases *complete* withdrawal of carbohydrates is necessary to cause the sugar to disappear entirely from the urine, but other patients can take a *small* quantity of carbohydrates without the glycosuria returning. In testing the tolerance in these cases, a diet practically free from carbohydrates is given; and when sugar has disappeared from the urine, a little bread is allowed, and this is gradually increased, the quantity being accurately noted, until glycosuria reappears. The amount of bread added is an indication of the tolerance for carbohydrates. It often varies from time to time.

These are points of practical importance with respect to the examination of the urine in mild cases of diabetes, and especially in the examination of the urine in cases of life assurance. If the sample be taken from the morning urine, just before breakfast, it may be free from sugar, and yet the patient may suffer from glycosuria. Also, before testing the urine, it ought to be known whether the diet is mixed or entirely nitrogenous, as the latter diet may have caused a glycosuria to disappear. If the urine passed two or three hours after a meal of mixed diet be free from sugar, then glycosuria of any degree may be excluded.

In the *severe* cases of diabetes sugar is present in the urine, in spite of the withdrawal of all carbohydrate food. In some cases, when the patient is taking a restricted diet, containing, however, a large quantity of flesh meat (1000 grms. daily), sugar is present in the urine; but when the flesh meat is reduced to 500 grms., the glycosuria disappears (v. Noorden).

When a diet is prescribed free from carbohydrates, the amount of sugar remaining in the urine is a measure of the severity of the disease. In severe cases, sugar is present in the urine even during fasting. Schmitz (4) points out that in the severe forms the night urine (*i.e.* that passed early in the morning before breakfast) may contain the greatest amount of sugar (see p. 307).

In the mild forms of diabetes only the sugar derived from the food appears in the urine; in the severe cases sugar appears to be formed from albuminous bodies in the system.

Influence of food on sugar excretion.—No case is so severe that no portion of the carbohydrates of the food is burnt up in the system; but some carbohydrates are utilised better than others. Grape sugar (dextrose) is the carbohydrate which causes sugar to be eliminated in the greatest quantity in the urine; whilst starch and other carbohydrates are less injurious. Fruit sugar (lævulose) is only about half as injurious as grape sugar; milk sugar and cane sugar stand intermediate between grape sugar and lævulose. Fats never increase the sugar excretion, either in human diabetes, or in the pancreatic diabetes, or phloridzin diabetes of animals. Alcohol in moderate quantity does not increase the amount of sugar in the urine.

Muscular exercise diminishes the sugar excretion in well-nourished patients at an early stage of the disease; the sugar

being apparently burnt up in the muscles; and Finkler (5) has shown that massage has the same action. But in other cases, when the patient is wasted and the disease chronic, exercise increases the sugar excretion (Külz).

It has been pointed out that mental shock, etc., may act as an exciting cause of the disease; clinical experience also shows that cases of diabetes are made worse, and the sugar excretion greatly increased, by nervous excitement, mental worry, etc. The sugar excretion is increased by a long journey, and after admission to a hospital, frequently it is higher on the first day than a few days later. Gastro-intestinal symptoms, loss of appetite, and diarrhœa cause a diminution of the glycosuria.

Diminution or arrest of sugar excretion by intercurrent affection.—It has long been known that the sugar excretion may be diminished or entirely checked by certain intercurrent diseases.

(*a*) *Febrile affections* often have this effect, as, for example, typhoid fever, pneumonia, influenza, and chronic febrile conditions. Thus, in a case of diabetes of the mild form, in a very stout elderly woman at the Manchester Royal Infirmary, the sugar disappeared from the urine during an attack of influenza, to the great delight of the patient, but returned again when the symptoms of influenza subsided.

(*b*) When *phthisis* occurs as a complication of diabetes, the sugar excretion often diminishes, and sometimes ceases entirely for a short time before death (see cases on p. 211).

(*c*) When *ascites*, due to cirrhosis of the liver, is present in diabetic patients, sugar sometimes disappears from the urine.

Pusinelli (6) records an instructive case of diabetes associated with cirrhosis of the liver. The amount of sugar in the urine was from 2 to 5 per cent.; but when ascites developed, the glycosuria entirely ceased. After paracentesis for the fourth time, the ascites disappeared, and then glycosuria returned. Two and a half years later the ascites reappeared, and then the glycosuria diminished.

(*d*) During an attack of *gout*, sugar may disappear from the urine.

(*e*) Also during an attack of *jaundice*, the sugar has been known to disappear.

(*f*) When *granular kidney* is associated with diabetes

mellitus, at the terminal stage the sugar excretion may entirely cease (see p. 218).

(*g*) *Pneumaturia*, an exceedingly rare complication in diabetes mellitus, may cause the glycosuria to disappear. Both in diabetic and non-diabetic patients, pneumaturia may be due to the entrance of air into the bladder from the intestine, owing to a fistulous connection between the two. In these cases, if the patient be diabetic, the sugar is still present. But pneumaturia is occasionally the result of the decomposition of sugar in the bladder, owing to the presence of micro-organisms or yeast fungi. In such cases the sugar disappears from the urine, and gases (carbonic acid, hydrogen, and carburetted hydrogen) are formed in the bladder.

(*h*) In *diabetic coma*, often the amount of sugar diminishes considerably.

It is important to bear in mind that a diminution of the thirst, diuresis, and sugar excretion is not necessarily a favourable sign in the most *severe* forms of diabetes; on the contrary, it is sometimes a serious indication. In such cases, if the general condition is becoming worse, and the weight of the patient diminishing, then the prognosis is bad whatever may be the change in the sugar excretion, diuresis, and thirst. Very often the chart shows a pleasing diminution of sugar and urine, and yet the general condition may be gradually becoming worse. On the other hand, in severe cases at an advanced stage, by a less rigid diet the sugar may be increased, but often the general condition is improved.

Glycogen.—According to Leube ([7]), the urine of diabetic patients contains a small quantity of a substance which gives a dark brown reaction with iodine and iodide of potash, and which is converted into grape sugar by boiling with dilute sulphuric acid. This substance he regards as glycogen. In normal urine, and in the urine of a case of diabetes insipidus, no glycogen was found.

Urea.—The amount of urea in the urine is generally stated to be increased in diabetes. The increase, however, is largely due to the great quantity of nitrogenous food taken. In order to decide whether the diabetic patient excretes more urea than a healthy person, it is necessary to keep both on exactly similar diet. The experiments of Pettenkofer and Voit have shown that, even when fasting, a diabetic patient excreted about 8 per cent.

more urea than a healthy person. When both were on the same medium diet, once the nitrogen excreted was the same in each case, three times it was higher in the diabetic patient. When both were fed on a non-nitrogenous diet, the nitrogen excreted was considerably greater in the case of the healthy person than in the diabetic patient.

Gaethgens also found that diabetics excrete more nitrogen than healthy persons, when both are taking the same diet.

Seegen (8), from his own observations, draws the following conclusions:—(*a*) The urea excretion is increased (but generally not markedly) in almost all cases of diabetes. (*b*) There is no relation between the excretion of urea and sugar. (*c*) The urea excretion is chiefly dependent upon the nitrogen of the food: the richer the diet in nitrogenous matter, the greater is the excretion of urea. In only a few cases is the urea excreted so abundantly that it is necessary to refer its origin to the destruction of albumin of the body.

Leo (9) has shown that carbohydrates diminish the nitrogenous metabolism. In two severe cases of diabetes, the patients were kept for some days on uniform diets, rich in albumin, but containing very little carbohydrate. The nitrogenous excretion was estimated, and, after this had become stationary, a definite quantity of carbohydrates was allowed in addition to the previous diet. The nitrogen in the urine and fæces was again carefully estimated, and the results showed that the nitrogenous excretion in the urine was diminished distinctly when carbohydrates were added to the diet.

Uric acid.—Not infrequently a small deposit of uric acid crystals is seen at the bottom of the urine glass, especially in mild cases of diabetes. Seegen and Pavy both point out that a dark urine and a deposit of uric acid are indications of a mild form of the disease. In the severe cases it is somewhat difficult to estimate the amount of uric acid, since it is dissolved in a very large quantity of fluid, and, as Seegen points out, the usual method of estimation is not satisfactory.

Külz has found that, in the severe cases of diabetes, the uric acid (as estimated by a method of his own) is a little less than the normal quantity.

Ammonia.—In health, according to Hallervorden (10), 0·5 to 1·0 grm. of ammonia is excreted in the urine daily, and on a meat diet the amount may increase to 1·2 or 1·5 grm. (v. Noorden).

In many cases of diabetes, but not in all, the excretion of ammonia is increased, and may equal from 3 to 6 grms. A moderate increase may be present for weeks or months (v. Noorden). In diabetic coma the amount is greatly increased, but the urine has still an acid reaction; and, as Stadelmann [11] points out, since the basic elements are out of proportion to the acids known to us, it is probable that some unusual acid is present in these cases. Stadelmann thought that this acid was crotonic acid; Minkowsky and Külz believed it to be β-oxybutyric acid.

The *kreatine* of the urine is greatly increased in diabetes, owing to the excess of nitrogenous food, and to the increased muscular wasting.

Oxalates.—Sometimes an abundant deposit of oxalate of lime is found in diabetic urine, both in mild and severe cases.

Inorganic salts.—Sodium chloride, the sulphates and phosphates, are increased, owing to the large amount of nitrogenous food and to the great destruction of albuminoids. Many observers [12, 13] have shown that the excretion of lime salts in the urine is increased in diabetes. Recently Teubaum [14] has reinvestigated this point. From the results of his observations on twelve cases, he concludes that in the severe form of the disease the excretion of lime salts is considerably increased, whilst in mild forms the excretion is normal, or only a little above the normal amount.

The proportion of total solids to the water is diminished. Indican is often present in excess.

In diabetic urine generally there is no deposit at the bottom of the urine glass, but, as already mentioned, occasionally there is a deposit of uric acid, or oxalates, or a mixture of mucus and phosphates.

Albuminuria.—Sometimes albumin as well as sugar is found in the urine of diabetic patients. The proportion of such cases is estimated differently by various authors—from 5 to 66 per cent. Schmitz [15] found albuminuria present in 824 out of 1200 diabetic cases. But some authors include in their statistics of albuminuria only those cases in which there is distinct evidence of nephritis; whilst others include all cases in which there is the slightest trace of albumin. Much depends also on the class of cases from which the statistics are drawn.

The albuminuria of diabetes may exist in two forms—(1)

In the most common form only a small quantity or a trace of albumin is detected, and there are no other indications of kidney mischief. (2) In the second form, in addition to the albuminuria, there are other signs of Bright's disease (œdema, headache, albuminuric retinitis, cardio-vascular changes, etc.). There may be all the indications of parenchymatous nephritis, and a large quantity of albumin along with casts may be found in the urine; the albumin may gradually increase, and the sugar gradually diminish, until finally the sugar disappears, and the albumin only remains. In other cases, symptoms of granular kidney are present; the specific gravity of the urine diminishes, and finally the sugar often disappears. The disappearance of the sugar and the change of the general symptoms to those of chronic Bright's disease are grave prognostic signs.

In the second group of cases, the kidneys, on post-mortem examination, present well-marked signs of chronic parenchymatous or interstitial nephritis, but in the first group only slight and microscopical changes are met with. These are described on p. 220.

Bouchard points out that a slight albuminuria is often observed when phthisis occurs as a complication of diabetes. Also in elderly diabetics a small quantity of albumin is not infrequently met with in the urine, and is often accompanied by an excess of uric acid.

In the majority of cases of diabetes met with in hospital practice in Manchester (most of which belong to the severe form of the disease, accompanied by marked wasting), not a trace of albumin can be found in the urine when the patient comes under treatment, but, as the disease advances, albumin appears. At first only the slightest trace can be detected, but in time the amount of albumin often increases a little; it nearly always remains small in quantity, however, and other indications of nephritis do not develop. This small quantity of albumin often disappears and reappears. In the last stage of these severe cases, a trace or small quantity of albumin is nearly always present.

A large amount of albumin and other indications of nephritis are not common in cases of diabetes seen in hospitals, but in private practice, where many cases of the mild form of diabetes in elderly people are met with, this complication is more frequent.

Albuminuria in 100 *Cases of Diabetes.*

(Mostly hospital patients, suffering from a severe form of the disease, and often at an advanced stage.)

	Cases.	Remarks.
Albumin absent when urine first examined in	70	In fourteen of these a trace of albumin appeared at a later date.
Small quantity or a mere trace of albumin in	26	Seven of these were at a very advanced stage; one was comatose when first examined. In two the albumin disappeared at a later date.
Large or considerable quantity of albumin in	4	
	100	
Albumin present in 30 per cent. of patients when first examined. ,, ,, 42 per cent. at a later stage.		

In ninety-six of the hundred cases there were no indications of nephritis or organic disease of the kidney.

With respect to the traces of albumin, it is well to bear in mind that not infrequently the saccharine urine gives rise to irritation of the prepuce, and balanitis results; and in the female, inflammation of the vulva may arise from the same cause. A little purulent discharge becomes mixed with the urine in either case, and occasionally this is the cause of a trace of albumin in diabetic urine; but no doubt in many cases the albumin is of renal origin.

In all the cases of diabetic coma which I have examined, the urine has contained a trace or small quantity of albumin (see p. 285), and Maguire ([16]) states that albuminuria is *always* present in diabetic coma. The urine may be quite free from albumin shortly before the onset of coma. Sometimes the appearance of albumin is the forerunner of coma; but, on the other hand, a trace of albumin is often present for a long period, and coma may never develop, and the patient may die of phthisis or some complication.

Casts.—With the exception of the cases in which diabetes is complicated by parenchymatous or interstitial nephritis, casts are not usually detected in the urine, even in the severe forms

when a trace or small quantity of albumin is present. But when diabetic coma occurs, as Külz ([17, 18]) has pointed out, an abundant deposit of casts is met with. In these cases the urine is often slightly turbid when first passed, from the presence of minute floating particles. On standing, a greyish-white sediment is deposited at the bottom of the urine glass, and if a little be examined under the microscope, it is found to consist of enormous numbers of casts. Often a remarkable appearance is presented, the whole field of the microscope being crowded with tube-casts. The casts are granular or hyaline, studded with fine granules. It is important to watch the urine in advanced or severe cases of diabetes for the appearance of this greyish-white or flocculent deposit. It has been already pointed out that there is occasionally a deposit of mucus and phosphates in diabetic urine; but usually it does not sink quite to the bottom of the urine glass. The deposit of casts, however, lies exactly at the bottom of the glass, it is more of a greyish colour, and more opaque than the mucus deposit. If a deposit should appear in the urine in severe or advanced diabetes, it ought to be examined carefully for casts; when detected they are generally, though not invariably, a sign of approaching coma (see p. 285).

Diabetic urine, when allowed to stand, soon becomes opalescent, owing to the development of yeast fungi; and when kept for some time a white deposit may form, which, under the microscope, is found to consist of fungus spores. But occasionally, even when recently passed, the urine contains fungus spores and mycelia with a few pus cells and epithelial scales. As will be mentioned on p. 224, in diabetes sometimes an inflammation of the prepuce in the male, or of the vulva in the female, is produced by the constant irritation of saccharine urine. In these cases there is often a growth of fungus on the inflamed mucous membranes of the genital organs, and from these inflamed parts, fungus spores and mycelia, pus cells and epithelial scales may be washed away, and give rise to a slight deposit or turbidity in the urine.

Thus, in a case of diabetes of four years' duration, the urine, when recently passed, presented a slight turbidity, and numerous flocculent masses were seen suspended in it. Under the microscope I found these flocculent masses to consist of epithelial scales, a few pus cells, fungus spores, and mycelia. The urine gave the very slightest reaction for albumin. An examination

of the genital organs revealed œdema of the prepuce and penis, with marked phimosis and balanitis. The end of the prepuce was much inflamed, and coated with a number of white patches. When scraped away and examined microscopically, these white patches were seen to consist of epithelial scales, mixed with fungus spores and mycelia. The epithelial scales, fungus spores, and mycelia in the urine had evidently been washed away from the penis.

In another case (a youth of 19) the recently passed urine contained a small white sediment. On examination microscopically, I found it to consist of epithelial squames, with fungus spores and mycelia. This patient was suffering from balanitis, and on the mucous membrane of the glans penis a few white patches were seen; when scraped away and examined microscopically, they were found to consist of epithelial squames, pus cells, fungus spores, and mycelia. The fungus spores and mycelia in the urine were evidently derived from these patches.

In a third case a diabetic urine was slightly turbid and a trace of albumin was present. Microscopical examination revealed the presence of a considerable number of pus cells and epithelial scales. On examination of the penis, a slight balanitis was found, and there were a few white patches on the glans penis. By strict cleanliness the balanitis disappeared in a few days, and the urine became quite free from turbidity and albumin.

I have sometimes found the urine of female diabetic patients slightly turbid, owing to the presence of numerous epithelial and pus cells. In these cases there has been great irritation of the vulva by the saccharine urine.

Gerhardt's reaction; brownish-red coloration with perchloride of iron; diacetic acid.—In the severe forms of diabetes, especially in young patients, or in patients who are markedly wasted, the urine often gives a dark brownish-red coloration with a solution of perchloride of iron. In these cases a few drops of the liquor ferri perchloridi (B.P.) added to the diabetic urine, generally causes a slight white precipitate of phosphates at first, which disappears on adding a little more of the perchloride solution, whilst the fluid becomes of a dark brownish-red or Bordeaux-red colour (Burgundy wine colour). The coloration is usually attributed to the presence of diacetic acid. On this point there is a little difference of opinion, however, and some authors believe that it is not due to diacetic acid, but to the presence

of an organic compound closely allied to it. The exact cause of the perchloride of iron reaction is fully discussed by Macmunn in his work on the "Clinical Chemistry of Urine" (19).

Salkowski could not obtain the perchloride of iron reaction in the ether extract from the urine, but could do so in the ether extract when (for a control experiment) diacetic acid was added to normal urine.

The urine has frequently a peculiar smell resembling chloroform — the so-called acetone smell — when the reaction with perchloride of iron is obtained.

It is often stated that if the urine be boiled before the perchloride of iron solution is added, then no reaction occurs; also that the colour produced by perchloride of iron disappears on boiling. But boiling for a few minutes is not sufficient. In many cases which I have examined, I have found, after vigorous boiling for *several minutes*, that the urine gave a much fainter reaction when perchloride of iron was added, but a slight brown colour was still obtained. Also by vigorously boiling the urine, for a few minutes only, *after* the perchloride of iron has been added, I have found that the dark brown colour diminishes, but does not entirely disappear. For the detection of diacetic acid in the urine, v. Jaksch (20) gives the following process:—

"To the urine a fairly concentrated solution of perchloride of iron is cautiously added, and if a phosphatic precipitate forms, this is removed by filtration and more of the perchloride of iron solution supplied. If the Bordeaux-red coloration appears, one portion of the urine is boiled, whilst another is treated with sulphuric acid and extracted with ether. If, now, the urine which has been boiled shows little or no change, whilst the perchloride of iron reaction in the ethereal extract is no longer evident after twenty-four to forty-eight hours; and if at the same time (on testing the urine directly and its distillate) it is found to be rich in acetone, the condition may be inferred to be that of diaceturia."

This coloration with perchloride of iron is not found in all cases of diabetes; it is not present in all severe cases, but it is present in a large proportion of such cases at a late period of the disease; whilst in the mild form of diabetes, and in the earlier stages of the severe form, it is generally absent. It is usually, though not invariably, associated with marked constipation. The reaction is always an indication of a severe

form of the disease, and in cases in which it is obtained it is important that the diet should not be too rigid, *i.e.* that carbohydrates should not be excluded entirely. If this be done there is considerable risk of diabetic coma developing. The reaction with perchloride of iron often varies very much from time to time. In severe forms of diabetes, when phthisis has developed as a complication, sometimes the sugar excretion finally ceases, and a reaction with perchloride of iron can no longer be obtained. In diabetic coma the urine generally gives the reaction with perchloride of iron, but not invariably. I have often found that the reaction has become more and more marked for a few days before the onset of coma, but when the comatose symptoms have developed the reaction has become a little less marked.

This brown-red coloration with perchloride of iron is occasionally met with in other diseases besides diabetes, though such cases are rare. It has been observed sometimes in febrile affections, and in acute diseases, in measles, scarlet fever, pneumonia, etc. It has also been met with occasionally in cases of cancer of the stomach, and cancer of other organs, in Bright's disease, perityphlitis, strangulated hernia, hysterical anorexia with vomiting, and, according to Dreschfeld, occasionally in Graves' disease. A similar coloration is obtained with β-oxybutyric acid. The urine of patients who are taking salicylic acid, salicylate of soda, or salol, contains salicyluric acid and gives a purplish-brown coloration with perchloride of iron. This resembles somewhat the above mentioned brownish-red coloration obtained in diabetic urine, and often it is inferred that the urine of these patients contains diacetic acid. But if the coloration be carefully noted, a difference will be readily detected by the naked eye; that given by perchloride of iron in the urine of patients taking sodium salicylate has much more of a violet or purple tint, that given with diabetic urine has more of a brownish colour. The difference in tint is very marked if the contents of the test tube be placed in a urine glass, and well diluted with water in each case.

A coloration resembling Gerhardt's reaction is obtained with perchloride of iron in the urine of patients taking other drugs—antipyrin, thalline, phenocoll, salipyrin.

Acetone.—Urine which contains diacetic acid, or which gives a brownish-red coloration with perchloride of iron, generally

contains a considerable amount of acetone also. The following are the chief clinical tests for this substance:—

Legal's test.—To several c.c. of urine in a test tube a few drops of a concentrated, freshly made solution of sodium nitroprusside are added. The mixture is then made alkaline with liquor potassæ. A red coloration is produced which soon disappears; but when a little acetic acid is added, a deep violet-red coloration is the result, if acetone be present. If acetone be absent, the urine has its usual yellow colour after adding the acetic acid.

Le Nobel's test is also useful ([21]). To an ounce of urine add a drachm or two of a solution of nitroprusside of sodium (5 grs. to the ounce), and then a few drops of liquor ammoniæ; dilute with water, and allow to stand. After a short time a pinkish violet coloration will develop.

The production of *iodoform* from the distillate of the urine is the most delicate test for acetone. About half a litre of urine is placed in a retort and distilled, a little dilute phosphoric acid being added to prevent too great effervescence of the liquid. (The reaction may also be obtained from a few ounces of urine.) To about 20 c.c. of the distillate a few drops of a solution of iodine in potassium iodide are added, and a few drops of a solution of caustic potash. When acetone is present, a precipitate of iodoform will occur. It is light yellow in colour, and has the characteristic smell of iodoform, which can be detected readily. Under the microscope this precipitate is seen to consist of hexagonal plates, or stars or rosettes of the hexagonal system.

Other substances in the urine, such as alcohol and lactic acid, give a similar reaction, however.

Ralfe has proposed the following test for acetone:—Dissolve 4 drms. of potassium iodide in 1 oz. of liquor potassæ. Place 1 drm. of this solution in a test tube, and boil. Then very carefully add a drachm of urine so as to float on the surface of the alkaline iodide solution. At the line of junction a white cloud of phosphates will form, which after a short time will become yellow if acetone be present. The feathery phosphates will be seen tipped with yellow points where iodoform is deposited; these after a time fall through the cloud, and deposit at the bottom of the test tube.

v. Noorden ([22]) gives the following method for the quantitative estimation of acetone:—

To 100 c.c. of urine, 1 c.c. of concentrated glacial acetic acid is added, and the mixture distilled until three-fourths of the fluid have passed over. To the distillate five drops of dilute sulphuric acid (25 per cent.) are added. Urea crystals are removed, and after cooling well the fluid is again distilled. To the second distillate caustic potash is added, and then an excess of a solution of iodine in potassium iodide. A precipitate of iodoform forms. This is collected, after six hours, on a weighed filter and washed with distilled water. After the filter and precipitate have become dry, they are placed in an exsiccator with sulphuric acid, and weighed after one and a half to two hours. One grm. of iodoform corresponds to 0·147 grm. of acetone.

The urine and the breath of patients suffering from the severe forms of diabetes have often a peculiar sweet smell—sometimes described as a chloroform smell. This smell resembles that of acetone; and acetone may be detected chemically both in the urine and in the breath in such cases. This acetone smell of breath and urine is generally noticed in diabetic coma. A similar smell of the breath is sometimes met with in febrile affections.

During the last ten years the occurrence of acetone and diacetic acid in the urine (acetonuria and diacetonuria) has been carefully studied by v. Jaksch, Biermer, Hirschfeld, Rosenfeld, and many others. According to v. Jaksch, normal urine contains *minute traces* of acetone. It is very often present in large quantity in diabetic urine, especially in the severe forms of the disease and in diabetic coma. In the mild forms of the disease both acetone and diacetic acid are absent. Acetone is also present in some mental disorders, and in these cases may be the result of a gastro-intestinal auto-intoxication. Acetonuria occurs sometimes in febrile affections, such as typhoid, scarlet fever, measles, in some cases of cancer of the stomach and other organs, in some cases of gastric disorders, and in starvation. It has been attributed to increased albumin destruction in the system, and to fermentative changes in the alimentary canal.

Hirschfeld ([23]) has shown that in healthy persons acetone is excreted in quantity in the urine, if the diet consist only of albuminous and fatty food; but it is at once reduced (to the normal trace) if carbohydrates be added to the diet. The action

of carbohydrates is to spare the destruction of albumins; but a quantity of carbohydrate food, too small to influence the albumin metabolism very much, has a marked action on the acetone excretion. Also, when the destruction of albumin is spared, and the loss of albumin has ceased, owing to the addition of fatty food to a nitrogenous diet, Hirschfeld has found that the abundant acetone excretion still continues. It appears, therefore, that the absence of carbohydrates from the diet is a cause of acetonuria. The acetonuria of fevers, cancer, or gastritis disappears when carbohydrates are taken and assimilated (Hirschfeld).

Rosenfeld ([24]) has shown that if a healthy person be put on an exclusively nitrogenous diet, which is commenced in the morning, then acetonuria occurs by the evening of the second or by the morning of the third day. He found that the acetonuria produced by a flesh diet was removed by the addition of carbohydrates, and he points out, also, that whenever there is great destruction of the albumin of the body, it occurs if carbohydrates be excluded from the food. It is present, for example, in starvation, or when a purely nitrogenous diet is taken. In the mild form of diabetes, acetonuria is only produced by a nitrogenous diet, just as in healthy persons; but in the most severe cases, it occurs in spite of carbohydrates being present in the diet. In severe cases of diabetes there is then a true pathological acetonuria,—an acetonuria which cannot be removed by the addition of carbohydrates to the food,—and often there is also diacetonuria. A strictly nitrogenous diet generally produces acetonuria in healthy persons, but in such cases diacetonuria rarely occurs, and, if present, it is very slight. In diabetic coma, acetone is almost invariably present in the urine; and it has often been observed that, after giving an exclusively nitrogenous diet, in severe cases of diabetes, acetonuria and coma have developed.

According to Hirschfeld, a high degree of acetonuria, or an increase of the acetone in the urine, are indications of approaching coma.

A number of observations, recorded during the last five years, appear to show that, in patients who have shown signs of commencing coma, these symptoms have sometimes been arrested by the addition of a small quantity of carbohydrates to the diet (see p. 329).

β-oxybutyric acid.—This acid is found in the urine in certain cases of diabetes of the severe form, and its presence in considerable quantity (*i.e.* more than several grammes per diem) is of grave prognostic significance. In most of these cases, if the excretion of β-oxybutyric acid continues for a few days or weeks, diabetic coma develops. Though this is the general rule, there are exceptions, and occasionally the acid is excreted for a long period without the development of coma.

According to v. Noorden ([25]), the presence of β-oxybutyric acid may be inferred—

(1) When the amount of sugar indicated by the titration method with Fehling's solution is considerably higher than the estimation by polarisation. Grape sugar rotates the plane of polarised light to the right, oxybutyric acid to the left; hence, when the latter is present, part of the dextro-rotatory power of the grape sugar is neutralised, or, if a great quantity of oxybutyric acid is present, the urine may even rotate the plane of polarised light to the left.

(2) When the urine, after complete fermentation with yeast, rotates the plane of polarised light to the left.

(3) When the urine, after precipitation with basic acetate of lead and ammonia, rotates polarised light to the left. By this treatment the grape sugar is precipitated whilst oxybutyric acid remains in solution and passes over in the filtrate.

v. Noorden points out that positive results with these tests render the presence of oxybutyric acid exceedingly probable. The patient ought not to be taking benzosol, however, since this substance renders the urine levo-rotatory. The presence of lævulose in the urine does not lead to any fallacy, if the second and third tests give a positive result.

In order to detect β-oxybutyric acid with absolute certainty, however, other more complicated methods must be employed.[1]

THE BLOOD.

A drop of blood, obtained by pricking the finger of a diabetic patient, does not generally present any change to the naked eye. It has sometimes appeared to me, however, that diabetic blood was slightly darker in colour than normal blood.

[1] See Minkowski, *Arch. f. exper. Path. u. Pharmakol.*, Leipzig, 1886, Bd. xxi. S. 140; and Külz, *Ztschr. f. Biol.*, München, 1887, Bd. xxiii. S. 321.

Reaction.—The blood is alkaline in diabetes. Even during coma the reaction is distinctly alkaline. Nevertheless, careful estimations by many observers have shown that the alkalinity is diminished in severe forms of diabetes with loss of flesh, whilst it is normal, according to v. Noorden ([26]), when the general condition is good. In cases of diabetes in which oxybutyric acid is present in the urine, and in cases of diabetic coma, the alkalinity of the blood is said to be greatly diminished, and to be lower than in any other disease (v. Noorden). But the reaction of the blood is never acid, and by using litmus test papers containing varying quantities of oxalic acid (specially prepared for determining the alkalinity of the blood, according to the method proposed by Haycraft and myself ([27])), I have always obtained a very decided alkaline reaction, even in diabetic coma shortly before death.

Percentage of water.—According to Leichtenstein and v. Jaksch, the percentage of water in diabetic blood is slightly diminished, and according to the latter author ([28]) the percentage of albumin is increased. But v. Noorden points out that this slight diminution of the percentage of water and increase in that of the solids is not constant; in some cases, the proportion is normal, or there may be even an increase of the percentage of water.

The specific gravity of diabetic blood has been stated to be increased, but James ([29]) has found it to be within the normal limits in ten cases, which he has recently examined (according to Roy's method).

Number of red corpuscles and amount of hæmoglobin.—Many observers have found that in diabetes mellitus both the number of red corpuscles and the amount of hæmoglobin in the blood are often actually greater than normal. Leichtenstein and others have suggested that the cause of this condition is the poverty of the blood in water, and the consequent concentration thereof, owing to the polyuria. James has shown that, in thirteen cases, the red corpuscles were over 6,000,000 per c.mm. in 5; 5,000,000 (*i.e.* normal) in 5; 4,000,000 in 2; 3,000,000 in 1. The hæmoglobin was over 100 per cent. (*i.e.* above normal) in 3; 60 per cent. in 8; 50 per cent. in 2. In these cases the specific gravity, as ascertained by Roy's method, showed no distinct increase, as would have been expected if the increase of blood corpuscles had simply been due to deficiency in the percentage of water.

The following are the results of the enumeration of red blood corpuscles in a few cases of diabetes which I have recently examined, the greatest care being taken to avoid any source of fallacy in the examination :—

	Age.	Form.	Wasting.	Appearance of Face.	Red Corpuscles per C.mm.
Ada O'N. . . .	32	Severe.	Considerable.	Rather pale.	6,730,000
Examination at another date .	...	...	...	...	5,945,000
Robert H. . . .	18	,,	,,	Pale.	5,550,000
Alfred S. . . .	43	,,	Slight.	Not anæmic.	5,760,000
Fred D.	63	Mild.	Very slight.	Sallow, slight jaundice tinge.	6,150,000
Reuben B. . . .	50	Severe.	Slight.	Pale.	4,760,000
James M. . . .	35	,,	Very slight.	Not anæmic.	3,600,000
Patrick M. . . .	42	,,	Slight.	,,	5,160,000
Herbert J. . . .	23	,,	Considerable.	Pale.	5,340,000
Louisa C. . . .	18	,,	Slight, thin girl.	Not anæmic.	5,910,000
Leah S.	55	Mild.	Stout.	,,	5,340,000
Thos. J. . . .	56	Severe.	Very slight.	,,	5,090,000
Edward G. . . .	40	,,	Moderate.	,,	5,180,000
John R. . . .	33	,,	Marked.	,,	5,440,000

The following table shows the number of red blood corpuscles, the percentage of hæmoglobin, and the specific gravity of the blood in fourteen cases of diabetes, examined by James :—

Diabetic Blood.

Red Corpuscles per c.mm.	Hæmoglobin per cent.	Specific Gravity of Blood.
1. 6,730,000	66	1056
2. 6,100,000	61	1059
3. 4,800,000	58	...
4. 5,250,000	60	...
5. 5,600,000	65	...
6. 3,550,000	52	1054
7.	...	1060
8. 5,300,000	75	1056
9. 6,280,000	118	1055
10. 5,380,000	96	1055
11. 5,564,000	112	1056
12. 6,200,000	112	1057
13. 4,460,000	55	1054
14. 6,000,000	96	...

The above figures show that often there is an increase in the number of red corpuscles in diabetes; but this condition is not constant, and sometimes they are diminished. Diabetes mellitus appears to differ, therefore, from many chronic ailments, in the

fact that it is not necessarily associated with any diminution of the number of red corpuscles, the number per cubic millimetre being frequently actually increased. The amount of hæmoglobin is sometimes normal, sometimes diminished, sometimes increased, as shown by the above table. In cases examined at the Manchester Royal Infirmary, it has been sometimes normal and sometimes increased slightly.

Leucocytes.—There is no definite change in the proportion or the number of white corpuscles of the blood in diabetes, but, according to v. Limbeck ([30]), the leucocytosis accompanying digestion is frequently very well marked in severe cases.

Glycogen in the blood.—Gabrischewsky ([31]) has drawn attention to the excess of glycogen, which can be detected by microscopical examination of a cover-glass preparation of the blood in diabetes. A small drop of diabetic blood is placed on a cover-glass, another cover-glass is placed on the top of it, and then lightly drawn over the first one—care being taken to avoid pressure as much as possible. In a few seconds the thin film of blood is dry, and the cover-glass may then be mounted in iodine gum of the following composition:—

Iodine	1
Potassium iodide	3
Water, to which an excess of pure gum-arabic has been added	100

The glycogen of the blood can be detected in two forms—(1) In the multinuclear neutrophile leucocytes, as intracellular glycogen; (2) as free extracellular glycogen, which arises from the degeneration of leucocytes. In normal blood only the extracellular glycogen can be recognised with certainty by the action of iodine on cover-glass preparations; but in diabetic blood, minute specks of glycogen, stained deep brown with the iodine, may be seen distinctly in some of the leucocytes, and the amount of extracellular glycogen is two or three times more than that seen in cover-glass preparations of normal blood.

Lipæmia.—A milky appearance of diabetic blood has occasionally been observed on post-mortem examination. In other cases it has been reported to have had a pink colour, and on standing a milky or cream-like serum has separated on the surface. This cream-like condition of the serum has been shown,

by microscopical and chemical examination to be due to the presence of fat globules.

Analysis of the blood in a number of cases has shown that sometimes the percentage of fat has been greatly increased. The mean amount of fat in human blood (including under this term all the constituents of the ethereal extract of blood, namely, neutral fats, cholesterin and lecithin) is stated by Becquerel and Rodier to be 1·6 parts per 1000 of blood, the maximum being 3·25 and the minimum 1·00. Gamgee ([32]) obtained the following results, however, on examination of the blood from two cases of diabetes terminating in coma:—

CASE 1.

	Blood drawn during Life.	Blood collected after Death.
Water in 1000 parts. .	744·6	757·7
Total solids	255·4	242·3
Ethereal extract { Neutral fats, Lecithin, Cholesterin }	10·8 1·96	{ 9·86, 1·55 } - 13·35 2·14

CASE 2.—*Blood collected after death.*—Ethereal extract of 1000 parts of blood, 1·88 parts; cholesterin contained in ethereal extract, 0·642 parts.

Schmidt found the amount of fat in the blood of two cases of diabetes 1·82 and 2·13 per 1000 respectively. Hoppe-Seyler found the fat considerably increased in the blood in four cases of diabetes.

During life I have examined drops of the blood from numerous diabetic patients microscopically, but have never met with any indication of fat globules in the serum; also, the addition of perosmic acid has not revealed the presence of any fat globules. Frerichs has obtained similar negative results.

Acetonæmia.—On post-mortem examination the blood of diabetic patients has sometimes the same peculiar smell as that which is often noticed in the breath of severe cases during life—the so-called acetone smell. By distillation, acetone has been obtained from the blood of patients who have died of diabetic coma, by several observers, but has not been obtained by others.

Glycolytic ferment.—The observations and the views with

respect to the presence of a glycolytic ferment and the amount thereof, in normal and in diabetic blood, are discussed on p. 79.

Sugar in the blood.—It was shown long ago that the blood of diabetics contains an excess of sugar, and the sugar in the urine, in most cases, if not in all, is the consequence of this hyperglycæmia. According to Pavy ([33]), there is a constant relation between the sugar in the urine and that in the blood, any increase in the latter is shown by an increase in the glycosuria.

Normal blood contains a small quantity of sugar. In the blood from the general circulation this sugar is glucose, as shown by its reaction to fermentation, polarisation, Fehling's solution, and phenlhydrazin; but in the blood of the portal system the sugar has a lower cupric-oxide reducing power than that of glucose (Pavy).

From a collection of upwards of a hundred observations upon the dog, cat, rabbit, sheep, ox, horse, and pig, Pavy concludes that the amount of sugar normally present in the blood of the general circulation may be stated to range from about 0·6 to 1·0, or a little over 1·0 per 1000.

Seegen ([34]) has obtained results somewhat similar in animals (the figures being a little higher, however). He has also estimated the quantity of sugar in normal human blood obtained by wet cupping. In the blood from ten healthy men the average quantity was 0·17 per cent.

In diabetes the amount of sugar is often greatly increased; it may reach 2·7 to 5·7 per 1000 (Pavy); Seegen has found it as high as 0·47 per cent. Seegen states that whilst the blood, in the severe form of the disease, contains a great excess of sugar, in the mild forms sometimes the percentage of sugar has not been above the normal limit. It is interesting to note that in phloridzin diabetes it is stated that the blood sugar is not increased, though this has been disputed.

The estimation of the amount of sugar in normal and diabetic blood requires considerable care and some experience of delicate chemical analysis. In a work devoted to the consideration of diabetes from the clinical standpoint, it is scarcely necessary to describe the usual method of quantitative estimation, since they can only be applied to large quantities of blood; and as venesection is not now performed in cases of diabetes, such quantities can rarely be obtained in medical practice.

The reader may be referred to the following works for

details as to the method of quantitative estimation of sugar in the blood :—

PAVY, F. W.—"Croonian Lecture on Certain Points connected with Diabetes," London, 1878 ; "Physiology of the Carbohydrates," London, 1894, pp. 58–80. SEEGEN, J., "Die Zuckerbildung im Thierkörper," Berlin, 1890, S. 11. v. JAKSCH.—"Clinical Diagnosis," translation by Cagney.

For clinical methods of estimation of the amount of glucose in the blood, see pp. 195–96.

A simple method of distinguishing diabetic from non-diabetic blood —The decolorisation of methylene blue.—In order to detect the difference between diabetic blood and non-diabetic blood, from the amount of sugar present in each, it is necessary to examine a considerable quantity of blood, and I am not aware that any method has hitherto been proposed by which the excess of sugar can be detected by the examination of a drop of blood obtained by pricking the patient's finger. But by the following method the difference between diabetic and non-diabetic blood can be easily demonstrated clinically ([35 and 36]).

Whilst making a number of blood examinations, it occurred to me to try the effect of adding a drop of diabetic blood to a solution of methylene blue.[1] I was surprised to find that diabetic blood was much more powerful than non-diabetic blood in removing the colour from a warm alkaline solution of methylene blue. I found that, on heating a small quantity of blood and methylene blue solution in certain proportions, the colour was removed in the case of diabetic blood, but not when non-diabetic blood was employed. The reaction is so sensitive, that the difference between non-diabetic blood and the blood from a well-marked case of diabetes can be easily demonstrated in a drop of blood obtained by pricking the finger, and I have frequently demonstrated this difference to medical students and friends.

The following is the exact method which I have used : —

A small *narrow* test tube[2] is well cleaned, and at the bottom of the tube are placed 40 c.mm. of water. To measure this I

[1] By mistake the term methyl blue was used in place of methylene blue in my first description of the above method, published in the *Brit. Med. Journ.*, London, Sept. 19, 1896.

[2] It is important to use a narrow test-tube, so that the upper surface of the fluid, with which the air comes in contact, may be as small as possible.

have used the capillary tube of a Gowers' hæmoglobinometer, which is graduated for 20 c.mm. The tip of one of the patient's fingers is cleaned and dried, then pricked, and when a large drop of blood has escaped, it is sucked up into the small capillary hæmoglobinometer tube; 20 c.mm. of blood are taken up from the finger. The blood is then blown gently into the water at the bottom of the small test tube. If it should adhere to the side of the tube, it must be carefully shaken to the bottom. Then 1 c.cm. of a 1 in 6000 watery solution of methylene blue is added. (To measure this I have used the 1 c.cm. tube supplied with Southall's ureometer.) To the mixture, finally 40 c.mm. of liquor potassæ are added. The contents of the tube are then well mixed by shaking. As a control experiment, a second test tube of similar size is taken, and into this is placed the same quantity of non-diabetic blood, with the same proportion of water, methylene blue, and liquor potassæ.

FIG. 11.—Author's test for diabetic blood: end of reaction: fluid in tube containing normal blood, blue; that in tube containing diabetic blood, yellow.

The fluid in each tube has a fairly deep blue colour. Both tubes are then placed in a beaker, capsule, or very wide test tube containing water. Heat is applied by a spirit-lamp until the water boils; it is allowed to continue boiling for about four minutes. By the end of this time the fluid in the tube containing the diabetic blood changes its colour from fairly deep blue to a dirty pale yellow (almost the colour of normal urine). Whilst the fluid in the tube containing the non-diabetic blood remains blue, occasionally it becomes bluish green, sometimes pale violet, but it is never decolorised, that is, it never loses its blue colour. The tubes should be kept quite still whilst in the water bath, as, by shaking, the decolorised methylene blue is oxidised by the oxygen of the atmosphere, and a blue tint may then return to

the fluid. This is the reason why it is necessary to use a water-bath, since, if the test tubes be heated directly over the spirit-lamp, it is difficult to avoid shaking of the fluid.

I have made fifty examinations of diabetic blood according to this method, in twenty cases of diabetes mellitus. Seventeen were suffering from a very severe form of the disease. In every examination, in all of the twenty cases, a 1 in 6000 solution of methylene blue was readily decolorised when the test was carried out, as described above. In very severe cases a solution of methylene blue of double strength (1 in 3000) was also decolorised. I have made a large number of examinations of normal blood, but have never found the methylene blue solution to be decolorised when the above-described proportions of fluid were used. I have also examined the blood in 100 patients who were not suffering from diabetes. These 100 cases included the most varied ailments, often at a very advanced stage, such as diseases of the heart, lungs, stomach, liver, nervous system, the various forms of anæmia and Bright's disease, purpura, leucocythæmia, gout, rheumatism, lead-poisoning, cancer of various organs, jaundice, and many other affections. I have never met with any case amongst the non-diabetic patients, in which a 1 in 6000 solution of methylene blue was decolorised when the test was carried out as above described. On the other hand, diabetic blood has always decolorised it readily.

With respect to the cause of this marked difference between diabetic and non-diabetic blood, it is most natural to attribute it to the excess of sugar present in the former. It is known that grape sugar readily removes the colour from a warm alkaline solution of methylene blue. I have found that diabetic urine decolorises a 1 in 3000 solution, even when diluted to such an extent that the amount of sugar is only 0·07 per cent.

If the decolorisation produced by diabetic blood be due to the excess of sugar present, then one would expect that by using a larger proportion of normal blood a similar decolorisation would result, since the percentage of sugar in many cases of diabetes is not more than three times the normal percentage. Thus one would expect that the amount of sugar would be almost the same in a mixture of 20 c.mm. of blood from a severe case of diabetes + 1 c.cm. of methylene blue solution + 40 c.mm. of liquor potassæ, as in a mixture of 60 c.mm. of normal blood + 1 c.cm. of methylene blue solution and 40 c.mm. of liquor

potassæ. I have found that when the last-mentioned proportions of normal blood and solution are used, the blue colour is removed, as in the case of diabetic blood. But since diabetic blood and normal blood differ in other respects, in addition to the difference in the percentage of sugar, I have not been able to prove that the above reaction, in the case of diabetic blood, is due simply to the excess of sugar, and it is quite possible that there may be some other causes.

In one case which I examined, the patient was suffering from a severe form of the disease, the urine contained a large amount of sugar, and the methylene blue solution was readily decolorised by the blood. In this case phthisis developed; and when the lung symptoms became very advanced, the amount of sugar in the urine greatly diminished, until finally the urine did not give any immediate reaction on boiling with Fehling's solution; oxide of copper only being thrown down when the solution was cooling. Nevertheless the methylene blue solution was still decolorised fairly well by 20 c.mm. of the patient's blood, though it is probable that at this late stage the blood only contained a small excess of sugar. In another mild case of diabetes (in which there was no thirst, no diuresis, and in which the total quantity of sugar excreted per diem was only 1008 grs.) this blood reaction was obtained distinctly. In a very mild case of glycosuria, in which there was no excess of urine, I obtained the reaction quite well. The test is exceedingly delicate, but it is possible that in the mildest forms of glycosuria the reaction may not always be obtained, or may only be obtained when different proportions of the fluid are used.

I believe by the above-described simple method—by the decolorisation of a warm alkaline, 1 in 6000 solution of methylene blue—it is possible to easily distinguish the blood of an ordinary case of diabetes mellitus from that of a healthy person or non-diabetic patient; and the test is so sensitive that it can be employed when only a drop of blood can be obtained, as by pricking the patient's finger.

In cases in which the urine cannot be obtained for examination, this blood test will be of service in diagnosis.

The reaction is interesting pathologically, and it might be of value clinically if a diabetic patient were seen for the first time in a comatose condition, and no urine could be obtained for examination.

My observations have been since confirmed by Lépine and Lyonnet ([37] and [38]), by P. Marie and Le Goff ([39] and [40]), Loewy, Goldscheider, and others ([41]).

Le Goff ([42]) has made a number of observations on the amount of methylene blue solution which is decolorised by diabetic blood. His researches show that not only will diabetic blood decolorise a larger quantity of alkaline methylene blue solution than normal blood, but also the rapidity of the reaction is greater. Thus Le Goff found that 20 c.mm. of the blood of a diabetic patient was able to decolorise 1 c.c. of a methylene blue solution in one to two minutes, whilst 20 c.mm. of normal blood decolorised the same quantity only at the end of ten minutes.

Two clinical methods of estimating the amount of sugar in the blood, based on the methylene blue reaction, have recently been worked out by Lyonnet and Le Goff respectively.

Lyonnet's ([38]) method is as follows:—

The small tube of a Malassez's hæmoglobinometer is filled with blood up to the mark 1, and with distilled water up to 100. The mixture is then placed in a glass tube, and two drops of potash solution are added. The tube is placed in a small vessel of boiling water. Then drop by drop, from a graduated tube, a 1 in 4000 solution of methylene blue is added, until the mixture acquires a persistent blue colour. When the blood of the dog is employed, it is necessary to add ten drops, in order to obtain a persistent blue colour. In man the results are practically the same.

In cases of cardiac disease, dyspepsia, cancer of the uterus, and gangrene, the number of drops of methylene blue solution required were 11, 9, 8, 9, respectively.

In the case of a dog rendered diabetic by the removal of the pancreas, thirteen to fourteen drops were required.

The results obtained in three diabetic patients were as follows:—

Case 1.—Urine, 50 grms. of sugar per litre . .						20 drops of methylene blue required for above reaction.	
„ 2.	„	36	„	„	13	„	
„ 3.	„	18	„	„	12	„	

Lyonnet thinks that there is a certain relation between the

glycosuria and the quantity of methylene blue decolorised by the blood of diabetic patients, and that this method, even if not exact, will indicate roughly whether a small or large quantity of sugar is present in the blood.

Le Goff ([43]) estimates the amount of sugar in the blood roughly, by ascertaining the quantity of an alkaline solution of methylene blue which must be added to a definite quantity of blood before a persistent blue colour is obtained when the fluid is heated. The method is as follows :—

Twenty c.mm. of blood are taken from the finger and placed in a small tube, with 1 c.c. of a 1 in 5000 solution of methylene blue (containing 1·5 mgrms. of potash per c.c.). After mixing well, the tube is placed in boiling water. The blue colour of the mixture disappears. More of the alkaline methylene blue solution is added, until a blue colour is obtained, which persists for at least a quarter of an hour.

With normal blood, the mean quantity of methylene blue solution required was found by Le Goff to be 1256 c.mm. With diabetic blood the quantity was always great—2550 to 3000.

P. Marie and Le Goff ([39 and 44]) have employed the following clinical method for estimating the quantity of sugar in the blood more exactly :—

By means of a graduated Pravaz syringe, 1 c.c. of blood is taken from one of the veins in front of the elbow, and added drop by drop to 6 or 8 c.c. of alcohol (96°) in a small glass tube. The mixture is well shaken for ten minutes, and then allowed to stand for twenty-four hours. The albumins, hæmoglobin, and glycogen are precipitated. The precipitate is filtered off, washed in alcohol, and the sugar in the alcoholic extract estimated by an alkaline solution of methylene blue of the strength given above. 6500 c.mm. of the solution correspond to 1 mgrm. of glucose. The tube containing the alcoholic extract is not placed in boiling water, but in hot water having a temperature of 80° to 90°.

The following is an example of this method :—

One c.c. of blood was taken from a diabetic patient, and treated as above described. The alcoholic extract amounted to 6 c.c. One c.c. of this extract was mixed with 3000 c.mm. of alkaline methylene blue solution, and the tube placed in hot water at 90° at 3.15 A.M.

At 3.25 the fluid completely decolorised; 250 c.mm. of m.-blue added.
„ 3.30 „ „ 250 „ „
„ 3.37 „ „ 250 „ „
„ 3.44 „ „ 250 „ „
„ 3.45 „ „ 100 „ „
„ 3.47 „ „ 150 „ „
„ 3.55 „ „ 250 „ „
„ 4.15 the blue colour persists.

Total quantity of methylene blue solution added to 1 c.c. of the alcohol extract = 4500 c.mm.

Quantity required for the 6 c.c. = $6 \times 4500 = 27$ c.c.

The strength of the blue solution is such that 6·5 c.c. corresponds to 1 mgrm. of glucose. Hence the sugar in the alcoholic extract is $\frac{27}{6{\cdot}5} = 4{\cdot}15$ mgrms. Therefore the blood contained 4·15 grms. of sugar per litre.

Staining of red corpuscles in diabetes.—Bremer ([45]) has discovered that the red corpuscles of diabetic blood stain green when a cover-glass preparation is treated according to a certain method, with a special solution of eosin and methylene blue, whilst the red corpuscles of non-diabetic blood stain purple or madder colour when treated in the same manner. Lépine and Lyonnet ([46]) have confirmed Bremer's observations, but have also found that the red corpuscles of the blood in a case of leucocythæmia stained green just in the same manner as the red corpuscles of diabetic blood.

The following are the details of the Bremer method:—

A cover-glass preparation of blood is made in the usual manner, and a thin, even film obtained. For comparison, a similar preparation of normal blood is made. Both are placed in a wide-mouthed bottle or glass, containing equal parts of alcohol and ether (10 grms. of each). This vessel is then placed in hot water, and the ether-alcohol allowed to boil for four minutes. The cover-glasses are then stained in a solution prepared in the following manner:—Saturated watery solutions of eosin and methylene blue are mixed in equal parts. A precipitate forms; this is filtered off, washed, and dried. It is then reduced to a powder, and one twenty-fourth part of eosin and one-sixth of methylene blue are added. From 0·025 grm. to 0·05 grm. of this mixture is dissolved in 10 grms. of a 33 per cent. solution of alcohol. This staining fluid does not keep well, and must be freshly prepared shortly before the cover-glasses are stained.

After remaining in the above fluid for four minutes, the cover-glasses are washed in water. The film of diabetic or glycosuric blood is stained sap or bluish green, the non-diabetic blood reddish violet. Under the microscope the red corpuscles of diabetic or glycosuric blood are stained green, whilst those of non-diabetic blood are stained of purple or madder colour. Bremer found this reaction in fifty cases of diabetes mellitus or glycosuria, and believes that in these diseases a diagnosis can be made by examination of a drop of blood. In a postscript he adds that in one case recently examined he has obtained negative results.

Le Goff ([47]) has carefully investigated the colour reactions of diabetic blood. He has employed eosin-methylene-blue for this purpose. A saturated watery solution of eosin is mixed with a saturated watery solution of methylene blue (the proportion of the two solutions is not stated—probably the author intends equal volumes to be used). The precipitate which forms is washed in water, then dried. Five cgrms. of this substance are dissolved in 20 to 25 grms. of alcohol (30°). The solution is then filtered. Cover-glass preparations of blood (normal and diabetic) are heated in a hot chamber for two hours, at a temperature of 120° C., and then stained in the above solution, washed in distilled water, dried with filter paper, and mounted in xylol balsam. The red corpuscles of normal blood are stained, the colour varying from a clear purplish rose colour to a dark maroon, whilst the red corpuscles of diabetic blood are pale green, yellowish green, yellowish or unstained. The nuclei of the white corpuscles are stained blue, and in other respects are the same, both in normal and diabetic blood.

Le Goff has confirmed the results of Bremer, and has recorded a number of interesting observations on the colour reactions of diabetic blood.

More recently Bremer ([48]) has pointed out that the blood of patients suffering from diabetes mellitus can be distinguished from normal blood by the following reactions to aniline stains:—

A drop of blood is smeared by means of a slide over a second slide, so as to cover about one-third or one-half of the surface. A number of slides are prepared from diabetic and non-diabetic blood (the latter for control staining). As the reaction can be seen by the naked eye, tolerably thick layers of blood are

employed, and these have, as nearly as possible, the same thickness. The blood preparations are now heated in a hot-air chamber for six to ten minutes, at a temperature of 125° C. It is important to avoid heating the preparations over 140° C.; also they should not be heated for more than ten minutes. The slides are then stained in a 1 per cent. watery solution of one of the following stains:—Congo red, methylene blue, Biebrich scarlet, or in Ehrlich-Biondi's staining fluid. Slides of diabetic and non-diabetic blood are treated exactly in the same manner for comparison. The results are as follows—Congo red: stain for one and a half to two minutes, then wash rapidly in water, and dry; the non-diabetic blood is stained, whilst the diabetic preparation is not stained, or only indifferently stained. Methylene blue stains non-diabetic, but not diabetic blood. With Biebrich scarlet the diabetic blood is stained deeply, the non-diabetic is unstained. If preparations be placed in Ehrlich-Biondi's fluid two to three minutes, the diabetic blood is stained orange, whilst the non-diabetic blood is stained violet. Beautiful contrasts are obtained by double staining. Preparations of diabetic and non-diabetic blood are stained in a 1 per cent. watery solution of methylene green for one and a half to two minutes and then washed. Both preparations are green, the diabetic being more deeply stained. They are next placed in a $\frac{1}{8}$ per cent. watery solution of eosin for eight to ten seconds. The diabetic preparations remain green; the non-diabetic take the eosin stain. Similar results are obtained with methyene blue and eosin.

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CHAPTER X.

SYMPTOMS, COMPLICATIONS, AND PATHOLOGICAL CHANGES IN CONNECTION WITH THE VARIOUS SYSTEMS.

Besides the changes in the urine and blood, there are a number of prominent symptoms. The most important are:—Thirst and increased appetite; great weakness and emaciation in the severe forms of the disease; a harsh, dry skin; often a red, raw-looking tongue. These will be best considered, however, under the abnormalities met with in the various systems.

Temperature.—In diabetes the temperature is generally normal or subnormal.

In diabetic coma it is usually very low—95°, 94°, or lower. Occasionally, though exceedingly rarely, it is high, just before death in diabetic coma. A high temperature may be also caused in diabetes by the occurrence of various complications.

The Alimentary Canal, Liver, and Pancreas.

Saliva.—The mouth of the diabetic patient is dry, and the saliva as a rule scanty; occasionally, though very rarely, pytalism occurs. The reaction of the saliva, even the parotid fluid collected from Steno's duct, is usually acid. Almost without exception, the saliva is free from sugar—Frerichs (1), v. Noorden (2).

v. Noorden states that sometimes he has failed to obtain the sulphocyanide reaction.

Gums and teeth. — On the gums and soft palate white patches are sometimes seen in advanced cases. These are due to the growth of fungus spores and mycelium on the superficial epithelium, and may be prevented by careful cleanliness.

The gums often become red and inflamed; they are sometimes spongy and swollen, and bleed easily. The teeth often become loose and fall out; they are frequently carious; and

sometimes these dental troubles occur at an early stage of the disease. Alveolar periostitis occasionally occurs.

The tongue is often very red and abnormally clean; frequently the surface is cracked and raw in appearance, the epithelium being deficient. In mild cases, however, the tongue is often moist, and coated with a thin yellowish-white fur.

Thirst is one of the most characteristic symptoms, and often the first indication of the disease. The onset of thirst is occasionally quite sudden, and the patient is able to state definitely the time of the day or the hour when it first commenced (see p. 164). The patient takes enormous quantities of liquids, 10 to 15 pints or even more per diem, and still the thirst continues. Some diabetics complain more of dryness of the mouth than of thirst. In a case already referred to, the patient complained of a salty taste. Sometimes the thirst is so great that sleep is prevented or much disturbed; as a rule it runs parallel with the sugar excretion, and diminishes when this is reduced or arrested by a restricted diet (see p. 167). In some of the very mild cases of diabetes, thirst is absent or very slight, and even in severe cases, which run a fairly rapid course, occasionally thirst is not a very prominent symptom; the patient does not complain of it, but when questioned admits that he is more thirsty than formerly. At the last stage of the disease, when phthisis occurs as a complication, the thirst may diminish and finally disappear just before death.

The *appetite* is generally increased, often enormously so. As Seegen puts it, many patients describe their condition as if they had "a hole in the stomach." This great increase in the appetite is met with chiefly in the severe forms of the disease, or in the mild cases, so long as carbohydrate food is taken in large quantities. In the latter class of cases, if carbohydrate food be excluded from the diet the hunger subsides.

Thirst is a much more constant symptom than hunger. Sometimes, in the very severe form of diabetes, the appetite is not increased or is only slightly increased, especially at a late stage when there is great wasting, when advanced phthisis is a complication, or when catarrh of the stomach is present, owing to a prolonged nitrogenous diet, or to other causes; and in certain mild cases there is no increased appetite. In the last stage of the disease there is often marked anorexia.

The digestive power of diabetic patients is generally very

good, and persons whose digestion has previously been feeble often improve markedly in this respect after diabetes develops. Dyspeptic individuals who have previously found it necessary to be very cautious in the choice of their diet, often lose all their dyspeptic troubles after the onset of diabetes, and can take large quantities of food with impunity.

Sometimes signs of *gastric catarrh*, impaired digestion, and loss of appetite are met with, when the patient has been kept for some time on a very rigid diet. Occasionally *dilatation* of the stomach occurs as a complication, especially when the treatment has been neglected, and when the patient has taken enormous quantities of food. *Gastric ulcer* has also been recorded as a complication, but it is exceedingly rare.

The gastric juice has been examined by Gans (3), Honigmann (4), Rosenstein (5), and others, but the variations in the amount of hydrochloric acid have been mostly within the normal limits; sometimes, however, free hydrochloric acid has been absent. Rosenstein has shown that free hydrochloric is sometimes temporarily, sometimes permanently, absent from the gastric juice. He believes the former cases to be due to gastric neurosis, and the latter to interstitial gastritis, with extensive atrophy of the mucous membrane.

Karl Grube (6) has observed gastric crises, resembling those of tabes dorsalis. The patient is suddenly seized with violent pain in the abdomen, especially at the pit of the stomach; this is accompanied by abdominal distension and eructations. Nausea and vomiting of acid material occur, and sometimes diarrhœa and cramps in the legs follow.

Intestines.—Diabetic patients very frequently suffer from constipation, which is sometimes very obstinate, and which is increased if a nitrogenous diet and opium are prescribed. The constipation is in part the result of the nitrogenous diet; but this is not the only cause, since constipation is a common symptom, when the patient's diet has not been restricted; it is common also amongst diabetic patients on admission into hospital, even when there has been no restriction of diet and when no opiates have been taken. In severe cases of diabetes, when the bowels are markedly constipated, frequently the urine gives a dark brownish-red coloration with perchloride of iron (diacetic acid reaction), but if the constipation be relieved by purgatives, I have frequently found that the perchloride of iron

reaction has become less marked or has disappeared. Occasionally, but rarely, I have found the perchloride of iron reaction when the bowels have not been constipated.

Sometimes, especially in chronic cases, the patient suffers from *diarrhœa.* This is a serious complication, and rapidly undermines the patient's strength, since the absorption of food is hindered, and the amount of fatty food must then be limited. Hence diarrhœa ought to be energetically treated by opium, chalk, etc. Sometimes the diarrhœa is of a dysenteric character.

In diabetic coma the bowels are generally constipated (seventeen out of twenty-seven cases, see p. 275), and obstinate constipation often precedes coma, and appears to be a predisposing factor. Hence it is especially necessary to prevent prolonged constipation in advanced or severe cases of diabetes. Schmitz drew attention to this point. He thought it probable that when the bowels of diabetic patients remained constipated for a prolonged period, toxic substances were formed in the intestines, and to the absorption of these he attributed the coma. Sometimes, though very rarely, diarrhœa is present in diabetic coma, and an attack of diarrhœa at an advanced stage of diabetes occasionally appears to be the exciting cause of coma.

Fatty motions—steatorrhœa.—It is well known that sometimes in diseases of the pancreas, a great excess of fat is found in the motions, though this is by no means a constant symptom; also Abelmann has shown that after complete pancreas extirpation in animals, the fats of the food are not absorbed. Naturally one would expect that, in cases of diabetes associated with disease of the pancreas, analysis of the fæces would show an excess of fat. I do not know of any series of cases, of diabetes associated with pancreatic disease, in which such an analysis has been made.

Hirschfeld (7) has drawn attention to a class of cases of diabetes in which the *assimilation of albumins and fats is very considerably diminished,* and these he regards as forming a new clinical variety of the disease.

Marked pathological changes in the stomach and intestines are not frequent and not characteristic.

In ninety-two cases examined at the Vienna Pathological Institute, and recorded by Seegen (8), the following changes were noted:—

	Cases.
Dilatation of the stomach	in 6
Ecchymoses in the gastric mucous membrane . .	,, 5
Marked swelling and redness of the gastric mucous membrane	,, 3
Marked acute intestinal catarrh	,, 4
,, chronic catarrh of the large intestine . .	,, 1
Tubercular ulceration of the intestine, associated with tuberculosis of the lungs	,, 2

In the post-mortem records of fifty-five cases recorded by Frerichs (9), the stomach is often reported to be normal, often dilated, and often thickening of the walls is recorded; but no characteristic or important change was observed. In diabetes, complicated by phthisis, tubercular ulceration in the intestines was sometimes recorded, and in two cases a dysenteric condition of the large intestine was observed. A thick layer of fungus growth was often present in the mucous membrane of the œsophagus and fauces. In many cases the mesenteric glands were enlarged.

The liver.—Sometimes during life the liver is found to be *enlarged*, owing to hyperæmia, fatty infiltration, or cirrhosis. This enlargement is met with chiefly in obese or gouty diabetics who suffer from a mild form of the disease. Amongst hospital patients suffering from the most severe form of diabetes with wasting, generally no enlargement of any importance can be detected during life.

Glénard (10) states that he has found changes in the liver, on examination of the abdomen, in 60 per cent. of diabetic patients. Hypertrophy was the most common change (34·5 per cent. of the cases). But Glénard's statistics were based on 324 cases met with in private practice at Vichy, and these cases would no doubt include a large number of the mild forms of diabetes in gouty and elderly people. Certainly, in the severe cases of diabetes which have come under my observation, it has been rare to detect any noteworthy enlargement of the liver during life.

Obese diabetic patients sometimes suffer from gall stones; but in hospital patients this complication is exceedingly rare. Probably it does not occur in more than 1 per cent. of the cases.

The relation of liver affections to diabetes has been discussed

already on p. 116, and the diseases of the liver occasionally met with are there referred to.

Pancreas.—Changes in this gland have been already described (p. 140); but during life it is not yet possible to diagnose, with certainty, whether a case of diabetes is, or is not, due to pancreatic disease.

Lancereaux has drawn attention to the association of disease of the pancreas with a severe form of diabetes, in which there is marked wasting, and in which the disease runs a rapid course. But in diabetes of this form the pancreas is sometimes normal (as is shown on p. 156); also the pancreas has sometimes been found diseased when the patient has not been wasted.

As a rule, no evidence of pancreatic disease can be detected in the diabetic patient on examination of the abdomen during life.

v. Noorden ([11]) is inclined to attach some importance to the following symptoms as indications of pancreatic diabetes, though their occurrence, and especially their combination, is no doubt exceedingly rare:—

1. Proof of a tumour of the pancreas (carcinoma, cyst, hydatid, etc.).

2. History of severe colic, which cannot be referred either to the kidneys or liver, but which, from its position, is suggestive of a calculus in the pancreatic duct.

3. The occurrence of maltose in the urine (found twice; importance not clear).

4. Steatorrhœa or excess of fat in the motions, unassociated with jaundice.

5. Presence of great quantities of nitrogenous material in the fæces.

The Lungs.

The most important and most frequent lung complication in diabetes is *tubercular phthisis.*

As to the frequency of tubercular disease of the lungs in diabetic patients, there is considerable difference of opinion. v. Noorden ([12]) states that at least one-fourth of all diabetic patients in Germany suffer from phthisis. According to some writers, especially physicians who practise at the continental spas which are much frequented by diabetic patients, tuberculosis is not a common complication. But the discrepancies can be easily explained.

As has been pointed out by Seegen [13] and others, tubercular disease is most common in poor, hard-working people. These patients often do not come under treatment until a late stage of the disease, and their general conditions of life and surroundings usually predispose to phthisis. Hence phthisis is common in diabetic hospital patients. Age is also of importance. In young diabetic patients tuberculosis is frequent, and these cases usually terminate either in diabetic coma, or in phthisis; whilst in elderly persons, especially obese or gouty patients, tuberculosis is comparatively rare.

Physicians who practise at the various continental spas are consulted chiefly by patients in good circumstances, and see a large number of cases of the mild forms of the disease, such as occur in stout or gouty elderly persons; and these are just the patients who suffer least from tubercular complications.

In Manchester, tubercular disease of the lung is a common complication amongst hospital patients.

In the last 100 consecutive cases of diabetes, in which I have made a careful examination of the lungs, I have obtained the following results:—

	Cases.
Physical signs of advanced phthisis	14
(In twelve of these the signs were most marked at the apex of the lungs; in two, at the base.)	
Slight signs of phthisis at the apex	14
Tubercular phthisis found post-mortem, not detected during life	1
In 100 consecutive cases phthisis present in . . .	29

The majority of the cases were hospital patients, and most were suffering from an advanced or severe form of diabetes. In twenty-seven the signs were most marked at the apices of the lung. Many of these were proved to be tubercular, either by subsequent post-mortem examination, or by the detection of tubercle bacilli in the sputum. Probably all of the twenty-seven were tubercular. Of the two cases in which the physical signs were at the base, one was proved to be non-tubercular (see p. 212); in the other case the question was not definitely settled.

Next to coma, tubercular phthisis is the most common termination of diabetes. It is well known that when marked tubercular phthisis has once developed in a diabetic patient, as

a rule, death does not occur from coma. To this general rule there are occasional exceptions, however. I recently saw a case of diabetes in which there was very advanced tuberculosis of the lungs, and yet death occurred from coma; but such cases are rare. In young patients, if death does not occur at a comparatively early stage from coma or some accidental intercurrent disease, tuberculosis of the lungs generally develops.

In the last forty-two fatal cases of diabetes which have come under my observation, the termination has been as follows:—

	Cases.
Coma	29
Asthenia from phthisis and lung disease (six tubercular, one non-tubercular)	7
Acute double pneumonia	1
Cardiac failure	2
Gangrene of foot	1
Asthenia from cirrhosis of the liver	1
Pyæmic condition (multiple abscesses of the liver, cerebro-spinal meningitis)	1
	42

In the last twenty-four cases of diabetes which I have seen or have made the autopsy, there has been—

	Cases.	
Tubercular disease of the lungs in	12	54 per cent.
Non-tubercular phthisis in	1	
Lungs not affected by phthisis in	11	
	24	

Tuberculosis of the lungs was thus found post-mortem in about 50 per cent. of the cases; lung affections in 54 per cent. [These cases were mostly hospital patients.]

Seegen (14) gives the following results of the post-mortem examination of the lungs in ninety-two cases examined at the Pathological Institute of the Vienna General Hospital during the time Kundrat was professor of pathology:—

	Cases.
Tuberculosis of the lungs in	40
Croupous pneumonia	9
Lobular „	8
Œdema of the lungs	13
Carry forward	70

	Cases.
Brought forward . .	70
Hyperæmia	4
Diffuse gangrene of the lungs	2
Localised gangrene through the rupture of an extensive ulcerated cancer of the œsophagus	1
Hæmorrhagic infarct	1
	78

Tubercular phthisis is then by far the most common form of lung disease in diabetes. It was formerly stated that phthisis in diabetes was frequently non-tubercular, but certainly this is not correct. In all the cases of which I have seen the autopsy, the lung affection has been tubercular with one exception (this case will be referred to later). Frerichs ([15]) is very dogmatic on this point. The following are the changes in the lung found post-mortem in fifty-five of his diabetic cases:—

	Cases.
Tubercular disease (with pneumothorax in three) . .	21
Croupous pneumonia	1
Gangrenous pneumonia	7
Lobular pneumonia with suppuration	1
Lungs normal in	17

It has been stated that there is often difficulty in detecting tubercle bacilli in the sputum in the tubercular phthisis of diabetic patients. I have not found this difficulty myself. Gabbett's method of staining is the one I have always employed. In seven consecutive cases which I recently examined, I found tubercle bacilli readily in six; in the other case the sputum was frequently examined by myself and others with negative results, and the case proved to be non-tubercular post-mortem. Saundby ([16]) also states that he has not had any difficulty in detecting tubercle bacilli in the sputum.

There are several peculiarities with respect to tubercular phthisis occurring in diabetic patients, as was pointed out long ago by Jaccoud ([17]), Leyden ([18]), Seegen, and others ([19]). Tubercular lung disease in diabetes usually runs a comparatively latent course. Frequently tubercular phthisis is found post-mortem when the disease has not been diagnosed during life; and the post-mortem changes are nearly always much more extensive than has been suspected from the symptoms and physical signs.

Cough and expectoration are comparatively slight, as a rule. The temperature is not much raised; it may even be normal (Leyden). Hæmoptysis is very rare. In all the cases of tubercular phthisis which I have seen, hæmoptysis has been absent even up to the last.

To these general rules there are exceptions. I have occasionally seen abundant expectoration in later tubercular phthisis of diabetic patients, and Leyden mentions that he has seen slight hæmoptysis in a few cases.

In two cases which I saw a short time ago, the phthisical symptoms had chiefly attracted the attention of the patient and his medical attendant, and the primary diabetes had not been diagnosed.

Tubercular disease of the lung is a most serious complication of diabetes. The disease often runs a rapid course, and I am not aware that diabetic phthisis ever heals.

When phthisis, tubercular or non-tubercular, complicates diabetes, often the glycosuria finally diminishes, and it sometimes happens that sugar disappears from the urine shortly before death. Three such cases have come under my observation: the sugar disappeared a few days before death in one case, one week before death in the second, and six weeks before death in the third. All three had been most severe cases of diabetes, with marked thirst and diuresis, and the urine had given a distinct brownish-red coloration with perchloride of iron. With this disappearance of sugar the thirst and diuresis also ceased, and the whole clinical aspect of the cases, in the last stage of the disease, gradually changed from diabetes to phthisis with marked wasting.

The *pathological changes* in the lungs in diabetes have been very carefully described by Dreschfeld (20). Pathologically, the tubercular phthisis of diabetes is found to be due to a chronic caseous tubercular broncho-pneumonia. It generally runs a more rapid course than the tubercular phthisis of non-diabetic persons. Caseation occurs rapidly, and the diseased parts soon break down and form cavities. There is no tendency to cicatrisation. Anatomically, the usual phthisical changes are met with in the lungs—caseation, cavities, isolated tubercular masses, and sometimes pneumothorax also (Dreschfeld). Microscopically, the usual appearances are met with: peribronchial infiltration, interstitial changes, broncho-pneumonic infiltration

of the alveoli, giant-cells, and endarteritis. Thickening of the pleuræ, with adhesions and occasionally pleuritic tubercles, is also met with.

Leyden points out three pathological peculiarities, in a number of cases of the tubercular phthisis of diabetes which he reports.

1. That miliary tubercles were absent.
2. That giant-cells rarely occurred in the tubercular parts.
3. That obliterating arteritis was much more extensive than in ordinary cases in non-diabetic subjects.

Tubercular ulcers are sometimes present in the intestines in cases of diabetes complicated with pulmonary tuberculosis; but with the exception of the intestines, tuberculosis is generally limited to the lungs, and tubercular affection of other organs is very rare. Occasionally, however, tubercles have been found in the larynx, kidneys, and liver.

Chronic pneumonic (non-tubercular) phthisis.—Whilst phthisis in diabetic subjects is undoubtedly tubercular in the majority of cases, still occasionally, though very rarely, a non-tubercular form is met with — a chronic fibroid phthisis or chronic pneumonic non-tubercular phthisis. As above mentioned, in twenty-four cases of diabetes, at the autopsy tubercular phthisis was present in twelve, non-tubercular in one. This is the only case of non-tubercular phthisis I have ever seen in a diabetic subject. It was under the care of Dr. Harris at the Manchester Royal Infirmary, and is described by him in the *British Medical Journal*, 28th November 1896. In this case the sputum was repeatedly examined for tubercle bacilli with negative results. Guinea-pigs were inoculated with the sputum by Dr. Harris, but no tubercular disease was produced. Post-mortem examination showed that the disease was non-tubercular.

Similar cases of non-tubercular phthisis in diabetic patients have been recorded by Dreschfeld, and by Roque, Devic, and Hugounenq ([21]), in which no tubercle bacilli could be found, either in the sputum during life, or in sections of the lung tissue on pathological examination.

Gangrene of the lungs sometimes occurs in diabetic patients. It is a very rare complication, and generally follows broncho-pneumonia; occasionally it follows croupous pneumonia and severe forms of bronchitis, and occasionally it is due to trauma. The expectoration has an acid reaction, and, as Frerichs has

pointed out, is generally not fœtid. Dreschfeld states, however, that he has met with some cases of diabetic gangrene of the lung in which the expectoration has had a very fœtid character. According to Frerichs, foreign bodies are frequently found in the gangrenous patches; he believes that these bodies have been aspirated, and have given rise to gangrenous pneumonia.

Broncho-pneumonia sometimes occurs. It may terminate in caseation and lead to tubercular phthisis; or it may terminate in gangrene. According to Frerichs, it almost always leads to gangrenous patches of greater or less extent.

Acute croupous pneumonia is a rare complication. It occurred once in forty-two fatal cases in Manchester, nine times in ninety-two cases reported by Seegen, and once in fifty-five of Frerichs's cases.

According to Dreschfeld, "It runs a very acute course, and is very fatal. It resembles the pneumonia seen in alcoholics; commences insidiously without a rigor; runs its course, as a rule, without great rise of temperature, without perspiration, and without expectoration, except where the case goes on to gangrene."

During the attack of pneumonia, the amount of sugar excreted in the urine has been found to diminish, but it increases again at the crisis when the temperature falls. In thirteen cases of pneumonia in diabetic patients, Senator never found the sugar to disappear *entirely* from the urine during the course of this complication. Sugar has been found in the expectoration (0·25 per cent., Bussenius [22]).

Occasionally other lung affections, such as emphysema and chronic bronchitis, are met with. Bronchitis occurs chiefly in the chronic forms of the disease in elderly persons. Pleurisy and empyema are rare. Fat emboli have been found in the lungs of patients who have died of diabetic coma, by Sanders and Hamilton and others, and have been regarded as playing an important part in the pathology of this complication; but at present this view has not many supporters.

The breath of diabetic patients has often a peculiar smell, like that of decomposing sweet fruit (Seegen), rotten apples or pears. In diabetic coma the breath has a peculiar smell like chloroform or acetone, and Le Nobel has detected acetone in the expired air.

Oxalates in the sputum.—Fürbringer ([23]) has recorded a case of diabetes in which numerous octahedral crystals of oxalate of lime, or amorphous conglomerations of that salt, were found in the sputum.

The Heart.

The statements of various writers show that there is considerable difference of opinion as to the frequency of cardiac disease in diabetes mellitus. Possibly these discrepancies, like many others, may be explained in part by the fact that some writers have based their statistics on a series of cases which included a large number of the mild forms of the disease in elderly persons, whilst other writers have based their statistics chiefly on severe forms of the disease, such as are met with in young persons and in hospital patients.

In a large number of cases in which I have carefully examined the heart clinically, I have generally failed to detect any abnormality, or at least any abnormality of importance. These cases have been chiefly hospital patients suffering from a severe form of the disease. Thus, in the last 100 cases which I have examined, only seven have presented symptoms or physical signs of cardiac disease. In the remaining ninety-three cases the heart has been practically normal until the disease has reached a very advanced stage, when a feeble apex impulse and feeble pulse have been noted. Also, when diabetic coma has developed, the heart's action has become rapid and feeble.

The following are the changes which I have met with in the series of 100 consecutive cases:—

1. Systolic apical murmur; slightly accentuated aortic second sound; no cardiac enlargement. No other signs of cardiac disease.
2. Reduplicated first sound. No other signs of cardiac disease.
3. Alcoholic cardiac dilatation, with signs of cardiac failure.
4. Systolic apical murmur. No other signs of cardiac disease.
5. Cardiac dilatation and cardiac failure. (Mild cases of diabetes.)
6. Dilated left ventricle; apical systolic murmur.
7. Paroxysmal tachycardia.

Seegen ([24]) states that, with few exceptions, he has found the

heart normal, both as regards its size and the condition of the valves.

There can be no doubt that in the majority of patients who suffer from the *severe* forms of the disease, no abnormality of the heart can be detected during life, with the exception of the weak cardiac action at the last stage. Certain writers, however, have found cardiac changes in a small proportion of the cases of diabetes which they have examined.

The following are the cardiac changes which have been described:—

Cardiac enlargement—hypertrophy and dilatation.—J. Mayer ([25]) of Carlsbad found cardiac enlargement—hypertrophy or dilatation—in eighty-two out of 380 cases which he examined (*i.e.* in 21·6 per cent.); and in these cases there was no other disease to account for the cardiac trouble except diabetes. Mayer also found cardiac affections recorded in 13 per cent. of the cases of diabetes examined in the Pathological Institute of Berlin. Israel ([26]) found cardiac hypertrophy in 10 per cent. of cases of diabetes examined pathologically. When the heart has been hypertrophied, pathological examination has generally revealed hypertrophy of the kidney also; and this condition was present in all of the 13 per cent. of cases of cardiac hypertrophy referred to by Mayer. But, as will be pointed out on p. 219, hypertrophy of the kidneys is often present when the heart is normal or atrophied.

Israel and Mayer, from experiments and clinical observations, conclude that the cardiac hypertrophy is due to the circulation of some irritating chemical substance in the blood.

Cardiac weakness—atrophy and degeneration.—At the last stage in many severe cases of diabetes, the pulse, the apex impulse, and the heart's action become very feeble. This is not surprising, considering that marked emaciation and pulmonary tuberculosis are so often present. On post-mortem examination in these cases, the heart is often very small, and the weight greatly diminished. The muscle wall is sometimes pale, sometimes brownish red in colour. Fatty degeneration and glycogenic degeneration of the cardiac muscle are sometimes met with.

Dreschfeld ([27]), Frerichs ([28]), Schmitz ([29]), and others have drawn attention to the termination of diabetes with symptoms of comparatively rapid cardiac failure and collapse.

The pulse is small and quick; the apex impulse is scarcely

perceptible; the cardiac dulness is increased towards the right; and the first sound at the apex is very feeble (Schmitz). The extremities are cold; the patient becomes drowsy, and finally comatose. In these cases the urine does not contain diacetic acid. The patient is sometimes greatly wasted, sometimes well nourished, sometimes even obese. The above symptoms are those of one of the varieties of diabetic coma, and will be referred to subsequently. They are often excited by some unusual physical exertion, by over-strain, mental exertion, fright, anger, etc., or by some error in diet. Post-mortem examination has revealed atrophy of the heart, with fatty degeneration, and sometimes glycogenic degeneration, and to these changes in the cardiac muscles the symptoms have been attributed.

In the other two varieties of diabetic coma, as will be described subsequently, the heart's action and pulse are very rapid and feeble.

Valvular disease of the heart is sometimes met with as an accidental complication, the patient generally having suffered from rheumatism before or after the onset of the diabetic symptoms. Sometimes aortic valvular disease is associated with arterio-sclerosis in old-standing cases.

Functional disturbances—such as palpitation and paroxysmal tachycardia — have been occasionally met with, and angina pectoris is a rare complication.

In a case which recently came under my observation, the patient suffered from very sudden attacks of tachycardia.

Pathological condition of the heart in twenty consecutive cases. —In hospital patients suffering from a severe form of the disease, the heart is usually atrophied, and the valves normal.

In the last twenty cases of diabetes in which I have seen or made the autopsy, the heart has been enlarged in one only. This was a very mild form of diabetes, or rather chronic glycosuria, and the cardiac dilatation was probably due to alcoholism. The subject was a female, and the heart weighed 16 oz. In fifteen out of the twenty cases the heart was very small, and its weight much diminished. In one male subject the weight was only 6½ oz. (normal weight of male heart 11 oz.); in one female subject the heart only weighed 4 oz. 30 grs. (instead of 9 oz., the normal weight of the female heart). The heart muscle was often soft and flabby. In one case there was atheromatous thickening of the aortic valves, and in another the same condition of

both aortic and mitral valves. In the other eighteen cases the valves were normal.

All the cases were hospital patients, and nineteen suffered from a severe form of the disease with marked wasting.

The pulse.—The pulse is usually regular and of normal frequency. The tension is often normal, occasionally a little below normal; in other cases the pulse is hard, large, and of high tension. I have sometimes found the pulse remarkably hard, and the tension exceedingly high when there has been no kidney mischief, and the patient has been under middle life.

Arterio-sclerosis is often a complication of diabetes. The radial and other arteries frequently feel thickened. In many cases of diabetes, if three fingers be placed on the radial artery, and firm pressure be made with the finger nearest the elbow, so that the pulsation is arrested, then the artery can be rolled beneath the two fingers, as a hard cord, on the peripheral side of the point of pressure. In other superficial arteries the same condition is frequently present also. In some patients, especially in elderly persons, very marked atheroma can be detected; but even in young diabetics I have occasionally met with very marked arterio-sclerosis. Now, as diabetes and arterio-sclerosis are both diseases most commonly occurring after the age of 45, and as arterio-sclerosis is a common affection, it is not surprising that in many elderly diabetics the arteries should present this pathological condition. But the frequency of arterial thickening in diabetics under 45 appears to indicate that the association is not always accidental, and that probably in certain cases there is some connection between the two diseases. The relation between arterio-sclerosis and diabetes is discussed on p. 156.

The Kidneys.

It has already been pointed out (p. 175) that slight albuminuria is frequently met with in diabetes ([30]), but that it is somewhat rare to find albumin present in the urine in large quantities. In most of the cases in which albumin is present in small quantity, there are no other indications of kidney lesions, and post-mortem there are no signs of actual nephritis, though slight changes may be present in the renal epithelium.

This slight albuminuria has been attributed to excess of nitrogenous food in some cases, to catarrh of the bladder in

others (R. Schmitz). I have found a trace of albumin present, however, when the patient has been taking ordinary diet. As mentioned on p. 177, it appears probable that occasionally the trace of albumin is the result of a balanitis and the mixture of a little pus from the inflamed parts with the urine.

In only four out of 100 consecutive cases of diabetes (mostly hospital patients suffering from a severe form of the disease) were there indications of nephritis and abundant albuminuria (see p. 176).

One Hundred Consecutive Cases.

	Cases.	
Albumin absent when urine first examined in	70	In fourteen of these a trace of albumin appeared at a later date.
Small quantity or a mere trace of albumin in	26	Seven of these were at a very advanced stage. One was comatose when first examined. In two the albuminuria disappeared later.
Large or considerable amount of albumin in	4	
	100	

In the chronic mild form of diabetes in elderly people, the proportion of cases in which a large amount of albuminuria is present is probably much greater.

For other points with reference to the albuminuria of diabetes, see p. 176.

In diabetes, therefore, two forms of albuminuria may occur: (1) very slight albuminuria not associated with nephritis; (2) albuminuria due to nephritis. In these cases the albumin is abundant, or there are other indications of Bright's disease. When there are signs of interstitial nephritis, the urine is abundant, but the specific gravity diminishes, though it often still remains above normal. When the kidney condition is one of parenchymatous nephritis, the quantity of urine is less than in the interstitial variety, but almost always above the normal amount.

In cases of diabetes presenting signs of nephritis, often the albumin and sugar bear no relation to each other; but in some cases, as the kidney changes advance, the albumin increases, and the sugar decreases.

When diabetes is complicated with granular kidney after the renal changes reach a certain stage, the glycosuria gradually diminishes, and finally disappears, and the symptoms remaining are those of chronic interstitial nephritis. This rare termina-

tion may occur in cases of diabetes complicated with obesity or with gout, and, according to v. Noorden, scarcely ever in any other forms. The disappearance of the diabetic symptoms, and their gradual replacement by those of chronic nephritis of either form, is a bad prognostic sign. The cases of diabetes complicated by actual chronic nephritis—as indicated by symptoms or post-mortem evidence—are rare in hospital patients and in the more severe forms of the disease; they are more common in elderly persons suffering from the mild forms, and in the diabetes of obese or gouty persons.

Œdema occasionally occurs in the feet in diabetes when albumin and signs of nephritis are absent (see p. 227).

Pathological changes in the kidneys.—The following are the changes which were met with in the kidneys, post-mortem, in ninety-two cases of diabetes examined at the Vienna Pathological Institute, from 1870–1892, during the professorship of Dr. Kundrat (quoted by Seegen [31]):—

	Cases.
Parenchymatous and fatty degeneration . . .	in 24
Acute hæmorrhagic nephritis	„ 1
Granular kidney	„ 9
Chronic tuberculosis of the kidney	„ 2
Hypertrophy (in one of these cases small cysts were present)	„ 4

In twenty consecutive cases of diabetes amongst hospital patients in which I have recently seen or made the autopsy, the condition of the kidneys (on macroscopic examination) was as follows:—

Renal hypertrophy was present in eight. (In one male subject the kidneys weighed 11 oz. each; in another, 10½ and 12 oz. respectively.)

The kidneys were normal or slightly diminished in size in twelve.

In one case there were tubercles in the kidneys. The only other change met with was hyperæmia.

In none was there any naked-eye evidence of nephritis (parenchymatous or interstitial), and in none was there any indication of nephritis during life.

The macroscopical changes ([32]).—*Hypertrophy of the kidneys.*—On post-mortem examination the kidneys are often enlarged in diabetes. As already mentioned, Mayer, Israel, and others have

found cardiac hypertrophy associated with hypertrophy of the kidneys in some cases. Cardiac enlargement, however, is certainly very rare in the severe forms of diabetes which have come under my observation in hospital practice, and yet in these forms the kidneys were often enlarged (eight out of twenty cases). In none of these cases was there any cardiac hypertrophy; in six the heart was diminished in size.

Though the kidneys are often congested and enlarged, on the other hand they are sometimes small and pale; but increase in the connective tissue is rare in the severe forms of diabetes.

Nephritis.—Occasionally chronic interstitial nephritis is met with, but almost exclusively in obese or gouty patients. Parenchymatous nephritis is also an occasional complication. A diffuse nephritis, in which the parenchyma is chiefly affected, but in which there is a certain degree of interstitial sclerosis also, has been found in a few cases.

Abscesses, amyloid degeneration, tubercles, and fat emboli are changes which have been occasionally, though very rarely, observed.

Microscopical changes in the renal epithelium.—Often the renal epithelium cells present microscopical changes.

(*a*) *Hyaline degeneration of renal epithelium.*—Cantani has recorded the changes observed by Armanni (33) in three of his cases. These consisted of a hyaline degeneration of the epithelial cells. The cells affected presented a swollen translucent appearance, as if transformed into large hyaline vesicles with distinct cell walls. The nuclei stained well, and were often seen pushed towards the periphery of the cells.

Armanni described these changes in the cells of the collecting tubules and the tubuli recti of the medulla. Cantani attributes them to a dropsy of the cells.

Other observers have recorded similar changes. Stephen Mackenzie (34) has found this condition of epithelium only in the cells of the collecting tubes; Saundby found the changes confined to the cells of Henle's tubes; Ebstein detected them in the loop of Henle.

(*b*) *Necrosis of epithelium.*—Ebstein (35) has drawn attention to a necrosis of the renal epithelium cells in diabetes, similar to the "coagulation necrosis" described by Weigert, in other diseases. The nuclei of the cells gradually atrophy; they do not stain or stain badly with the usual staining agents; the

protoplasm of the cells degenerates and becomes granular, and, finally, simple or fatty detritus is found in many places.

(*c*) *Fatty degeneration of renal epithelium.*—Fichtner [36] has described a form of fatty degeneration of the renal epithelium of the greater part of the kidney cortex in cases of diabetic coma. He regards the following points as characteristic: (1) the arrangement of fat globules in a row at the periphery or attached part of the cells lining the tubules; (2) the affection of those renal tubules only which are lined by the so-called "cloudy" epithelium.

Fatty degeneration of the renal epithelium is frequently met with, however, in other chronic diseases, such as cancer, phthisis, pernicious anæmia, and in many febrile affections.

(*d*) *Glycogenic degeneration of renal epithelium.*—Ehrlich and Frerichs [37, 38] have described a glycogenic degeneration of the renal epithelium of Henle's tube. This they state to be a constant change. The glycogenic degeneration can be detected macroscopically by treating the section of the kidney with Lugol's iodine and iodide of potassium solution. By the action of this reagent, small brown streaks are produced about the junction of the medullary and cortical parts of the kidney. They correspond to the markedly dilated tubules at the isthmus of Henle's loop. Under the microscope the epithelium cells are found to be enlarged at this point; they are polygonal, clear, and, when stained with iodine gum, they are seen to contain large or small masses which are coloured more darkly than the protoplasm of the cells. The protoplasm is stained pale yellow; the darkly stained parts vary in tint from yellow up to pure mahogany colour.

Ehrlich and Frerichs think that this change is due to the presence of glycogen in the epithelium cells at the most narrow part of the uriniferous canal; they believe that absorption of sugar probably occurs, and that this is transformed afterwards into glycogen.

Straus [39] believes that the hyaline changes described by Armanni, and the glycogenic changes of Ehrlich, are really of the same nature. He thinks they occur very frequently, though not constantly; and, when present, he regards them as characteristic. In a later paper [40] he points out that in some cases in which the hyaline changes described by Armanni are particularly distinct, glycogen cannot be detected in the cells. In such cases he believes

that an infiltration of the cells with glycogen had existed at one time, but that the glycogen had disappeared during the life of the patient, leaving only the hyaline changes. Straus believes the hyaline changes to be more frequent than the glycogenic, but thinks both have the same significance, and are equally characteristic.

Cystitis occasionally occurs in diabetes. It is due to the irritation of the mucous membrane of the bladder by the saccharine urine. Schmitz ([41]) recognises three forms of chronic cystitis in diabetic patients. In the mildest form, subjective symptoms are absent; the urine is faintly acid; it contains a few pus corpuscles, calcium phosphate, and bacteria. In the second form the urine is turbid, the smell objectionable, the reaction very faintly acid or neutral; pus corpuscles, triple phosphates, calcium phosphate, and bacteria are present; micturition is frequent. In the third form the ordinary subjective symptoms of cystitis are present; the smell of the urine is offensive; the reaction is ammoniacal; pus cells, triple phosphates, calcium phosphate, urate of ammonia, fungi, and bacteria are present. A portion of the sugar in the urine undergoes fermentation, carbonic acid gas is formed and often collects within the bladder, and is passed with the urine. Cystitis has been present twice only amongst the last 140 cases which have come under my observation.

The Skin.

In severe cases of diabetes the skin is dry, and feels rough when touched; but sometimes it appears and feels normal; and occasionally diabetic patients perspire freely, even when lung disease or other complications, liable to give rise to perspiration, are absent. Unilateral sweating has been recorded in diabetes, but of course it is exceedingly rare. The sweat of diabetic patients has been examined for the presence of sugar, with varying results. Griesinger, Vogel, Fübringer, and Forster have been able to detect sugar in the sweat; but Frerichs and others have not been able to detect a trace. v. Noorden examined the sweat of six diabetic patients after the injection of pilocarpine, but even with the phenylhydrazin test could not obtain any evidence of sugar. The skin of diabetic patients, especially in the severe forms, often

feels cold when touched. During diabetic coma, coldness of the skin is a common symptom.

Itching of the skin, pruritus, is sometimes troublesome; occasionally it is one of the first symptoms. It is diminished by a diet or treatment which causes a reduction in the sugar excretion.

This pruritus may be general or local. General pruritus is very rare; it has been attributed to irritation of the peripheral cutaneous nerves owing to dryness of the epidermis, or to the circulation of fluids containing an excess of sugar. Another explanation is, that central irritation is projected towards the periphery (v. Noorden). Local pruritus, in the genital organs, is a common symptom. It is more frequent in females; and sometimes medical advice is sought on account of pruritus or eczema of the vulva, this being the first symptom of the disease which has attracted the patient's attention. Hence, in all cases of pruritus or eczema of the vulva, the urine ought to be examined for sugar. The parts affected first are the labia minora, then the labia majora, and, finally, the skin of the thighs adjacent to the genital organs. All those parts with which the urine may come in contact are liable to be affected. The itching is excited by the irritation of the sugar in the urine and by the growth of fungus on the genital organs. Pruritus is usually accompanied by congestion and redness of the vulva, and may be followed by general eczema.

In the male, pruritus of the glans penis and prepuce sometimes occurs, and occasionally the scrotum is affected; but these conditions are much more rare than pruritus of the vulva.

Eczema and erythema.—The genital organs are most commonly affected owing by their irritation by saccharine urine and fungus growth. But sometimes eczema and erythema occur in parts with which saccharine urine does not come in contact.

Eczema of the vulva is the most common affection. The irritation of saccharine urine causes pruritus and a burning sensation in the region of the vulva. The parts become congested, and, owing to the irritation, excoriations are produced; also fungus spores and mycelia develop in the mucous membrane, which, being frequently wet with the saccharine urine, forms a suitable soil for their growth. Both the conditions lead to the development of eczema. On the affected

parts whitish crusts and scabs are found, which consist of epithelial scales and dried secretion mixed with fungus spores and mycelia. Eczema of the vulva may lead to dermatitis or hypertrophic vulvitis; or, if septic organisms penetrate deeply into the affected parts, boils and phlegmonous vulvitis may develop; sometimes the eczema extends to the mucous membrane of the vagina. Pruritus and eczema of the vulva are much more common in dirty patients than in clean patients.

The majority of cases of eczema of the vulva occurring about the climacteric period of life are due to diabetes.

The amount of sugar in the urine is sometimes only small, and often there is great improvement under treatment, especially in females at the climacteric period.

In the male, pruritus of the penis or scrotum may occur, owing to the irritation of the saccharine urine. Erythema around the meatus is liable to develop, and this may spread over the glans penis; finally, a balanitis may be produced, and fungus spores and mycelia may develop under the prepuce. This condition is met with chiefly in patients who have a long prepuce. The mucous membrane may become fissured and thickened, the prepuce may lose its elasticity, and finally phimosis may develop. The integument of the prepuce may also become thickened; sometimes the prepuce becomes very œdematous, and even sloughing and gangrene have been observed. Pus cells and sometimes fungus spores and mycelia may be washed away from the penis, and cause a trace of albumin and a slight deposit in the urine.

Eczema of the male genital organs is occasionally met with: it starts from the glans and prepuce, and may extend to the neighbouring parts. Sometimes white patches of fungus growth are found on the glans penis and prepuce.

Thus in a case of diabetes of four years' duration, the end of the prepuce was red, thickened, inflamed, and œdematous, and there was also phimosis. The mucous membrane at the end of the prepuce was studded with small white patches, which, on microscopical examination, were found to consist of fungus growth and epithelial scales.

In another case, a severe form of diabetes in a youth of 19, the prepuce was inflamed and thickened, and when retracted, a number of small white patches were seen on the glans penis. Scrapings from these patches, when examined microscopically,

were found to consist of epithelial cells, a few pus corpuscles, and fungus spores and mycelia.

Boils.—Boils are amongst the most common of the skin lesions in diabetes. They often occur at an early stage, and sometimes they are the first symptoms noticed by the patient. Seegen states that he has never seen boils in an advanced stage of the disease. In the advanced cases of diabetes admitted into the Manchester Royal Infirmary, certainly they are very rare. Boils generally occur in stout patients; they may be single or multiple; they usually develop upon the neck, back of the shoulders or buttocks, but they may occur at any part. In females, sometimes they form on the labia of the vulva.

Boils are, of course, due to other causes besides diabetes; but a large proportion of all cases (one-fourth according to v. Noorden, one-third according to Marechal) are due to this disease. In diabetic patients, as in other subjects, infection with micro-organisms is the exciting cause, and pure cultures of the staphylococcus aureus have been obtained from the boils of diabetic patients.

Carbuncles are less frequent than boils; they may be amongst the earliest symptoms, however, which have attracted the patient's attention, and he may come under treatment for this complication before diabetes has been diagnosed. Carbuncles may also appear at an advanced stage of the disease. They occur mostly in the neck, occasionally on the face or other parts of the body. They have a tendency to extend and become gangrenous, or to give rise to surrounding cellulitis, or to great destruction of tissue; and very often they lead to a fatal termination. Like boils, carbuncles are excited by the action of micro-organisms. They occur in other diseases besides diabetes, but the two affections are so frequently associated, that it is important to examine the urine of every person who suffers from carbuncles.

Gangrene is a complication sometimes met with. It may be primary, or secondary to wounds, contusions, boils, carbuncles, or cellulitis.

The lower limbs are most often affected, the gangrene commencing in the toes, and not infrequently at a part which is subject to the pressure of a tight boot. Just as in the case of boils and carbuncles, gangrene is sometimes the first symptom to attract attention to diabetes in an apparently healthy person,—

hence the necessity of examining the urine for sugar in all cases of gangrene.

Diabetic gangrene may be moist or dry. Before early middle age, spontaneous gangrene does not occur, or occurs only very rarely in diabetic patients. I have never seen gangrene amongst the numerous cases of the severe forms of the disease under the age of 40 at the Manchester Royal Infirmary. All the cases have been over that age.

Godlee ([42]) points out that there are three exciting causes of gangrene in diabetic patients: (1) Inflammatory conditions; (2) atheroma of the vessels; (3) neuritis in the peripheral nerves.

A large proportion of cases of diabetic gangrene of the leg are due either to atheroma or neuritis.

Koenig ([43]) attaches great importance to the association of extensive atheroma of the arteries with diabetic gangrene. He states that thrombosis of the larger vessels is often present, and generally there is marked atheromatous degeneration of the smaller arteries (nine out of eleven cases examined). Sometimes both atheroma and neuritis play a part in the development of diabetic gangrene.

When gangrenous inflammation appears in a diabetic patient, severe symptoms develop; the patient becomes drowsy, and delirium, loss of appetite, and coma may occur. These symptoms are more marked when the gangrene is moist than when it is dry.

Wounds of the skin heal badly in diabetic patients, and sometimes become gangrenous. Operation incision wounds generally heal badly also, and though the results are now much better than formerly, surgeons still avoid operations on diabetic patients if possible. The operation for phimosis is said to be particularly unsatisfactory (v. Noorden). There is one exception to the above statement, *i.e.* the operation for diabetic cataract, which is now very often successful.

Perforating ulcers, chiefly on the soles of the feet, and about the toes, especially about the big toe, are occasionally met with in diabetes. The ulcers resemble those seen in locomotor ataxia, and the knee-jerks are frequently absent in these cases. Hence, if the urine be not examined, a diagnosis of early locomotor ataxia is liable to be made. Often the patients complain of pains in the legs, and the calf muscles are tender. Sometimes there are other signs of peripheral neuritis.

Pathologically, parenchymatous neuritis of the peripheral nerves of the legs has been found in some of the cases of diabetic perforating ulcer, and it is probable that the ulcers are due to neuritic changes (44).

Often the starting-point of a perforating ulcer is a large corn or bunion, which is cut by the patient, the skin around and beneath being injured in the process. In other cases a patch of superficial necrosis develops; this separates, and an ulcer forms. Sometimes a hæmorrhage, just beneath the skin, appears to be the starting-point of a superficial necrosis and ulcer (45).

It is important to examine the urine for sugar in all patients who suffer from perforating ulcers of the feet.

Amongst the last 140 cases of diabetes which have come under my observation, perforating ulcers have been present in four only. The ages of the four patients were 52, 55, 55, and 67 respectively. All were suffering from a mild form of the disease. In the first case, distinct symptoms of peripheral neuritis were also present, and the knee-jerks absent; in the second case, the knee-jerks were absent; in the third case, one knee-jerk was absent, the other very feeble; and in the fourth case, both knee-jerks were present. In one case the ulcer was just below the external malleolus; in one case in the centre of the sole; and in two cases near the toes.

Vasomotor changes—bulbous fingers. — In three cases of diabetes I have observed a peculiar condition of the fingers The extremities of the fingers were much swollen, bulbous, hyperæmic, and of a bright red colour; and the patients complained of burning and tingling of the finger-tips. Sometimes there was also hyperæmia of the palms of the hands. The toes were affected in a similar manner, but to a less degree. One of these patients was suffering from advanced phthisis, another from early phthisis, and in the third, signs of phthisis appeared soon after the bulbous condition of the fingers was noted.

Spontaneous shedding of the nails has been recorded in a few cases of diabetes (46).

Anasarca without any signs of cardiac failure, and without the presence of albumin in the urine, is an occasional complication of diabetes. It has not been well marked in more than 5 per cent. of cases which have come under my observation. The œdema is chiefly in the legs, and there is pitting of the skin about the ankle, on the dorsum of the foot, and over the tibia.

Occasionally œdema affects the hands, face, and other parts. Thus in the case of a diabetic patient, æt. 34, under the care of Dr. Leech at the Manchester Infirmary, after the disease had been present for five years, there was well-marked œdema of the feet, scrotum, and penis. The œdema varied from time to time; some days it was almost absent; on other occasions, after the patient had been walking about for some time, it was very well marked. There was no albumin present in the urine, and no indication of cardiac or vascular trouble. At a later date, there was also great œdema of the dorsum of each hand, and marked pitting on pressure, but this disappeared rapidly after rest in bed. Sir William Roberts ([47]) draws attention to a slight pitting over the tibiæ, which he attributes to the soft atonic state of the subcutaneous tissues rather than to true œdema. Frerichs ([48]) found œdema, without kidney mischief, in twenty-five out of 400 cases. Ascites with œdema of the arms and hands is mentioned by Roberts, who also quotes a similar case recorded by Fischer. I have seen two cases of slight ascites in diabetes and one marked case, but in the latter the liver was cirrhosed; in the other two there were no signs of liver disease.

Xanthoma diabeticorum.—This is a very rare complication. Morris ([49, 50, 51]) has collected twenty-one cases from literature, and the following account is based chiefly on his description. The affection is evidently directly due to the diabetic conditions. When the excretion of urine and sugar diminishes the eruption disappears, but reappears with the return of the glycosuria. The skin eruption consists of small papules or nodules about the size of a pea; they have a rounded or conical form, and may be discrete or confluent. Some are surmounted by a yellowish apex, which gives them a deceptive resemblance to pustules of solid consistence. They are firm to the feel, and are essentially inflammatory. Subjective sensations of heat, burning, and itching are present. Sometimes the nodules have a reddish tinge, and only appear yellow when the skin is stretched. They are found on the forearms, buttocks, and knees, and may extend to the scalp, face, and trunk; but in some cases the eruption is universal. The papules may remain stationary for months or years, and then undergo rapid involution and leave no trace behind. They occasionally re-develop two or three times. The presence of this eruption may be the first indication of diabetes.

Morris gives the following points of difference between

diabetic xanthoma and the non-diabetic varieties:—(1) While ordinary xanthoma planum and multiplex is slow in evolution and generally permanent, xanthoma diabeticorum appears suddenly and subsides almost as suddenly. (2) While xanthoma planum almost invariably begins on the eyelids, and is usually confined to them, and whilst xanthoma multiplex chiefly affects the flexor and extensor surfaces of the limbs, the eyelids, and the palms, the diabetic variety for the most part attacks the neck, trunk, and extensor surfaces of the limbs. (3) While jaundice is a very frequent accompaniment of ordinary xanthoma in adults, and diabetes mellitus has never been recorded as occurring in association with it, the reverse is the case as regards xanthoma diabeticorum, in which sugar in the urine is a constant feature, and jaundice an unknown complication.

But Morris thinks that xanthoma planum and xanthoma multiplex are members of the same group, and that anatomically the three varieties are practically identical.

In addition to the above-mentioned skin complications, the following affections have also been described in association with diabetes:—Psoriasis, acne cachecticorum, dermatitis herpetiformis, herpes zoster with persistent neuralgia, eczematous impetigo, lichenoid eruptions, chronic papular urticaria, purpura hæmorrhagica, erysipelas, and dermatitis diabetica papillomatosa (Kaposi).

Recently attention has been drawn to a form of diabetes associated with bronzing of the skin, and the disease has been described as *diabète bronzé*. An account of this affection is given on p. 308.

The Eyes.

Defects of vision are not uncommon in diabetes, and sometimes the patient first seeks medical advice on account of ocular symptoms. Some of these ocular affections are merely accidental complications, or are only very indirectly the results of the diabetes, whilst others are directly caused by the disease. The latter group includes—(1) Cataract; (2) pure accommodation paralysis in middle age; (3) short-sightedness, developing later in life, between the ages of 40 and 60 years, without any opacity of the lens (Hirschberg [52]); (4) vitreous opacities; (5) retinitis; (6) amblyopia, like tobacco amblyopia. Retinitis and amblyopia are very rare.

Cataract.—This is the most common ocular affection, which gives rise to marked defect of vision in diabetic patients.

Diabetic cataract is usually bilateral; it is met with in children, as well as in adults and old persons. I have seen it in a girl æt. 11, in another æt. 15, and in a youth of 20. It is generally of the soft variety, but not invariably, and in old diabetic patients it may present the same characters as in non-diabetic patients. It does not disappear, as a rule, under anti-diabetic treatment (Hirschberg). Seegen ([53]), however, mentions two cases in which the opacity of the lens diminished with improvement of the symptoms and the diminution of the sugar excretion, but increased when the patient became worse again. A case of spontaneous disappearance has been reported by Nettleship ([54]).

In persons under middle age, diabetic cataract generally develops quickly; and the rapid development of double cataract in a young person ought always to raise the suspicion of diabetes. Diabetic cataract can now be removed successfully, and the results are almost as good as in non-diabetic cases. The operation is sometimes followed by diabetic coma, however.

In the last 100 consecutive cases of diabetes (mostly at an advanced stage of the disease), in which I have examined the eyes, cataract was present in nine. The ages of the patients were—12, 15, 20, 40, 40, 40, 47, 56, and 59 years respectively.

Cataract is not confined to markedly wasted patients; the patients may even be well nourished. Seegen points out that a large amount of sugar is always present in the urine, and states that he has never seen diabetic cataract when the urine contained only a small quantity of sugar, though in these cases other visual symptoms are often present. A satisfactory explanation of the origin of diabetic cataract has not been given. It has been attributed to general marasmus, to the presence of sugar in the lens, to the abstraction of water from the lens owing to the sugar in the adjacent media, and to the conversion of grape sugar in the aqueous humour into milk sugar. But there are objections to all these views. Recently vascular disease in the ciliary processes has been regarded as the cause of nutritional changes in the lens ([55]).

Diabetic retinitis.—Retinal changes in diabetes mellitus were recorded first by Edward Jaeger, and have since been described by

various observers during the last forty years. In a large proportion of the cases both sugar and albumin have been present in the urine, and in these cases, therefore, it is somewhat difficult to say, in the absence of a pathological examination of the kidneys, whether the retinal changes were not entirely or in part the result of renal disease. But in other cases retinal changes have been found, when there has been no albumin in the urine. There is undoubtedly, then, a form of retinitis occurring in diabetic patients, which is not an "albuminuric" retinitis. The retinitis of diabetes also differs somewhat from that of chronic Bright's disease.

It appears to me that the frequency of retinitis in diabetic patients has been over-estimated, however. Many text-books of medicine simply make the statement that retinitis is met with in diabetes, and give no information or hint as to the frequency of this complication. Hence the medical student often receives the impression from such book, that retinitis occurs as commonly in diabetes as in chronic Bright's disease; but, as a matter of fact, diabetic retinitis is rare. The percentage of cases of diabetes in which retinal changes are met with is very small—much smaller than the proportion of cases of retinitis in chronic Bright's disease. Also, when present, the retinal changes appear to be less extensive, as a rule. Eales has estimated that retinitis is met with in 28 per cent. of the cases of chronic Bright's disease; Gowers ([59]) also estimates the proportion to be about 1 to 3½. In the first *fifty consecutive cases* of diabetes mellitus, however, which I carefully examined at the Manchester Royal Infirmary (always using the direct method of ophthalmoscopic examination), I did not meet with a single instance of diabetic retinitis, and yet the majority of these patients were suffering from the most severe form of diabetes —often at an advanced stage. I have examined altogether 100 diabetic patients ophthalmoscopically, with considerable care, but have only met with retinal changes in seven cases. Five cases were specially sent to me by my friend Dr. Edward Roberts, whom they had consulted on account of ocular troubles. In three of the seven cases the urine contained so much albumin, that kidney disease could not be excluded as a cause of the retinal changes: in two there was only a trace of albumin present, but no other signs of nephritis. In two cases albumin was absent. These figures show that retinitis is a very rare

complication in diabetes, and it presents in this respect a marked contrast to the retinitis of chronic Bright's disease.

Diabetic retinitis is met with almost invariably in middle-aged and elderly patients—over the age of 45. As a rule, retinal changes only occur when diabetes has existed for a long period.

A good number of the patients I examined were under the age of 45, and in many cases the disease was of an acute form. Had there been a greater proportion of elderly persons amongst these cases, probably retinal changes would have been

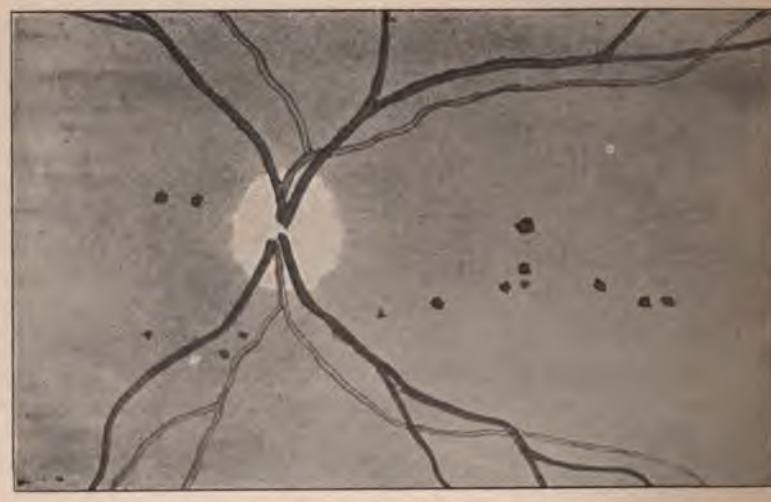

FIG. 12.—Retinitis hæmorrhagica diabetica.

found more frequent. From the fact that retinitis is so rare in the severe forms of diabetes, in persons under 45, I am inclined to believe that there is some other factor necessary for its production, in addition to the diabetic condition of the blood.

The changes in diabetic retinitis consist of hæmorrhages and white patches, both of which are often so small that they cannot be detected unless the direct method of ophthalmoscopic examination be employed. Hirschberg (56) recognises three varieties of diabetic retinal disease—(1) Retinitis hæmorrhagica diabetica; (2) retinitis centralis punctata; (3) combined form. Both eyes are generally affected.

1. *Retinitis hæmorrhagica diabetica.*—In this form small dark

red dots or punctiform patches of hæmorrhage are scattered over the retina; occasionally they are striated. They are generally situated behind the vessels; they may occur alone, but more frequently are associated with white patches, as in the third variety—the combined form.

2. *Retinitis centralis punctata.*—The retinal changes may develop gradually or suddenly. They consist of small bright white patches, which are situated in the deeper retinal layers. They are found chiefly near the centre of the retina, between the upper and lower temporal branches of the central artery.

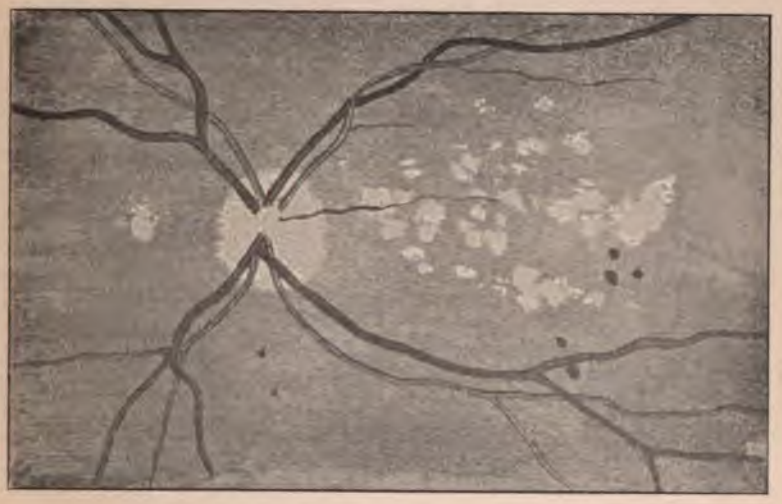

FIG. 13.—Retinitis centralis punctata.

They are also found near the optic disc, and to the nasal side thereof. The smaller patches consist of little white dots or specks, which have been described as "curdy." If larger, they may appear like white stripes; or they may be clustered together in the form of a semicircle or incomplete circle around the macula; occasionally there are two incomplete concentric rings of white patches. But the white patches are never arranged, like those in the retinitis of chronic Bright's disease, in a star-shaped or fan-shaped form, radiating from the yellow spot. There is no pigmentation around the retinal patches.

3. In the *combined form*, both hæmorrhages and white patches are met with.

Blurring of the margin of the disc and optic neuritis are absent in diabetic retinitis, whilst blurring of the margin of the disc or slight neuritis is very frequent in albuminuric retinitis. It is stated that occasionally the retinal changes are associated with primary optic atrophy; whilst optic atrophy is very rare in albuminuric retinitis, and, if present, generally follows neuritis. Frequently, diabetic retinitis is associated with opacities of the vitreous, the latter being due to minute hæmorrhages: the association is always suggestive of diabetes. Occasionally diabetic retinitis has been followed by

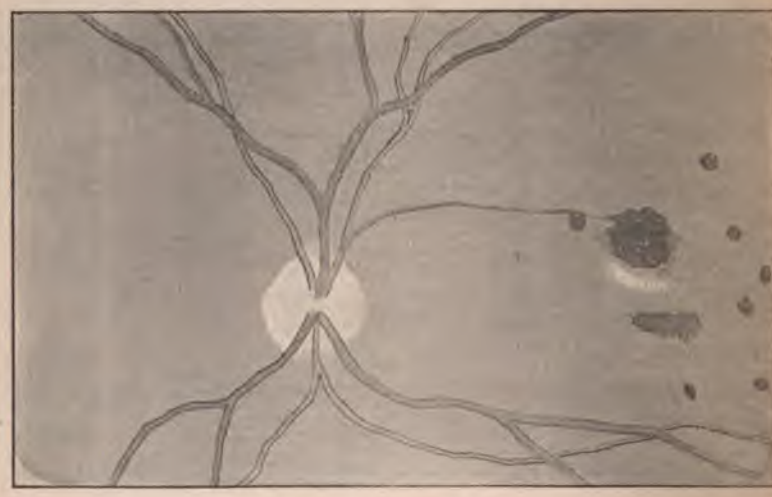

FIG. 14.—Retinitis, combined form.

hæmorrhagic glaucoma. Sometimes, though very rarely, the patient comes under treatment on account of the defect of vision produced by the retinal changes. Often, however, well-marked symptoms of diabetes have caused the patient to seek medical advice, long before the retinal changes have developed.

The symptoms produced by diabetic retinitis are failure of sight and difficulty in reading. The patient may complain of a haze, or of a mist, or of dark specks before the eyes. The retinal changes are progressive, and recovery never occurs.

Saundby ([80]) believes diabetic retinitis to be of grave prognostic significance, though he is not able to support this view by statistics, and, owing to the rarity of the complication, statistics

would be difficult to obtain. When diabetic retinitis develops in any given case of diabetes, the prognosis in *that* case is naturally worse than if retinitis were absent. Nevertheless the prognosis in diabetes is so much influenced by the form of the disease, the age of the patient, and other conditions, that the prognostic significance of such a rare complication as diabetic retinitis is very difficult to estimate. Retinal changes are not found in young persons and in acute cases, but are met with chiefly in elderly patients, and in these cases the prognosis is best. Hence the prognosis will be probably worse in a young patient without retinal changes than in an old person with retinal changes. But of elderly persons the prognosis would naturally be worse, other things being equal, when retinal changes were present, than when they were absent.

The following are some of the points of difference between diabetic and albuminuric retinitis:—

Diabetic Retinitis.	Albuminuric Retinitis.
1. Patches of retinitis distributed irregularly over the central part of the retina; not specially localised to the region of the macula; no tendency to grouping of the patches in a star-shaped or fan-shaped manner around the macula; sometimes patches arranged in an incomplete circle around this region.	Patches frequently most numerous at the macula; often localised to this region; often grouped in a star-shaped or fan-shaped cluster around macula.
2. Not associated with optic neuritis.	Often associated with optic neuritis; and when marked optic neuritis is absent, the disc is often cloudy and the margins indistinct, even at an early stage.
3. Optic disc not affected, or, if affected, condition is one of primary optic atrophy. Atrophy is exceedingly rare.	Optic atrophy rare; occurs only very late in the disease, and follows optic neuritis; is generally associated with typical albuminuric retinitis.

4. Hæmorrhages as a rule are punctiform.	Hæmorrhages generally striated or irregular in shape, not punctiform.
5. Retinal arteries and veins not much changed in appearance.	Arteries small, veins often dilated and slightly tortuous.
6. No diffuse retinitis.	Often diffuse retinitis present.
7. Often associated with hæmorrhages into the vitreous.	Not associated with vitreous opacities.

Nettleship ([57]), in a case of diabetic retinitis, in which he examined the eye microscopically, found œdema of the retina and hyaline degeneration of the intima of the small arteries. He also found that the capillaries were distended, and that minute globular aneurysms were connected therewith. The vessels of the brain, kidney, and spleen also presented similar minute aneurysmal dilatations.

Occasionally, though exceedingly rarely, a cerebral tumour has given rise to optic neuritis and glycosuria in the same patient.

Sometimes, though very rarely, albuminuric retinitis occurs in a diabetic patient who is also suffering from granular kidney. Primary optic atrophy has been met with in a few cases, but it is exceedingly rare, and probably only indirectly connected with diabetes. In the two cases of diabetes associated with acromegaly, recorded pp. 137–8, there was primary optic atrophy. In both cases a sarcoma of the pituitary body was found; the growth had compressed the optic chiasma and optic nerves, and so given rise to optic atrophy.

Diabetic amblyopia.—Occasionally a defect of vision, resembling tobacco amblyopia, is met with in diabetes. In many of these cases naturally the patients have been tobacco smokers, and the visual defects have probably been due to tobacco amblyopia in diabetic patients. Also, cases have been recorded in which anti-diabetic treatment was ineffectual until smoking was discontinued. But the same kind of amblyopia has been met with in diabetic patients who were not smokers.

In these cases the vision is impaired, but ophthalmoscopic examination reveals no changes in the disc or retina. A perimetric tracing shows that peripheral vision is normal, but that

there is a central scotoma for colours, or for both white and colours. Diabetic amblyopia is thought to be due to a retrobulbar neuritis. In the two following cases amblyopia of this nature was present:—

CASE 1.—A. R.; the patient suffered from a severe form of diabetes. Sight had been gradually failing for fourteen weeks. He had been a smoker, but when I examined him had not smoked for three weeks, nevertheless the vision had not improved but had become worse. Distant vision was $\frac{3}{24}$ in each eye. The media, optic disc, and retina of each eye were normal, but there was a central scotoma. Red and green were not recognised at the centre of the field, but were recognised at the periphery.

CASE 2.—J. B., æt. 30, suffered from a severe form of diabetes. Vision was greatly impaired, R. V. = $\frac{3}{60}$, L. V. = $\frac{3}{60}$. Ophthalmoscopic examination showed that there were no opacities of the cornea, lens, or vitreous, and the retina and optic disc were normal in each eye. There was no hemianopsia, the pupils reacted to light and accommodation, and there was no paralysis of the ocular muscles. Examination showed a central scotoma for red and green. Blue and yellow were seen in all parts of the field. The patient had smoked half an ounce of tobacco daily.

Schmidt-Rimpler, in the examination of 140 diabetic patients, obtained evidence of retrobulbar neuritis (which could not be traced to alcohol or tobacco) in thirty-four. In one case of diabetes with central colour scotoma, distinct atrophy of the macular fibres of the optic nerve was found on microscopical examination.

The following ocular affections have been also met with in diabetes, but probably most if not all of these are mere accidental complications:—Diplopia due to paralysis and paresis of ocular muscles, loss of the power of convergence, iritis, corneal inflammation, conjunctival hæmorrhages, furuncles and eczema of the eyelids, hemiopia.

THE SEXUAL ORGANS AND FUNCTIONS.

The affections of the skin of the genital organs have been described already on p. 223.

In addition to these cutaneous affections, the sexual functions are often markedly altered in diabetes. In *the male*, diminution

or loss of the sexual power is not infrequent. The loss of sexual power varies in degree from a defective power of erection to total extinction of sexual desire. It may occur not only in advanced cases, but sometimes it is one of the early symptoms, and occasionally the patient first seeks medical advice on account of impotence.

Frerichs ([61]) mentions the case of a diabetic gentleman, whose illness dated from a violent fit of passion, brought about by the discovery of the deception of his steward. The next day sugar was found in the urine, and at once impotence was noticed. Seegen records similar cases. Usually, however, the sexual weakness is only noticed after the disease has been present a long time.

In the milder forms of diabetes, when the symptoms improve under treatment, often the sexual functions are restored. Seegen ([62]) points out that diabetic patients frequently note that, with an improvement of other symptoms under treatment, erections again occur.

Loss of sexual power does not always occur, however; even when the disease is advanced, the sexual function may be unimpaired. In some cases, both increased sexual power and increased sexual desire have been noted.

In *females* the sexual desire is said to diminish greatly in severe cases, whilst in elderly women who suffer from the milder forms of diabetes it is said to be increased ([63]).

Amenorrhœa is sometimes a symptom at an early stage; in other cases, menstruation occurs at regular or irregular intervals, until a later period of the disease.

Conception may occur in diabetic women, and pregnancy and parturition may be apparently unaffected by the disease, but there is a great tendency to abortion. According to Gaudard ([64]), 33 per cent. of pregnant diabetic women abort. During pregnancy and the puerperal state the disease often advances markedly. According to Gaudard, 41 per cent. of children born of diabetic women die.

(Matthews Duncan's ([65]) conclusions with reference to the relation between diabetes and pregnancy are given on p. 114.)

The Ears.

Diseases of the ear are not common in diabetic patients.

Many authors ([66]), however, regard diabetes as an occasional predisposing cause of furunculosis of the external auditory meatus. Also a number of cases have been recorded of acute inflammation of the middle ear in diabetic patients. The course is said to differ from that of ordinary acute middle-ear catarrh, by the rapid onset, the abundant suppuration, the tendency to severe hæmorrhage, and the early extension of the disease to the mastoid process.

Pathological examination has shown that the petrous and mastoid portions of the temporal bone are implicated early, and that often extensive caries or necrosis occurs. Frerichs ([67]) records a case in which otitis media and caries of the mastoid process were followed by thrombosis of the lateral sinus.

Acute otitis media is not common in diabetes. It has been present twice only amongst 140 patients who have come under my observation in Manchester. In one case the affection was bilateral and the suppuration profuse.

The Nervous System.

1. *Mental Condition.*

Often there is a marked change in the mental state in diabetes. Mental dulness, apathy, or drowsiness, are frequently noticed, especially in advanced cases. The patient is often disinclined to perform mental or bodily work; he is frequently sorrowful, despondent, melancholy, and depressed: sometimes hypochondriacal, and occasionally has suicidal tendencies. He often speaks and looks like a man who recognises his condition to be hopeless; and it is somewhat rare amongst the severe forms of the disease, such as are met with in hospital practice, to find a cheerful, hopeful patient; and in this respect the wasted diabetic differs from the wasted phthisical patient.

It is not to be wondered at that the patient's character often alters as the disease advances. He frequently becomes disagreeable, bad tempered, and sulky. He may become deceitful, untruthful, and cunning. A cheerful, good-natured, well-behaved, and agreeable man may gradually become dull, sulky, disagreeable, rude, and deceitful, as was the case with a diabetic patient whom I had the opportunity of carefully observing for five years.

Weakness of mental power, of judgment, of memory and

will, may occur, but, as a rule, the intellect remains clear up to the last.

Mania has been recorded in a very few cases. Insomnia is sometimes a troublesome symptom, but periodic attacks of somnolence have also been described.

Epilepsy and diabetes.—Diabetes and epilepsy are very rarely associated in the same subject, though epilepsy, diabetes, and mental disease are sometimes met with amongst various members of the family of a diabetic patient. In only one case of diabetes which has come under my observation was the patient subject to fits, but he had suffered from epilepsy for some years before the onset of diabetes.

As regards the relationship of the two diseases, Ebstein ([68]) points out that glycosuria may be (1) the cause of epilepsy, (2) the result, (3) or both conditions may arise independently of each other, but may be due to a common cause.

(1) Cases in which epilepsy is caused by diabetes may be divided into two classes: (*a*) Epilepsy may be due to cerebral lesions which sometimes occur in the course of diabetes (as in a case recorded by Lépine and Blanc, in which hemiplegia and epileptic attacks occurred in a diabetic patient, and both were due to a microscopical lesion of the cerebral cortex). (*b*) It is possible that epilepsy may be occasionally due to the action of toxic products, formed in the system of the diabetic patient. But the connection is certainly very rare. Thus Dreschfeld ([69]) states that convulsions were present once only out of sixteen cases of diabetic coma, and in eighty cases collected from literature he found convulsions recorded in six only. Jacoby ([70]) has reported three cases of epileptic attacks in diabetic patients, which he regards as the result of acetonæmia; but certainly convulsions in diabetic coma are quite exceptional. In twenty-seven cases of diabetic coma which have come under my observation in Manchester, convulsions were absent in all.

(2) Epilepsy is thought by some authors to occasionally cause glycosuria. Some of the older observers state that glycosuria may be produced by an epileptic fit. Ebstein states, however, that he has never found sugar in the urine as the result of a fit. I may also add that many years ago I frequently examined the urine of epileptic patients, when house physician to the National Hospital for the Paralysed and Epileptic, Queen's Square, London, but never met with any case in which sugar was present

in quantity sufficient to give a reaction with Fehling's solution; neither have I met with any instance since then. Probably glycosuria is only very rarely produced by an epileptic fit.

When diabetes is detected after an epileptic attack, it is difficult or impossible to prove that the former affection is the result of the latter. The coexistence of the two affections may be merely accidental; and Ebstein concludes that, from the few facts recorded, it appears at present impossible to prove that epilepsy produces diabetes, or even acts as a predisposing cause.

(3) With respect to the occurrence of diabetes and epilepsy simultaneously, Ebstein points out that, since epilepsy frequently alternates with diabetes and mental disorders in neuropathic families, it would not be in the least surprising if an individual affected with hereditary neuropathy developed simultaneously epilepsy and diabetes. Also, in other cases, there may be predisposing causes determining simultaneously diabetes and epilepsy.

Diabetes and insanity.—In cases of insanity, sometimes sugar is found in the urine; but in these cases the condition is generally one of slight glycosuria, or a mild form of diabetes. The mental condition is primary, and the glycosuria a secondary complication (see p. 92).

Landenheimer ([71]) has recently very carefully reviewed the relationship of diabetes to general paralysis of the insane. He concludes that there is no clear evidence that diabetes can produce general paralysis, but that in a few rare cases symptoms resembling those of general paralysis have been met with in diabetic patients, and in such cases improvement has occurred under anti-diabetic diet.

2. *Localised Brain Lesions.*

A few cases are on record of cerebral symptoms, such as hemiplegia, monoplegia, aphasia, hemianopsia, localised epileptic convulsions, etc., occurring in the course of diabetes, and yet on post-mortem examination the brain has been found apparently normal. These symptoms appear to be due to the action of some toxic substance, and such cases resemble those of paralysis, etc., occurring in uræmia, in which brain lesions are not discovered post-mortem.

Occasionally diabetes is associated with symptoms of disease

of the brain during life, and post-mortem the usual changes, such as softening, hæmorrhage, etc., are found. In some cases the association is merely accidental; in other cases the brain lesions play some part in the causation of the diabetes; whilst in a third group of cases they are connected with diabetes indirectly. Thus it is possible that arterio-sclerosis may be the cause of diabetes, by producing pancreatic changes, or some lesions in the medulla; and in such cases the arterio-sclerosis may also lead to cerebral hæmorrhage or thrombosis. Again, it is possible that syphilis may be the cause of diabetes, by producing changes in the medulla; and in these cases other syphilitic lesions of the nervous system may develop. The condition of the brain in diabetic patients, and the significance of the various cerebral lesions detected, has been already discussed.

3. *Diabetes and Lesions of the Spinal Cord.*

Glycosuria or diabetes is sometimes associated with symptoms indicating disease of the spinal cord; in other cases, changes in the spinal cord are discovered post-mortem, though there have been no indications of spinal disease during life. In by far the majority of cases, however, there are no indications of spinal disease, either during life or on post-mortem examination.

(1) Bearing in mind the results of physiological experiments on the spinal cord, recorded on p. 65, it is by no means improbable that spinal cord disease is occasionally, though very rarely, the cause of glycosuria or diabetes.

A number of cases of locomotor ataxia and disseminated sclerosis, associated with glycosuria, and occasionally with true diabetes, have been recorded ([72-76]). It is probable that in some of these cases the glycosuria or diabetes has been produced by sclerosis, extending to the medulla. Such cases are exceedingly rare, and in most of them the nervous disease has been associated simply with glycosuria, very seldom with true diabetes.

(2) In another group of cases of diabetes or glycosuria associated with spinal disease, it is not clear whether the spinal disease is the cause of the diabetes, whether both are due to some common cause, or whether the association is merely accidental.

Cases of diabetes associated with chronic anterior polio-

myelitis—such are those recorded by Nonne ([77]) and Strümpell ([78]) —would belong to this class.

(3) In a third group of cases, changes are found in the spinal cord, which are probably the result of diabetes, and due to some toxic substance in the blood.

The following are abstracts of notes in two such cases of diabetes, in which I found pathological changes in the posterior columns of the spinal cord:—

[The first case was under the care of Mr. Milner, M.B., at the Salford Union Hospital; the second was under the care of Dr. Steell, at the Manchester Royal Infirmary. To the kindness of these gentlemen I am indebted for the opportunity of making the clinical and pathological examinations.]

CASE 1.—J. D., æt. 52—*Paresis and wasting of right deltoid, pectorals, biceps and triceps muscles; on left side the same muscles affected, but to a less extent.*—Previous health good until nine months ago, when he suffered from a severe cold. Whilst recovering he began to be troubled with great thirst. No family history of diabetes. No history of injury or alcoholism. Six months ago the left arm became weak. At that time no weakness of the right arm had been noticed. Three months later the patient regained power in the left arm, but the right arm then became weak, and has continued weaker than the left up to the present time.

30*th May* 1892.—*Present state.*—Patient is much wasted. Urine 1040, no albumin; contains a large amount of sugar, 20 to 26 grs. to the ounce; quantity of urine, 140 to 170 oz. daily. Arteries atheromatous, radials calcareous. No affection of heart or lungs can be detected. The patient cannot raise the hands to the mouth, but can flex at the elbows and perform movements of fingers. Abduction and other movements at shoulders very feeble. Slight foot-drop. Patient can dorsiflex feet, though feebly. He complains of numbness of the legs, and frequent cramp in the calves of the legs at night. Knee-jerks both absent.

29*th June.*—Patient is able to walk, but drags his legs and walks with his feet widely apart. No ataxia. Slight dropping of the feet. When in bed he can raise his legs in the extended position quite well. The thigh muscles are in a fairly good state of nutrition. Slight œdema of the feet. Both knee-jerks are now present, but very feeble. Frequent cramps in the calf muscles at night. No other sensory symptoms in the legs. Wasting of biceps, triceps, deltoid, pectorals, and scapular muscles of each side, especially the right. The forearms and hands are only very slightly wasted, and present a well-marked contrast to the shoulder and upper arm muscles. The posterior borders and

lower angles of the scapulæ project, especially the left. This projection is more marked when the arms are raised. When the patient shrugs his shoulders, the upper part of each trapezius is felt to contract. Patient has difficulty in placing right hand on left shoulder, but can place left hand on right shoulder fairly well. The clavicular part of the right pectoral is markedly wasted, and there is a deep depression below the clavicle. When the hands are clasped together firmly between the knees, the left pectoral muscles become much more prominent than the right. Patient is only able to abduct at the shoulder to a slight extent; he cannot raise the arms into a horizontal position. Flexion (forwards) at the shoulder is much more feeble on the right side than the left; the arm cannot be brought into horizontal position; it can only be raised to an angle of about 45°. The left arm can be flexed (forwards) at the shoulder into the horizontal position. Patient can extend at the shoulders (backwards) fairly well on both sides, and he is able to place each hand on the sacrum. Extension of both elbows feeble; flexion at the right elbow very feeble; flexion at the left elbow somewhat feeble, but much better than on the right side, and much better than extension at the same joint. Patient has great difficulty in raising the right hand to his mouth. He is obliged to feed himself with the left hand. He cannot raise a pot of water to his mouth with the right hand, but is able to do so with the left. (Patient is a right-handed man.) He complains of a cold feeling in the fingers and hands, also of numbness and tingling in the fingers. He has often to place them in warm water to "get the feeling back." The fingers are swollen, especially the terminal phalanges, which are bulbous, but the skin is pale. He is able to feel slight tactile sensations, and to distinguish between the head and point of a pin on each arm and hand.

20*th July*.—Knee-jerks now normal, no ankle clonus; right plantar reflex present, left absent. Abdominal epigastric and cremasteric reflexes normal. Patient is able to feel and localise touch with a pin's-head, and to distinguish between the head and point of a pin quite well all over the arms and legs. Flexion at the right elbow exceedingly feeble, and only the slightest prominence of the belly of the supinator longus can be felt when the elbow is flexed, the forearm being midway between pronation and supination. The left supinator longus is felt readily, when same movement performed. Right biceps and supinator longus greatly wasted.

There is no ataxy in walking, and no symptoms of tabes are present. Death occurred from phthisis, about eleven months after the onset of the disease.

Necropsy.—Body wasted. A considerable amount of serous fluid in the abdominal cavity. Tuberculous disease of the lungs. Pancreas firm; weight, 3 oz.; microscopical examination, after hardening,

revealed cirrhosis. No changes of importance in the heart, liver, kidneys, or spleen. Atheroma of the aorta. Attached to the left side of the lumbar vertebræ (first and second) was a firm oval tumour the size of an egg. Microscopical examination showed that it was a fibroma. The brain (including medulla and floor of fourth ventricle) and the spinal cord appeared normal to the naked eye. The arteries and their smallest branches to the biceps muscles on each side were completely calcified.

The spinal cord was hardened in Müller's fluid. On section of the hardened cord, in the lumbar region, the cut surface appeared quite normal, but in the cervical and dorsal regions there were marked naked-eye changes in the posterior columns. Portions of these columns were much paler than the rest of the white matter of the cord. The colour of the affected parts resembled closely the colour of tracts of ascending degeneration —in cases of transverse lesion of the cord—after hardening in Müller's fluid. In the lowest dorsal region this change (marked paleness) was seen only at the posterior half of Goll's column and the posterior third of Burdach's column on each side. A little higher, the whole of both posterior columns, with the exception of a narrow area in front, was much paler than the rest of the white matter (see Fig. 15, *c*). Higher still, about mid-dorsal region, these changes were seen in Goll's columns and the median halves of Burdach's columns. At one spot in the upper dorsal region the cord was slightly bruised in removal; but examination of the bruised part showed the absence of compound granular cells or other evidence of myelitis. In the uppermost portion of the dorsal region, just above the bruised part, the changes (marked paleness) affected Goll's columns chiefly, but extended slightly into Burdach's columns. In the lowest cervical region the changes were very well marked, and affected Goll's columns only. They gradually diminished at the anterior parts of these columns, and in the highest cervical region only the posterior two-thirds of Goll's columns were affected, but the alteration in colour was quite distinct (see Fig. 15, *a*). With the exception of the posterior columns, the cord appeared quite normal to the naked eye.

On microscopical examination the changes found were very slight, and this was surprising, considering the well-marked naked-eye appearances. In sections stained according to Weigert's method, the posterior median columns in the cervical

region were paler to the naked eye than the rest of the white matter. In the dorsal region they were very slightly paler than the other tracts of white matter, but the difference was less marked than in the cervical region.

In sections stained with aniline blue-black, the posterior median columns of the cervical region were slightly darker in colour than other parts of the white matter; but in the dorsal region the change could only just be detected.

Under the microscope, sections stained both according to Weigert's method and with aniline blue-black showed slight excess of neuroglia connective tissue in the posterior median columns of the cervical region.

In the posterior median columns (cervical region) many of the nerve fibres were swollen, and the part of myelin which, in normal nerve fibres, is stained black in Weigert's method (that

FIG. 15.—Naked-eye appearances of the spinal cord on section, after hardening in Müller's fluid; normal white matter is shaded. The portions of the posterior columns affected are pale. *a*, upper cervical region; *b*, lower cervical region; *c*, dorsal region.

is, outer part) was reduced to a very narrow rim. In sections stained with aniline blue-black, many of the axis cylinders of nerve fibres in the posterior median columns were seen to be swollen.

In sections stained according to Marchi's method, scattered degenerated fibres (stained black) were seen in the posterior columns (median and external) of the dorsal region and in the posterior median columns of the cervical region; they were more numerous in the latter region. Sections of the lumbar part of the cord appeared normal. At no part of the cord was there any evidence of myelitis. The pyramidal tracts (direct and crossed), the direct cerebellar tracts, and all other parts of the white matter were normal. In the lower part of the cervical region most of the nerve cells of the anterior horns of grey matter were pigmented, and some—chiefly those of the inner group—were perhaps slightly atrophied.

The finest nerve fibres entering the biceps muscles (branches of the musculo-cutaneous) were teased in osmic acid, but

microscopically they appeared quite normal; also sections of nerve fibres to the biceps muscles, hardened and stained according to Marchi's method, appeared normal.

CASE. 2.—E. B., æt. 21, gave a history of severe fright, followed by great mental distress and anxiety, twelve months previous to admission to the hospital. Prior to that date the patient had been in good health, but she has not been able to follow her employment (that of a dressmaker) since. Thirst and diuresis noted first about four weeks after the fright. The patient was considerably emaciated. The urine had a specific gravity of 1038; it contained a large amount of sugar, but no albumin; it gave a distinct (Gerhardt's) reaction with perchloride of iron, and a well-marked reaction for acetone (Legal's test). There were signs of tuberculous disease of the apex of the left lung, and the sputum contained numerous tubercle bacilli. The knee-jerks were present, but feeble. The pupils reacted to light and accommodation. A few days after admission the knee-jerks disappeared; they remained absent up to death, which occurred from asthenia about seven months after admission. During the last few days of life there were slight pains in the legs, chiefly about the ankles and soles of the feet, but there were no symptoms of locomotor ataxy or other cord lesion during the illness. Both lungs were extensively affected with tuberculous disease during the latter three months of the patient's life. The quantity of urine varied from about 90 to 116 oz. daily during the time the patient was in the hospital, and the amount of sugar from 28 to 32 grs. to the ounce.

At the necropsy there was extensive tuberculous disease of both lungs. The pancreas was small, and weighed 10 drms. 55 grs., but the heart and other organs were proportionally atrophied. On microscopical examination the pancreas appeared normal.

The spinal cord appeared normal at the necropsy, but after hardening in Müller's fluid, marked naked-eye changes were seen in the posterior columns, on transverse section. The affected parts appeared much paler than the rest of the cut surface, the colour resembling that of degenerated tracts above a transverse lesion of the cord, when the specimen has been hardened in Müller's fluid. In the lowest lumbar region no changes could be detected, but in the middle lumbar region the median thirds of both posterior columns (external and median) were slightly paler than the rest of the cut surface of the cord. In the upper lumbar region the change in colour was more distinct and the pale area more extensive (see Fig. 16, *c*). In the lower dorsal region there was a very pale streak in each postero-

external column. This was especially well marked in the upper dorsal region, and extended over the whole of each postero-external column (see Fig. 16, *b*). In the lower cervical region the postero-median columns presented this pale appearance. In the upper cervical region only the posterior halves of these columns were affected (see Fig. 16, *a*). The direct cerebellar tracts and other parts of the white matter appeared normal in all the regions of the cord.

Microscopical examination.—Sections were stained according to the same methods as in Case 1. In the pale tracts in the posterior columns numerous swollen nerve fibres were seen. Only a very narrow rim of the myelin of these fibres was stained black in the Weigert's specimens; no other changes were detected. Nerve fibres (branches of the anterior crural nerve)

FIG. 16.—Naked-eye appearances of the spinal cord on section after hardening in Müller's fluid. Changes in the posterior columns; normal white matter shaded, parts of white matter affected are pale. *a*, cervical region; *b*, upper dorsal region; *c*, upper lumbar region.

to the rectus femoris (left) appeared normal on microscopical examination.

In both cases the changes were detected much better by the naked eye than on microscopical examination.

I have examined the spinal cord in six other cases of diabetes, but the appearances above described were not met with.

Slight changes in the posterior columns of the cord, in diabetes mellitus, have been described by Sandmeyer ([79]), Minor ([80]), and Leyden ([81]). Since the above cases were published, Kalmus ([82]) has recorded two additional cases in which similar changes were found. In the first of his cases, on naked-eye examination of the spinal cord, after hardening in Müller's fluid, degeneration was found in the posterior columns. This was most marked in the cervical and lumbar enlargements. In the lower cervical and dorsal regions the lesion was confined to Goll's columns; above and below it extended laterally into Burdach's column. The sacral region was unaffected. In the lower dorsal region the

right posterior column was distinctly more markedly affected. In the second case, degeneration of the posterior columns was also found. It was limited to Goll's columns in the upper cervical region. In the lower cervical region it spread to Burdach's column, and was most extensive in the lower cervical and middle dorsal regions. Below the lumbar enlargement the degeneration ceased.

Somewhat similar changes in the posterior columns, more marked to the naked eye than on microscopical examination, have been reported by Minnich ([83]), Bowman, and others in cases of pernicious anæmia. Tooth ([84]) has pointed out that on the sixth day after section of the cord in animals, tracts of secondary degeneration are well marked to the naked eye (by their light colour) on hardening in bichromates, whilst the microscopical changes at this date after section are very slight, and consist chiefly in swelling of the axis cylinders and nerve fibres. Probably tracts of degeneration can be recognised by the naked eye, after hardening in bichromates, before any microscopical changes occur; and Tooth considers that the naked-eye changes are due to a preliminary chemical alteration in the nerve fibres. The condition of the posterior columns in the cases of diabetes recorded above, would appear to correspond closely to the early stage of degeneration described by Tooth. The changes in the posterior columns in the cases 1 and 2 were probably the *result* of the toxic diabetic blood condition.

Kalmus also regards the spinal changes in his cases as the result of the action of some toxic substance in the blood.

In case 2, p. 247, the knee-jerks were absent, and slight naked-eye changes were found in the lumbar region of the cord. As the peripheral nerves (fibres of the anterior crural to the rectus femoris) were normal, it is possible that these changes were the cause of the loss of knee-jerks. Eichhorst ([85]) has found degenerative changes in the peripheral nerves in two cases of diabetes in which the knee-jerks were lost; but in other cases the peripheral nerves have been normal. The absence of knee-jerks in some cases of diabetes may be due to slight changes in the lumbar region of the cord, such as those described above.

The spinal cord has always been normal in the cases which I have examined, with the exception of the two above described, and the case in which cerebro-spinal meningitis was present (see p. 117).

Considering the question of spinal cord complications from the clinical side, we find their occurrence exceedingly rare. Thus, in 140 cases of diabetes in Manchester, indications of spinal cord disease were present during life once only. This patient suffered from paresis of the legs with bladder symptoms, probably due to a transverse myelitis.

4. *Affections of the Peripheral Nerves.*

Sometimes one of the earliest symptoms of which a diabetic patient complains is cramp in the calves of the legs, especially at night; and often there are pains in other parts of the legs also. These symptoms are very common in the severe forms of the disease, and attention has been drawn to them by the late Sir B. W. Richardson, Unschuld, and others. In some cases the legs are very tender, so that the patient cannot bear one leg to lie on the top of the other in bed. Neuralgia and sciatica sometimes occur, but they are very rare in the severe forms of the disease, such as are met with in hospital practice and amongst young patients. Both neuralgia and sciatica are often bilateral; they have been known to appear at the same time as the glycosuria, and to increase along with the increase of the sugar in the urine, and to diminish or disappear when the sugar excretion diminishes or ceases. (Diabetes neuritis is described on pp. 259–66.)

Analgesia and thermo-anæsthesia.—Vergely has recorded cases of diabetes which have presented sensory disturbances like those which are so frequently met with in syringomyelia, *i.e.* loss of sensation to pain and temperature, whilst tactile sensation has been unaffected. I have examined a good number of diabetics for this symptom, but have not met with it.

5. *The Knee-jerks in Diabetes Mellitus.*

Many years ago Bouchard pointed out that the knee-jerks may disappear in diabetes mellitus ([86]). In a paper published in 1892, I recorded the condition of the knee-jerks in fifty cases of diabetes mellitus; in one-half of the cases both the knee-jerks were absent ([87]). I pointed out that previous statistics had varied considerably, and that much difference of opinion existed respecting the prognostic value of this sign. Thus Bouchard found the knee-jerks absent in 36·9 per cent. of his cases,

Auerbach [88] in from 35 to 40 per cent., Maschka [89] in 30·6 per cent., and Eichhorst [90] in 20·9 per cent. Soon afterwards, Karl Grube, of Neuenahr, recorded [91] the results of the examination of the knee-jerks in a series of cases of diabetes [92]. Grube pointed out that in his cases (131 in number) the knee-jerks were absent in 7·6 per cent. only. In a second paper [93] Grube adds other cases, and states that in the combined series the knee-jerks were absent in 13·5 per cent.

The great difference between 7·6 per cent. (Grube) and my own results, 50 per cent., caused me to examine carefully the condition of the knee-jerks in a second series of cases, in order to find out, if possible, the reason for this remarkable discrepancy in statistics. My results in the second series of fifty cases were, however, practically the same; the knee-jerks were both absent in twenty-four, both were present in twenty-three, and one was absent and one present in three cases. I may point out that the cases have been most carefully examined. In taking the reflexes, the skin over the patellar ligament has been well exposed and the ligament struck directly, no clothing intervening. If no knee-jerk has been obtained in the ordinary way, then Jendrássik's and Buzzard's methods have always been employed before the knee-jerks have been recorded as absent. (The patient is seated on a chair with his feet well in contact with the floor, and the knees bent at an angle just a little more than a right angle. He is made to look upwards, to link his fingers together and to pull tightly. The observer places one hand on the rectus femoris muscle, and strikes the patellar ligament with a percussion hammer or stethoscope. If the slightest knee-jerk be present, a contraction of the rectus muscle will be felt [94].) In many cases the knee-jerks appeared to be absent when an examination was made in the ordinary manner, but by the above method they were just obtained; and these cases, however feeble the reflexes, were classed amongst those in which the knee-jerks were present. Most of the cases examined were in-patients at the Manchester Royal Infirmary; they were examined repeatedly, often for weeks or months, and were thus under the most favourable conditions for examination. Hence I feel justified in believing that my figures represent fairly accurately the condition of the knee-jerks amongst hospital patients who suffer from diabetes mellitus in Manchester. The following are my results in 100 cases:—

	Cases.
Both knee-jerks lost in . . .	49
One present, one absent in . .	6
Both present in	45
	100

One of the cases in which the knee-jerks were present at first, came under observation for a second time, after an interval of eighteen months, and both knee-jerks were then absent. If this be added to the forty-nine cases, we have then the knee-jerks absent in 50 per cent. of the cases.

As above stated, Grube found the knee-jerks absent in only 7·6 per cent. of his first series of cases. What is the cause of this remarkable difference in statistics? I know Dr. Karl Grube to be such a careful and reliable observer, that I can place the greatest confidence in his observations, and, of course, am convinced that his statistics are correct with respect to the cases which he has examined. But I feel justified in believing my own statistics to be also accurate. The difference in results is interesting, and I believe the following to be the explanation. The 100 cases, on which I have based my statistics, have been mostly hospital patients in Manchester, who have been suffering usually from a very severe form of the disease. In a large proportion of cases the disease has been in a very advanced condition, and often the observations have been continued practically up to the last—in twenty-six out of the 100 cases up to the last few days, and in a large number of cases up to the last few weeks of life. The majority of the patients have been poor, hardworking people, and amongst the 100 cases there were very few examples of the mild form of the disease which is met with in stout or gouty old people. As regards age, eighty-one of the 100 cases were under the age of 50 years. On the other hand, Dr. Karl Grube states ([95]) that the majority of his patients were over the age of 50 years, and it is well known that the severity of the disease is much less in patients over that age. Then, again, Dr. Grube is engaged in private consulting practice at Neuenahr, a small town in West Germany, much frequented by diabetic patients on account of its alkaline mineral waters, which are regarded as being of great value in diabetes, especially in the diabetes of gouty persons. Also his

patients have probably been in a better social position, and have lived under more favourable conditions of life, than the hospital patients on whom my observations were made. Probably a large proportion of his cases would not be in the very last stage of the disease, otherwise they would not have been allowed to travel to Neuenahr. These I believe to be the causes of the difference of our results. I think it is a point of some interest that the knee-jerks should be absent so much more frequently amongst diabetic hospital patients, who usually suffer from the disease in its severest form. Eichhorst ([96]) has previously drawn attention to a difference between his hospital and private patients, the knee-jerks being absent in 42·9 per cent. of the former and 16·7 per cent. of the latter; but his observations were based on thirty-six private cases and only seven hospital patients.

In the earliest stage of diabetes, even in its most severe form, I believe the knee-jerks would be found present as a rule; but in these cases they are very often lost later. I have frequently observed that in the severe cases in which the knee-jerks have been present when first examined, they have finally disappeared if the cases have been under observation for a long period. Sometimes I have found the knee-jerks present in mild cases of long duration; once at the end of five years, once after the disease had been present seventeen years. In the 100 cases which I have examined, the knee-jerks, as above stated, were lost in 50 per cent., but in many cases I was not able to continue my observations up to the last. In twenty-six cases, however, in which I examined the knee-jerks up to the last day or last few days of life, I found they were both absent in nineteen (= 73 per cent.), and present in seven; but in four out of these seven cases they were exceedingly feeble. In the majority of cases I have found the knee-jerks to be absent during diabetic coma. Thus in twenty-one cases of diabetic coma which have come under my observation in Manchester, the knee-jerks were absent in eighteen, but in three cases they were present (in one case, half an hour before death; in another, three hours before death; and in the third case, at the commencement of coma). Generally, however, the knee-jerks were absent for a long period before the onset of coma. In one case they were present the day before the commencement of coma, but disappeared when the early symptoms of that complication were observed.

The following table (of 100 cases) shows that the knee-jerks are lost in a much greater proportion of cases under the age of 30 years than in cases over 30.

Table showing the Relation between the Presence or Absence of Knee-jerk and the age at which Diabetes occurs.[1]

Between the ages of	Knee-jerks absent.	Knee-jerks present.	Remarks.
10 and 20 years . . .	13	3	
20 and 25 years . . .	9	2	Under the age of 25, knee-jerks were lost in 81 per cent.
25 and 30 years . . .	8	4	Under the age of 30, knee-jerks were lost in 76·9 per cent.
Totals	30	9	
30 and 40 years . . .	8	10	Over the age of 30, knee-jerks were absent in 40·9 per cent.
40 and 50 years . . .	5	14	...
50 and 60 years . . .	9	4	...
Over 60 years . . .	3	8	...
Totals	25	36	

[1] This table is based on another series of 100 cases.

It is well known that in young persons diabetes is of a much more severe type than in middle or advanced life; and this may be the reason why the knee-jerks are absent in a greater proportion of cases under the age of 30.

Variability of the reflex.—A knee-jerk which has disappeared in a patient suffering from diabetes, may return again, and vary very much in the course of time. Thus in a case, J. L., æt. 36, in September 1890, the knee-jerks were *absent*. Urine, daily quantity 210 to 280 oz.; sp. gr. 1030; acid, no albumin; sugar = 27 to 30 grs. to the ounce.

25*th November.*—Knee-jerks *present*; urine, sp. gr. 1032; 26 grs. sugar to ounce; trace of albumin, marked reaction with Fe_2Cl_6.

30*th June* 1891.—Knee-jerks *absent*.

17*th September* 1891.—Patient improved; right knee-jerk *present*, but very feeble; left knee-jerk *absent*.

In another case, J. D., æt. 52 (urine, 1030; 26 grs. of sugar to ounce; amount of urine, 150 to 170 oz. daily), the knee-jerks were absent (Jendrássik's method), May 1892.

29*th June.*—Knee-jerks present.

20*th July.*—Knee-jerks well marked.

Relation to general nutrition.—In diabetic patients who are obese, as well as in those who are markedly wasted, the knee-jerks are sometimes absent, sometimes present; but they are more frequently absent in the latter cases than in the former. Thus in fifteen fairly stout diabetic patients, the knee-jerks were both present in twelve, absent in one; and in two cases one reflex was present, the other absent. In fifteen patients who were markedly wasted, the knee-jerks were absent in ten.

Relation to the condition of the urine.—Though the knee-jerks are more frequently lost in the severe than in the mild forms of the disease, there is no close relation between the state of the reflexes and the condition of the urine as regards specific gravity, quantity of sugar, perchloride of iron reaction. Occasionally they are absent when the urine only contains a moderate amount of sugar; sometimes they are still present when the urine contains a very large percentage of sugar.

When the perchloride of iron reaction is intense, the knee-jerks are sometimes present, sometimes absent.

Relation to pathological conditions.—The loss of the tendon reflex cannot be regarded as evidence of the nervous origin of the disease in any particular case, but must be looked upon simply as a complication. Thus in the case of diabetes presenting symptoms of gross lesion of the nervous system, recorded on p. 132, the knee-jerks were present.

In another case of mild diabetes, in which a tumour of the pituitary body was found post-mortem, the knee-jerks were present. On the other hand, they were absent in a case following a blow on the head, and in cases having a previous history of great mental worry.

Subcutaneous injection of strychnia does not cause the knee-jerks to return (Rosenstein).

As regards the *cause* of the loss of knee-jerks in diabetes, the frequent association of pain, numbness, muscular tenderness, and cramps points to an early peripheral neuritis ([97]); and a few cases have been recorded in which well-marked typical motor and sensory symptoms of peripheral neuritis have been present([98]); also in a few cases examined pathologically, parenchymatous neuritis of the peripheral nerves (branches of the anterior crural) has been found ([99]). But frequently when the knee-jerks are absent there are no other indications of slight peripheral neuritis, and the peripheral nerves may be normal on pathological examin-

ation. I have examined the small peripheral nerves in three cases of diabetes mellitus in which the knee-jerks were absent —in two cases the branches of the anterior crural in the thigh, in the third case branches of the anterior tibial. In all three cases the nerve fibres appeared normal. I have found slight changes in the posterior columns of the spinal cord in two cases of diabetes ([100]). Similar changes have also been recorded by Sandmeyer ([101]), Leyden ([102]), and Minor ([103]) (see p. 246). In one of these two cases the knee-jerks were absent, the peripheral nerves examined (branches of the anterior crural) were normal, but changes were found in the posterior columns extending down to the upper lumbar region. In other cases I have found the spinal cord normal, and many cases have also been recorded in which the knee-jerks have been absent, and yet the cord has been normal on pathological examination. Nonne has reported a case of diabetes complicated with progressive muscular atrophy ([104]). Pathological examination revealed chronic anterior poliomyelitis. The nerve cells and fibres of the anterior horns of grey matter were markedly degenerated at all parts of the cord; at a late stage of the disease the knee-jerks were absent. In one case in which the knee-jerks were absent during life, I found both the smallest peripheral nerves (branches of anterior crural) and the spinal cord normal on pathological examination, and others have recorded similar results ([105]).

The changes just mentioned (in the peripheral nerves or spinal cord) have been sufficient to explain the loss of knee-jerks in certain cases. But in other cases, in which both cord and small peripheral nerve present no recognisable changes histologically (and probably these are more numerous than the former), some other explanation is needed. Either changes (not yet described) are present in the most minute nerve fibres and motor end-plates, or the loss of the knee-jerk is due to some functional alteration in the spinal cord, peripheral nerves, or muscles. Marinesco ([106]) has recently recorded a case of diabetes in which both knee-jerks were absent, but after an attack of hemiplegia the knee-jerk returned on the paralysed side, the case being analogous to that of tabes reported by Dr. Hughlings Jackson and Dr. Taylor, in which, after an attack of hemiplegia, the knee-jerk returned on the paralysed side.

Prognostic value of absent knee-jerks.—Whilst some writers do not attach any prognostic value to the loss of knee-jerks,

others consider that the prognosis is distinctly more unfavourable in cases in which the knee-jerks are absent. Bouchard, Nivière, Marie, and Guinon ([107]) hold the latter view, and give statistics in favour thereof. As already mentioned, the knee-jerks occasionally persist up to the last. On the other hand, they are sometimes absent in mild cases. Nevertheless the knee-jerks are more frequently lost in severe than in mild cases, and though other symptoms give much more important prognostic indications, still the absence of knee-jerks must be regarded as an unfavourable sign.

The following table shows the duration of life in ten patients whose knee-jerks were absent, and in ten patients whose knee-jerks were present, on first coming under observation:—

Duration of Life from Date on which the Condition of the Knee-jerks was first ascertained.

	When patient first came under observation. Knee-jerks absent in ten cases.	Knee-jerks present in ten cases.
Died within two weeks	4	1
„ between two weeks and six months .	2	3
„ „ six months and twelve months	2	1
∴ died within twelve months . .	8	5
Died between one and two years . . .	1	3
Alive two years afterwards	1	2
∴ survived over twelve months . .	2	5

Conclusions.—(1) In Manchester, amongst hospital patients suffering from diabetes mellitus, the knee-jerks are lost in from 49 to 50 per cent. of the cases. These patients mostly suffer from a severe form of the disease; 81 per cent. are under the age of 50 years; frequently there is great emaciation, and the cases are often at an advanced stage. (2) In private practice, amongst patients who live under more favourable conditions, and in the milder forms of the disease occurring in gouty or well-nourished people over the age of 50 years, I believe the proportion of cases in which the knee-jerks are absent will be much less (knee-jerks were absent in 16·7 per cent. of private patients, Eichhorst; 7·6 per cent., Grube of Neuenahr—the

patients being mostly over 50 years). (3) The knee-jerks when present at an early period are frequently lost or diminished later. During the last few days of life the knee-jerks are lost in 73 per cent. of hospital diabetic patients in Manchester. (4) They were lost in eighteen out of twenty-one cases of diabetic coma (86 per cent.). (5) Amongst diabetic hospital patients the knee-jerks are more frequently lost under the age of 30 years than over 30. (6) Since the course of diabetes mellitus depends on so many circumstances, it is somewhat difficult to estimate the exact prognostic value of one symptom, which is occasionally absent even up to the last; but the above facts and considerations seem to show clearly that the loss of knee-jerks is more frequently associated with unfavourable prognostic indications.

6. *Condition of other Reflexes in Diabetes.*

In *severe* cases of diabetes the wrist-jerks are frequently absent. When the knee-jerks are lost in diabetic patients, I have usually found the wrist-jerks absent also; though this is not invariably the case. The following results are taken from my notes in fifty cases of diabetes (mostly severe forms):—

	Cases.
Both wrist-jerks absent in	30
Both wrist-jerks present in	19
One absent, one present	1
	50

[It is to be remembered, however, that the wrist-jerks are sometimes absent in health. A few years ago I examined the condition of the wrist-jerks in 110 persons, who were either in good health or were suffering from some local surgical affection not likely to have any effect on the reflexes. In this series of cases I found the wrist-jerks present in practically 75 per cent. and absent in 25 per cent.]

Of the nineteen diabetic cases in which the wrist-jerks were present, the knee-jerks were also present in eighteen; in the other case one knee-jerk was absent and one present. In the thirty diabetic cases in which the wrist-jerks were lost, the knee-jerks were also absent in twenty-five; in the other five cases the

knee-jerks were present, but in three of these they were very feeble. In the case in which one wrist-jerk was present and the other absent, both knee-jerks were lost.

As already stated, the figures given above indicate the condition in patients suffering mostly from the severe form of diabetes. I have not had the opportunity of making observations on an equal number of cases of the mild form, but I believe that in such a series the wrist-jerk would not be found absent much more frequently than in healthy persons.

The superficial reflexes—plantar, abdominal, and epigastric—are present as frequently as in health, whatever may be the condition of the deep reflexes. In the severe forms of the disease the superficial reflexes are usually well marked; and when the knee-jerks and wrist-jerks are absent, generally the superficial reflexes are readily obtained.

7. *Peripheral Neuritis in Diabetes.*

The occasional occurrence of various forms of paresis and paralysis, and the frequency of neuralgic pain in the limbs in diabetic patients, have been mentioned by many of the older medical writers, but it is only within recent years that any of these symptoms have been attributed to peripheral neuritis.

Some of the nervous symptoms met with in diabetic patients strongly resemble those of alcoholic and other forms of peripheral neuritis.

v. Ziemssen ([108]) was the first, in 1885, to attribute the neuralgia so often observed in diabetes, to peripheral neuritis. Soon afterwards v. Höesslin ([109]), and at a later date Eichhorst, supported this view.

Pryce ([110]) has reported a case of diabetes with ataxic symptoms, in which the peripheral nerves showed evidences of neuritis.

Leyden ([111]), Althaus ([112]), Charcot ([113]), Buzzard ([114]), Auche ([115]), Bruns ([116]), have reported cases of peripheral neuritis in diabetes, or, to be more exact, cases presenting symptoms similar to those of neuritis from alcohol or other causes.

More recently other cases have been recorded by Eichhorst ([117]), Pryce ([118]), and Fraser and Bruce ([119]), in which changes have been found in the peripheral nerves.

The proportion of cases of diabetes presenting marked

symptoms of peripheral neuritis is very small, but slight symptoms are common.

The following are brief notes of two cases presenting slight symptoms of peripheral neuritis, such as are frequently met with:—

Case 1.—T. R., æt. 26. Urine 1040; no albumin; loaded with sugar. When patient first came under my care, the knee-jerks were present, and there were frequent cramps in the legs. Ten months later he complained that he had to drag his legs in walking. There was slight tenderness of the calf muscles, and frequent cramps; he complained of great pain of a gnawing character in the calf muscles and in the front of the thighs; also he had pain over the tibiæ. Left knee-jerk absent; right, very feeble (Jendrássik's method). At a later date he also complained of tingling and numbness in the legs. No real paralysis, no anæsthesia.

Case 2.—J. R., æt. 47. When the patient first came under my care, the knee-jerks were absent, but there were no other signs of neuritis. Urine 1032, pale, acid, no albumin, contained a large amount of sugar. At a later date both legs became numb; there was also tingling and pain in the legs, and the calf muscles were tender. The legs became *so tender that patient "could not bear one leg on the top of the other in bed."* He could feel and localise a touch with a pin's head, and could distinguish between the point and the head of a pin. Movements legs weak, but no real paralysis.

In both of these cases the symptoms resemble those met with in the early stages of alcoholic peripheral neuritis. In neither case was there a history of alcohol, nor of anything to which the symptoms could be attributed except diabetes.

Many years ago, when house physician to Dr. Buzzard at the National Hospital for the Paralysed and Epileptic, Queen Square, London, I had the opportunity of observing a well-marked case of diabetic neuritis. Buzzard ([114]) has since recorded the case, and as it is one of the most marked on record, I add a brief abstract, taken from his report:—

J. K., æt. 55. Ten months before the patient came under Dr. Buzzard's observation, he began to suffer from severe pain and tenderness on the front of the right thigh, which soon extended down to the foot. A month later the left leg was affected in the same way. Both legs became weak, and at the end of three months he was unable to walk. He then began to suffer from "pins and needles" in the soles of

the feet, and at a later date had numbness and tingling in the tips of the fingers. Soon after the onset of illness, thirst, diuresis, and wasting became prominent symptoms.

During the time the patient was under treatment, the chief symptoms were—Loss of power in the legs; inability to dorsiflex the feet; dropped toes of left foot; wasting of muscles; reaction of degeneration in anterior tibial muscles; absence of knee-jerks and plantar reflexes; continuous pains in the legs and feet; tenderness of the legs and soles of the feet; numbness and tingling in the legs and diminished cutaneous sensibility; pains in the fingers and diminution of tactile sensation in the hands. The bladder was not affected. On the outer side of the right foot, just below the malleolus, was a deep ulcer surrounded by an area of congestion, and there was also a cicatrix of an old ulcer just below the metatarso-phalangeal joint of the great toe.

Urine, 57 to 84 oz. daily; sp. gr. 1042 to 1045. Sugar, 25 to 35 grs. per oz., according to diet. By rigid diet the sugar was reduced to 16 grs. to the ounce; the ulcers healed, and patient improved.

Such cases as the one just recorded are exceedingly rare. Amongst 140 diabetic patients who have come under my observation in Manchester, I have never seen any similar case presenting such distinct motor symptoms of peripheral neuritis.

I have met with two cases of diabetes, in which there has been neuralgic pain down the front and inner side of the right thigh (along the course of the anterior crural nerve), accompanied by paresis of the muscles which flex the thigh on the abdomen. In one case both knee-jerks were present, in the other the knee-jerk was absent on the affected side but present on the opposite side. Probably both were cases of localised neuritis in the anterior crural nerve. Bruns has recorded similar cases.

Lasègue, Charcot, and others have described a number of cases of monoplegia and paralysis of single groups of muscles in diabetic patients. Lecorché ([120]) points out the rarity of these cases, and states that they do not appear to be connected with any profound lesion of the nervous system; that they are characterised by the paralysis being incomplete, localised, and transitory; and, generally, sensory symptoms, hyperæsthesia, or anæsthesia are present. It seems probable that these cases are due to an affection of the peripheral nerves or peripheral neuritis.

Ulcers on the feet, especially about the toes, "perforating

ulcers," are sometimes met with in diabetic patients. Probably they are due to peripheral neuritis (see p. 226).

Résumé of symptoms in diabetic neuritis.—Slight symptoms of neuritis, such as pain in the legs, cramps, numbness, tingling, tenderness, and absence of knee-jerks are not infrequent, but marked paresis or paralysis is rare. The onset of symptoms is gradual or subacute.

On an analysis of sixteen cases, recorded by various authors during the last four years, the following description is based:—

Motor symptoms.—Paresis or paralysis, when present, most frequently affects the legs—diabetic neuritic paraplegia (Buzzard). In some cases—Buzzard ([114]) and Charcot ([113])—the anterior tibial muscles are chiefly affected. There is dropping of the toes and feet, and the patient is unable to dorsiflex the feet. In other cases, as in the two mentioned on p. 261, and in three recorded by Bruns ([116]), the paralysis affects chiefly the muscles supplied by the anterior crural and obturator nerves on the front of the thighs, and the symptoms are sometimes much more marked on one side than the other. In a case recorded by Auché these muscles were affected on one side only, and the patient was unable to go upstairs. In some cases—Leyden ([111]), Salomonsen ([122])—the motor symptoms are described simply as weakness in the legs. The arms may be affected without the presence of any paralysis in the legs. One arm only may be paralysed, or one arm may be affected at first, but at a later date both may be affected (Buzzard [114]). In other cases the muscles of the shoulder and upper arm may be affected on one or both sides (see also case recorded, p. 243); or the paralysis may be localised to a group of muscles, as the muscles supplied by the ulnar nerve (Ziemssen), or to a single muscle, as the deltoid (Althaus [112]).

The affected muscles are generally wasted. In one case (Charcot) they are said not to have been wasted. The knee-jerks are absent when the legs are affected. Diminished excitability to electricity, and partial or complete reaction of degeneration, have been often observed in the affected muscles.

The *sensory* symptoms are often more marked than the motor, and may be present when the latter are very slight or absent. When motor symptoms are present, the sensory are generally localised in the same region; in the legs below the knees, when the anterior tibials are chiefly affected; in

the front of the thighs, when the muscles of this region are chiefly affected (Bruns); in the arm (Buzzard); or in the region of the ulnar (Ziemssen) or the circumflex nerves (Althaus). In some cases in which the legs are chiefly affected, sensory symptoms are also present in the hands, and the grasp is weak.

The following are the chief sensory symptoms:—Pain, neuralgic in character, often described as intense or violent, shooting or tearing; hyperæsthesia, tenderness, and pain on pressure of muscles; tingling, numbness; sometimes a sensation of coldness in the hands and feet. Diminished tactile sensation is rare, but even anæsthesia may occur ([114]); also diminished sensation to pain is recorded. Neuralgia unassociated with motor symptoms often occurs in diabetes, and is characterised, according to Berger, by its spontaneous origin, by its frequent localisation in the branches of the sciatic, sural, and plantar nerves, by the violence and long duration of the attacks, by the occurrence of vasomotor disturbances in the district of the affected nerves, by the resistance to ordinary treatment for neuralgia, and by the improvement under anti-diabetic treatment. The cause of neuralgia, at least in a certain number of cases, is probably neuritis. In some cases the nerves affected have been noted to be tender on pressure.

The condition of bladder and rectum has frequently not been stated, and therefore probably it has been normal. In other cases both have been definitely stated to be normal. In one case (Charcot) there was slight incontinence of urine.

Small ulcerations about the toes, perforating ulcers like those of tabes ([110 and 114]), shining and glossy skin, ecchymoses, shedding of the nails, and œdema, have been recorded. Herpes zoster has also been described ([123]).

Ataxia has been occasionally noted ([118]).

Leyden recognises three forms of peripheral neuritis in diabetes:—

1. The *hyperæsthetic or neuralgic* variety, in which there is more or less severe pain. This variety may occur in the form of neuralgia (trigeminal neuralgia, sciatica, etc.), or as a multiple neuritis in the feet, legs, and hands. Usually there is weakness of the affected parts. Pain stands out as the prominent symptom.

2. The *motor or paralytic* form. In this form there is more or less marked paralysis of muscles of the legs or of other

parts. The knee-jerks are lost. Electrical changes are sometimes found. Often in this form there are neuritic pains.

3. The *ataxic* form, so-called pseudo-tabes. In this variety, besides ataxia, there are sensory symptoms, numbness, formication in the feet. The muscular power for coarse movements is maintained, or not essentially diminished. The tendon reflexes are lost. But the pupils react to light and accommodation, and in this respect, therefore, the cases differ from many cases of true locomotor ataxia. Some neurologists, however, doubt the occurrence of real ataxia.

As Charcot points out, however, occasionally, though *very rarely*, a patient may present symptoms of true tabes dorsalis along with diabetes. He recognises two groups of possible cases—(1) In cases of tabes dorsalis, symptoms of diabetes may occur, the latter being a complication, and due to the extension of the lesion to the floor of the fourth ventricle. In these cases gastric and laryngeal crises are often observed. Such cases, however, are exceedingly rare. Marie and Guinon examined the urine in fifty cases of tabes without finding glycosuria in a single case. Gillas found glycosuria three times only in 100 cases of tabes. (2) There is the possibility of the occurrence of tabes and diabetes in the same patient as a coincidence.

Pathological evidence.—In most of the cases of peripheral neuritis recorded, the diagnosis rests on clinical evidence—the similarity of the symptoms to those of neuritis produced by other causes; the absence of any symptoms definitely referable to the spinal cord or brain; and the absence of any of the other recognised causes of neuritis, such as alcoholism, plumbism, diphtheria, etc.

In a few cases the diagnosis has been confirmed by post-mortem examination—in three cases reported by Pryce ([110 and 118]), in two cases reported by Eichhorst ([117]), in three reported by Auché ([115]), and in one reported by Fraser and Bruce ([119]).

In all these cases microscopical examination revealed the existence of parenchymatous neuritis in the nerves of the affected parts. In the case reported by Fraser and Bruce the affected nerves presented changes similar to those described by Gombault, as *néurite segmentaire periaxile.*

In one of Auché's cases there was paresis of the legs, muscular cramps, and gangrene of the right foot. In another case there were itching, tingling, and pricking pains in the feet,

legs, and hands, and the knee-jerks were absent. In a third case there were violent cramps in the calves at night, slightly diminished sensation to a pin-prick on the dorsal surface of the forearms, subinguinal hæmorrhages, shedding of the nails.

In one of Eichhorst's cases the knee-jerks were absent, but there was no paralysis and no disturbance of the sensation. In the second case the knee-jerks were absent; the patient was able to move the arms and legs, but there was marked muscular weakness of the limbs. Examination of the anterior crural nerves in both cases revealed parenchymatous neuritis.

In the first case, reported by Pryce, there were perforating ulcers on both feet, diminished cutaneous sensibility of both feet, and of the lower thirds of both legs. The knee-jerks were absent. It is also stated that the patient had ataxic symptoms. The examination of the peripheral nerves (by Mr. Bowlby) revealed parenchymatous neuritis, but the ganglion cells of the lumbar region of the cord were atrophied also. In the second and third cases ataxic symptoms were present, cutaneous sensibility was diminished, the patients suffered from pain in the legs, and finally gangrene occurred.

In the case recorded by Fraser and Bruce the knee-jerks were absent, and the patient suffered from pains in the legs and tenderness of the calf muscles.

In most of the cases recorded the neuritis has occurred in patients over the age of 50 (in twelve out of sixteen cases).

All writers on the subject agree that the neuritis does not bear any relation to the amount of sugar in the urine. In many of the cases recorded the amount of sugar has been small; in one reported by Bruns it was not quite 1 per cent., and in another case it was between 1 and 2 per cent. Further, the symptoms continue if, by strict diet, the sugar can be made to disappear from the urine.

The above facts seem to indicate that the neuritis is not due directly to the presence of an excess of sugar in the blood. Auche has made experiments on the lower animals, and exposed the sciatic nerve to the action of different fluids containing sugar. His experiments show the sugar has only a slight action on the nerves, similar to that produced by water, and the changes in the nerves in diabetes are probably due to some other cause—the poverty of the tissues in water, the general disturbance of nutrition, acetone, or some unknown chemical substance in the

blood. Gowers believes that the neuritis is due to some toxic substance comparable to acetone, but not acetone, and he thinks the fact that the reduction of the sugar excretion has but little influence on the condition, suggests that the poison is not a product of the decomposition of sugar, but a material formed in place of sugar by some modification of the chemical processes that lead to the increased sugar production.

Changes in the muscles have been described by Fraser and Bruce ([119]) in the case in which the nerves showed the signs of peripheral neuritis.

The muscles, on microscopical examination, presented a slight increase in the distinctness of the longitudinal striation. This was due to the presence of rows of fine fat granules between the fibrillæ of the muscle. The granules were all extremely minute, and seemed to be developed from the cement substance rather than the muscle fibres. In the portions of the muscles where this degeneration was found, the transverse striation of the fibres had disappeared.

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CHAPTER XI.

DIABETIC COMA.

A DIABETIC patient may become comatose owing to various complications. Thus cerebral hæmorrhage or softening, meningitis, and interstitial or parenchymatous nephritis, may give rise to coma, when occurring as complications in a diabetic subject.

But apart from coma, produced by these and other complications, there is a special group of symptoms ending in coma, which is a frequent termination of diabetes. These symptoms are unaccompanied by any gross lesions of the organs, and are apparently due to the toxic condition of the diabetic blood. The name of diabetic coma has been given to this peculiar group of symptoms, ending in unconsciousness. It was first described in Germany by Küssmaul in 1874; and in England, Sir W. B. Foster drew attention to it in 1877. Diabetic coma has also been carefully studied by Dreschfeld, Frerichs, and numerous other observers more recently.

Generally, the patient comes under treatment for other symptoms of diabetes before the onset of coma; but occasionally, especially in acute cases amongst the poor, the patient is first seen during the comatose stage. Thus a man was recently brought to the Manchester Infirmary in a semi-comatose state. The symptoms and the condition of the urine showed the case to be one of diabetic coma, but the tubercular disease of the lungs from which he suffered had led the medical attendant to overlook the primary disease—diabetes. It is somewhat surprising that diabetic coma has not given rise to medico-legal difficulties more frequently; and this no doubt would happen if diabetes were a more common disease. It is possible that a few of the unsatisfactory cases of coma which have not been cleared up by post-mortem examination—cases which have been regarded as serous or simple apoplexy, or of sunstroke, etc.—have really been due to diabetic coma; and since there are no pathological

appearances which are characteristic of diabetes or of diabetic coma, a pathologist would not be able to arrive at a correct diagnosis, in the absence of a chemical analysis of the urine or blood.

Frequency of diabetic coma.—Coma is the most frequent termination of diabetes. Thus, in twenty-eight of the last forty fatal cases of diabetes which have come under my observation, the cause of death was coma.

Relation to phthisis.—When advanced phthisis is present as a complication of diabetes, death by coma does not usually occur; in most cases of diabetic coma, phthisis is absent, or the lung changes are slight. But to these general rules exceptions occasionally occur. Thus, in twenty-eight cases of diabetic coma, which have come under my observation during the last six years, there was extensive tuberculosis of the lungs (verified pathologically) in four.

EXCITING CAUSE, ETC.—Diabetic coma occurs both in the severe and mild forms of diabetes. It may terminate life in mild cases associated with obesity, but it is especially common in the severe forms of the disease. It may occur at any age, but it is very common in young persons and in persons under middle life.

Dreschfeld (1) found, from an analysis of eighty cases of diabetic coma, that 70 per cent. occurred between the ages of 20 and 40, and only 24 per cent. between 40 and 60, though death from diabetes is more common at the latter-mentioned period, as is shown by the tables on p. 97. Coma may terminate the life of a patient at an early date after the first appearance of the diabetic symptoms, or it may not occur for years after the onset of the disease. Examples of the early onset of coma, from two weeks to six months after the commencement of the disease, will be found mentioned on p. 275.

Dreschfeld refers to a case communicated to him by Charcot, in which the urine was examined and found free from sugar two months before death from diabetic coma.

Sometimes several members of a family suffer from diabetes, and die of diabetic coma. Quincke records the case of a girl who died of diabetic coma at the age of 16, the patient's brother died of diabetic coma at the age of 19, and an uncle at the age of 29.

It has long been known that the exciting cause is sometimes

a long railway journey—such as is necessitated in a visit to a town physician by a patient living in a distant country place. Frequently the journey to a continental spa, such as Carlsbad, has been the exciting cause of diabetic coma. Excessive muscular exertion is another exciting cause. Again, coma has often developed in diabetic patients somewhat suddenly after severe mental shock, anger, fright, disappointment, emotional disturbances, mental strain, and worry.

A sudden change of diet—from a mixed diet to a rigid—often appears to be the exciting cause of diabetic coma; and it is said that a sudden change from a rigid diet to a mixed diet has occasionally been immediately followed by coma. The opinion is gradually gaining ground, that a rigid nitrogenous favours the development of coma, especially in severe cases in which the urine gives a dark brown coloration with perchloride of iron. Ebstein (2), Hirschfeld (3), Schmitz (4), and Grube (5) have especially drawn attention to this point, and the three latter observers have advocated an increase of the carbohydrates in the diet when coma appears to be threatening. Diabetic coma may develop, however, when the patient's diet is not much restricted, and even when there is no restriction whatsoever.

In a large number of cases, prolonged constipation has appeared to play some part as an exciting cause, but it is not invariably present. On the other hand, an attack of severe diarrhœa has occasionally appeared to act as an exciting cause.

Often coma has developed very soon after a patient has been admitted into hospital. Of course this is sometimes due to the fact that he has been brought to the hospital because he was becoming rapidly worse; but in other cases the change of diet (sudden restriction) may have had some effect, though in most cases at the Manchester Royal Infirmary coma has developed when the patient's diet has been by no means rigid. Constipation produced by confinement to bed may also have aided in producing the comatose termination soon after the patient's admission into hospital. Exposure to cold, and alcoholic and sexual excess, have appeared to act as exciting causes in certain cases.

Diabetic coma appears to be occasionally excited by intercurrent affections or complications, as, for example, bronchitis, pleurisy, croupous or catarrhal pneumonia, gastritis, hepatic colic,

strangulated hernia, influenza, tonsillitis, carbuncles, and pharyngeal, ischio-rectal, or alveolar abscesses. The administration of anæsthetics, the performance of surgical operations, even cataract operations, have all appeared to occasionally act as exciting causes of coma.

Hirschfeld has drawn attention to rapid and marked loss of weight, which often precedes the onset of coma (see p. 321), and he believes that inanition is an important exciting cause.

Analysis of Exciting Causes in Twenty-seven Cases of Diabetic Coma.

These cases were mostly hospital patients at the Manchester Royal Infirmary. A few were cases in private practice. The following table shows the age and sex of these twenty-seven cases of diabetic coma :—

	Age in Years.	No. of Cases under 30.	Age in Years.	No of Cases over 30.
13 Males . . .	18, 19, 20, 26	4	31, 34, 35, 35, 43, 43, 45, 46, 51	9
14 Females . .	11, 17, 19, 20, 31, 21, 23, 26, 26, 29	10	34, 36, 44, 66	4
27 cases.	Under the age of 30	14	Over the age of 30	13

Thus, under the age of 30, coma occurred more frequently in females; over 30, in males. Half the cases of coma occurred under the age of 30, though 63 per cent. of the diabetic patients at the Manchester Infirmary are over that age. All these twenty-seven patients suffered from a severe form of diabetes with wasting, which was often very marked.

It is difficult to obtain reliable evidence as to the exact time of the onset of the disease in many diabetic patients, but the table of cases on the next page shows that the most prominent symptoms, thirst and diuresis, were often noticed only a short time before death occurred from diabetic coma. In two of the twenty-seven cases, coma appeared to have been excited by sudden mental shock and anxiety. Too great restriction of diet could not be regarded as the exciting cause of coma in any of the twenty-seven cases. In one case the patient was admitted into the hospital in a state of coma, and diabetes had not been previously recognised.

1. Boy	æt. 18,	death from coma within		2 weeks	After diabetic symptoms first noticed.
2. Man	„ 43,	„	„	1 month	
3. Woman	„ 34,	„	„	1 „	
4. Boy	„ 19,	„	„	6 weeks	
5. Girl	„ 11,	„	„	2 months	
6. Woman	„ 26,	„	„	2 „	
7. Girl	„ 19,	„	„	3 „	
8. Man	„ 20,	„	„	5 „	
9. Man	„ 45,	„	„	6 „	
10. Man	„ 31,	„	„	6 „	
11. Girl	„ 17,	„	„	6 „	
12. Man	„ 35,	„	„	6 „	
13. Man	„ 51,	„	„	6 „	
Ten cases. 3 women (æt. 19, 21, and 26)			„	12 „	
3 women (æt. 21, 23, and 26) 2 men (æt. 34 and 43)			about	12 „	
1 woman, æt. 66,	death from coma within			18 „	
1 woman	„ 44,	„	„	2 years	

Often coma developed very shortly after admission to the hospital. No doubt this was, in part, explained by the fact that the rapid advance of the disease had caused the patient to seek admission. But in many cases it appeared probable that the sudden change in the mode of life had played some part in exciting coma. Confinement to bed and constipation produced thereby, change in diet and the journey to the hospital, may have had an injurious effect. Amongst twenty-one hospital cases terminating by coma (cases in which there were no signs of coma on admission), in twelve death occurred within one week; in two cases coma developed on the second day after admission to the hospital; in one case on the third day; in six cases on the fourth day; in one case on the fifth day; and in one case on the sixth day; in one case within seven days.

As regards the condition of the bowels, in seventeen of the twenty-seven cases coma was preceded by obstinate constipation. Sometimes the bowels had been fairly regular until the patient was admitted into the hospital. Then for several days after admission there had been obstinate constipation, and coma had developed. The onset of coma was not invariably preceded by constipation, however. In several cases this symptom was absent, and in one case there was diarrhœa, but in this case the symptoms were those of diabetic collapse (see p. 281). In one

case the onset of coma followed the appearance of an ischio-rectal abscess.

SYMPTOMATOLOGY.—The symptoms often commence with lassitude, epigastric pain, nausea, and occasional vomiting. In other cases shortness of breath is one of the earliest symptoms. Headache is also sometimes an early symptom. The patient becomes anxious, restless, or excited; he tosses about in bed, turns from side to side, and sometimes the arms are thrown about wildly at frequent intervals. Speech becomes thick and incoherent; the patient becomes drowsy, and the drowsiness gradually develops into coma.

The pulse increases in frequency. Often the number of beats rises to 120 or 130, at the last to 160 or more, per minute, or the pulse, becomes so rapid and feeble that it cannot be counted at the wrist. The tension is low, and the beats feeble, but generally regular. The heart's action is rapid and feeble, but cardiac murmurs are not usually heard. Lépine regards rapidity of the pulse as an important early indication of commencing coma.

Dyspnœa is a prominent feature in the majority of cases, and it may be the first symptom, but it is not always present. The dyspnœa is inspiratory at first; later, both inspiration and expiration are deep and prolonged, and the breathing has a peculiar panting or sighing character. When the respirations are counted, it is found very often that there is no increase, or only a slight increase, in the number per minute. The respiratory difficulties are indicated by deep inspiration and expiration rather than by increased frequency of respirations. Not infrequently there is a moan or groan with each expiration, even when the patient is deeply comatose. The thorax expands well, and there is no obstruction to the entrance of air into the chest. Physical examination reveals nothing of importance, as a rule, in the heart or lungs to account for the great dyspnœa, and there is no distension of the veins of the neck. This peculiar dyspnœa has been described by Kussmaul as "air hunger."

The tongue is dry and red. The bowels are generally constipated, often markedly so, and frequently the onset of coma has been preceded by a long period of constipation. Occasionally diarrhœa has been present.

The face becomes pale and cold. In many cases there is slight cyanosis. The nose, lips, and ears appear slightly cyanotic; they feel very cold to the touch, and the circulation

in these parts is feeble. The limbs and trunk are often cold also, and usually the hands and feet are slightly cyanosed.

The temperature is generally subnormal; it may finally sink to 95° or 94° F., but occasionally at the last it rises to a great height, without any cause being detected clinically or at the autopsy for this pyrexia (see p. 284). The expired air feels colder than in the case of a healthy person.

Generally the breath has a peculiar odour. The smell is noticed all around the patient, but it is particularly strong in the breath. The urine also has the same smell. It is variously described—most frequently, perhaps, as a smell resembling chloroform. It has been compared also to the smell of ether, sour beer, apples, hay, or acetone. By allowing the patient to breathe into water, Dreschfeld has been able to detect acetone in the expired air, but no aceto-acetic acid was present.

This odour is sometimes detected for a considerable period before the onset of coma; but if not already developed, it is noticed when coma commences. The smell varies in intensity. Sometimes it is marked, at other times very slight. Some people can detect it very readily. A few physicians state, however, that they have never been able to recognise it. Nevertheless the odour undoubtedly exists. Junior students who see diabetic coma for the first time, and have never before heard of the symptom, often notice the peculiar smell. A short time ago I sent a junior student to the bedside of a patient who was suffering from diabetic coma, and asked him to make a diagnosis. The student had never heard nor read of diabetic coma. He returned rapidly, and stated that, from the smell about the patient, he believed he was still under the influence of chloroform, and that probably some operation had just been performed, for which chloroform had been given as the anæsthetic, though the patient was not in a surgical ward.

The acidity of the urine increases in diabetic coma; and a marked increase in the acidity of any diabetic urine is said to point to the onset of coma. The quantity of urine often diminishes a little, and the sugar frequently diminishes also. It is said that the sugar sometimes disappears, but certainly this is very rare. I have never met with such a case. The colour of the urine is often not so pale as before the onset of comatose symptoms; and in one case I noticed a slight pinkish tinge, though there was no indication of blood pigment, or any excess

of urates. The urine, in almost every case, has a peculiar chloroform or sweet smell, like that of the breath. This smell is often detected also in late stages of diabetes. The urine contains a small amount of albumin. Often in the late stage of diabetes, albumin is present; but if it has not already appeared, it does so just before, or just at, the onset of the comatose symptoms. The urine when passed is generally (if not always) slightly cloudy, and very minute floating particles can be recognised by the naked eye. On standing, there is nearly always a small deposit, greyish white or yellowish white in colour, which sinks quite to the bottom of the urine glass.

On examination of the deposit, it is found to consist of enormous numbers of casts. The field of the microscope is usually crowded with them, and a few degenerated epithelial cells are often present also. The casts are composed of a hyaline material with fine granules. In some cases the granules are few, whilst in others the casts appear to be composed of a mass of closely-packed granules. Occasionally the granular casts contain one or two degenerated epithelial cells. The deposit of casts appears shortly before the onset of comatose symptoms.

According to Maguire, albumin, in small quantity, is present in every case of diabetic coma, and Külz states that casts are always present also. Since becoming acquainted with their observations, I have examined the urine in diabetic coma for casts and albumin in every case which has come under my observation (sixteen in number), and I have always found both to be present. As regards casts, I have generally found enormous numbers present, so that the field of the microscope has been crowded with them.

Külz regarded the appearance of casts as a valuable premonitory sign of the onset of coma. I have frequently examined the urine of advanced cases of diabetes for casts or deposit, but generally both have been absent up to the last few days of life. Finally, however, a yellowish white deposit has appeared at the bottom of the urine glass. Microscopical examination has shown it to be composed of casts in enormous numbers, and coma has followed. Hence I believe that when a small amount of dense yellowish white deposit appears exactly at the bottom of the urine glass, and when this deposit consists of casts in great numbers, coma nearly always follows. To this general rule I

have found a few exceptions. Thus in two severe cases of diabetes with wasting, a deposit of casts appeared in the urine, though previously casts had been absent. The patient in each case became drowsy; the urine gave a deep reddish brown coloration with perchloride of iron, and contained a small quantity of albumin. The symptoms were very suggestive of the onset of diabetic coma, but in each case the drowsiness passed away, the casts disappeared from the urine in the course of a day or two, and coma never developed. Death occurred in each case some time afterwards from phthisis. Possibly these may have been cases of abortive coma. They show, however, that when casts appear, the cases do not invariably terminate in fatal coma.

It has been already mentioned that the urine gives a deep brownish red coloration with perchloride of iron (so-called diacetic acid reaction) in many advanced cases of diabetes. This reaction is nearly always obtained during coma, but exceptions occasionally occur.

In coma the urine also gives the reaction for acetone. It is often present in advanced cases of diabetes, but Hirschfeld has shown that the amount of acetone increases greatly just before death from coma. Acetonuria is no doubt increased by the withdrawal of carbohydrate food in the severe forms of diabetes, but it occurs also when carbohydrates are allowed, and may even occur when the patient is taking ordinary diet.

Stadelmann ([6]) states that diabetic coma occurs only when the urine contains *β-oxybutyric* acid (see p. 185). He attaches almost equal importance to the amount of ammonia in the urine, whilst its estimation is far easier. Diabetic patients excreting 2, 4, 6, or more grms. of ammonia need constant watching, and are in danger of coma.

If ammonia and oxybutyric acid cannot be determined, the urine should at least be examined with perchloride of iron.

Stadelmann points out the danger of a strict diet in the severe cases when a great amount of ammonia is excreted, or when oxybutyric acid is present, or when the urine gives a reaction with perchloride of iron.

The alkalinity of the blood is said to be much decreased in diabetic coma, but I have obtained decided alkaline reactions even shortly before death (see p. 186).

The blood presents no noteworthy change on microscopic

or spectroscopic examination. I have found that the blood in coma, as in all cases of diabetes which I have examined, decolorises a warm alkaline solution of methyl blue more readily than normal blood (see p. 192). It has already been mentioned that an excess of fat has been found in the blood in a few cases (see p. 188).

Convulsions as a rule do not occur, and in this respect diabetic coma differs markedly from uræmia. But there are few rules in clinical medicine which are absolute, and though their occurrence would be evidence against diabetic coma, still a few cases have been recorded in which convulsions have been noted (once in sixteen cases, Dreschfeld). Jacoby, Finlayson, and others have recorded cases in which convulsions occurred (see p. 240).

As already mentioned, the knee-jerks are frequently absent in the severe form of diabetes. (In the hospital patients at the Manchester Royal Infirmary they are absent in 50 per cent.) If the knee-jerks have not already disappeared, they usually do so when coma develops, but in a few cases they remain present up to the last. In twenty-one cases of diabetic coma in Manchester, the knee-jerks were absent in eighteen, present in three; in one case the knee-jerks were present half an hour before death.

The condition of the pupils varies; they react to light, though sluggishly. The eyelids are half closed as a rule. The fundus oculi appears normal, with the exception of those rare cases in which retinitis has been present.

As the coma increases it becomes more and more difficult to rouse the patient, and finally he becomes totally unconscious; but in some cases the coma does not become complete, and though the patient becomes more and more drowsy, and takes no notice of his surroundings, he can be roused to take his medicine up to the last.

Diabetic coma generally ends fatally within forty-eight hours; but abortive cases are common, according to Hirschfeld. I have met with three cases in which early symptoms of coma developed, but disappeared again.

The symptoms just recorded are those met with in the most common variety of diabetic coma, Kussmaul's "air hunger." But there are two other varieties in which the symptoms differ from those described above; these are (1) the alcoholic form of diabetic coma, and (2) diabetic collapse.

(1) *Alcoholic form.*—In this variety the symptoms resemble those of alcoholic intoxication. In a case recorded by Külz (quoted by Dreschfeld), a large amount of alcohol was found in the urine; the patient was excited; he sang and swore; the speech became thick, and he staggered like a drunken man; the pulse was quick; the conjunctivæ congested; coma soon developed, and terminated fatally.

An interesting case of this variety was met with by Dr. Cullingworth in Manchester, and is also quoted by Dr. Dreschfeld.

Dr. Cullingworth was consulted by a servant girl on account of great thirst and weakness; the urine had a specific gravity of 1035, and contained a considerable amount of sugar. He prescribed opium and nux vomica, and advised her to go to her home in Wales. On her journey home she left the train at one of the small stations, and seemed so excited that she was believed to be intoxicated. She was refused admission at one hotel, owing to her apparently drunken condition. "At last she was taken up by a policeman, who took her to a small inn, where she was seen by Mr. Reed, a local medical man, late at night." She was found to be in a semiconscious state; her face was very pale; the pupils were dilated and reacted slowly to light; her pulse was rapid, and the breathing quick. Next morning she was quite unconscious, the breathing rapid and noisy, and the extremities cold. The urine contained sugar. The coma deepened, and death occurred in the evening.

Frerichs has described similar cases.

In this form there is not the dyspnœa and feeling of anxiety which characterises the first variety. The patient has a feeling of intoxication, his gait becomes unsteady, he becomes drowsy, and the drowsiness gradually passes into deep coma. The breath has the characteristic smell, and the urine becomes reddish brown on the addition of perchloride of iron.

(2) *Diabetic collapse.*—This condition was first mentioned by Prout, and has since been carefully described by Dreschfeld, Frerichs (7), and others. The following is Dreschfeld's account. In these cases the patient suddenly begins to suffer from drowsiness and great weakness. The extremities become cold; the hands, feet, and face become livid; the pulse becomes quick, small, and threadlike, soon reaching 120 to 130. The respirations are only slightly quickened, they are shallow, and there is not much dyspnœa. The temperature gradually falls, the skin

in some cases becomes covered with perspiration, the patient becomes more drowsy and finally comatose, and death occurs from collapse in ten to twenty hours. The urine contains sugar, but no acetone or aceto-acetic acid, and the expired air has not the peculiar chloroform-like smell. There is no delirium.

Dreschfeld points out that diabetic collapse occurs chiefly, though not exclusively, in patients over the age of 40, and that it attacks persons who have suffered from diabetes for some time, and who are, as a rule, still stout and well nourished. In such cases the disease has run a chronic course, and is often associated with gout or nephritis. The exciting cause of diabetic collapse is some extra physical exertion or some sudden shock, in a few cases errors of diet or immoderate drinking.

Frerichs and Dreschfeld believe that the cause of this variety of coma is cardiac failure, owing to degeneration and atrophy of the cardiac muscle.

Analysis of Symptoms in Twenty-six Consecutive Cases of Diabetic Coma.

The following is an analysis of my notes on the symptoms of twenty-six cases of diabetic coma, most of which have come under my observation at the Manchester Infirmary; a few have been cases in private practice.

In most of the twenty-six cases, epigastric pain, nausea, and drowsiness were the first symptoms, and were generally followed by, or associated with, dyspnœa. The first symptom, in one case, was pain in the right lumbar and hypochondriac regions.

In most of the twenty-six cases the patients were restless, anxious, and somewhat excited at the onset; in one case the excitement was very great, and resembled that of early alcoholic intoxication.

In one case dyspnœa was the first and only symptom for several days. The patient had been under hospital treatment in Belfast. He had left the hospital, and crossed by steamboat to Liverpool, and had taken train to Manchester, where he arrived the day after leaving Belfast. His breathing had become difficult, somewhat suddenly, before reaching Manchester, and he came to the accident room of the Royal Infirmary on account of this symptom. I happened to see the patient in the acci-

dent room, and as the breathing was very laboured (both inspiration and expiration being very deep), and examination of the chest revealed no cause for the dyspnœa, commencing diabetic coma was diagnosed. There was then no coma or drowsiness whatsoever, and dyspnœa was the only symptom of which the patient complained. The urine was very acid; the specific gravity was 1036; sugar was present in large quantity, and there was a small amount of albumin present also. The urine gave a dark brownish red coloration with perchloride of iron. The man was admitted as an in-patient under the care of Dr. Steell, and the dyspnœa continued for five days, when death occurred, the other symptoms of diabetic coma having in the meantime developed. The respirations varied during the time the patient was in the hospital from 18 to 30 per minute; but the breathing was always laboured, inspiration and expiration being both very deep. The patient was only comatose during the last six hours of life. The interesting point about this case was the fact that dyspnœa was the prominent symptom, and persisted for five days. For four days the patient was quite conscious and intelligent, and actual coma only developed on the fifth day.

Dyspnœa was a very prominent symptom in nearly all of the twenty-six cases; in one, however, it was slight until the last few hours of life. The number of respirations per minute was often not much increased, frequently being only 18 to 20; in other cases the respirations were 25 to 35 or more per minute; but whether the number of respirations was normal or increased, the breathing was laboured, the inspirations and expirations were very deep, and the breathing had the peculiar sighing or panting character. When the patient was comatose, generally a groaning noise accompanied expiration. Cheyne-Stokes' respiration was never met with.

In nearly all of the twenty-six cases the pulse was very rapid—frequently from 120 to 180 per minute. It often became so rapid that it was impossible to count it. In several cases, however, the rapidity of the pulse diminished shortly before death to 90 or 100. In one case, in which I first saw the patient about half an hour before death, the pulse was only 66; about an hour previously, I was informed that it had been 80 per minute.

The condition of the bowels (obstinate constipation in seventeen cases) has already been referred to on p. 275.

In nearly all of the cases there was more or less cyanosis of the limbs and face.

The temperature was usually subnormal; it often sank rapidly to 96° F., and remained low. In one case it sank to

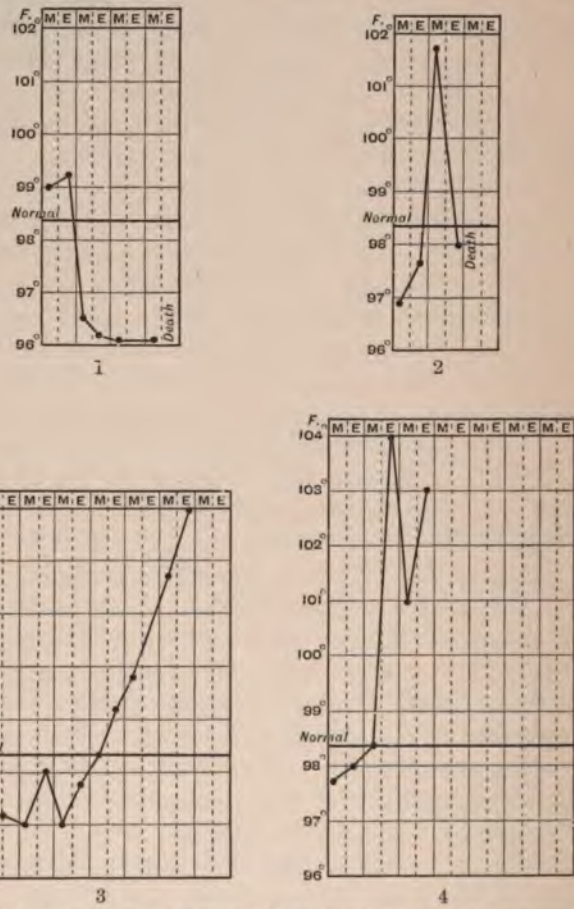

FIG. 17.—Temperature charts in diabetic coma. 1, chart showing usual fall of temperature; 2, 3, and 4, charts showing unusual high temperatures in three cases.

95°, but a few hours later it rose to 99° (just before death). In two cases the temperature was practically normal, and in six out of the twenty-six cases it was above normal. In one of these six cases it rose suddenly and reached 104°, in another it reached 103°, in a third to 101°·6, in two other cases the temperature

was only slightly above normal. In one case it fell to 96°, but next day rose to 101° F. Post-mortem examination made in five of these cases failed to reveal any cause for the pyrexia. No autopsy was obtained in the sixth case, but there was no evidence of any complication which would account for the high temperature (see Charts, Fig. 17).

The peculiar so-called acetone smell of the breath was a prominent feature in nearly all of the cases.

The quantity of urine and sugar excreted generally diminished during coma; but in none of the twenty-six cases did the sugar disappear.

The urine was tested with perchloride of iron in twenty-four cases; a deep brown-red coloration was obtained in all before the onset of coma. During the comatose condition a very marked reaction was obtained in twenty. In two cases a deep coloration was obtained with perchloride of iron just before the onset of coma, but during the comatose condition the reaction was much less. In two of the cases a deep coloration was obtained just before the onset of coma, but the urine was not tested with perchloride of iron during the comatose condition.

In sixteen cases, Legal's test for acetone was applied to the urine during the comatose condition; in fifteen the reaction was obtained; in one there was no reaction (in this case the perchloride of iron reaction was also slight).

The urine in nineteen of the cases was examined for albumin during the coma; it was present in all, but the quantity was generally only very small. In some of the cases a trace of albumin had been present for several days or weeks before the onset of coma, and in these cases the amount of albumin increased during the comatose stage. In other cases albumin had been absent until the commencement of coma.

In sixteen cases the urine was examined for casts—they were always present.

In fifteen cases enormous numbers of finely granular casts were present during coma; in one case only a few were seen. In many of the cases the urine had been frequently examined for casts, with negative results, just before the onset of coma. In all of the fifteen cases there was a small, opaque, white or yellowish white deposit exactly at the bottom of the urine glass. Microscopically this deposit consisted of enormous numbers of casts and a few epithelial cells. In most of the cases the urine

was carefully watched for a deposit for days before the onset of coma, but it was always absent until just before the symptoms of coma commenced; it generally first appeared about twenty-four hours before these symptoms were noted. In severe cases of diabetes, I believe the appearance of this deposit (if microscopical examination show it to be composed of casts) is a very important sign of the approach of coma (see page 278).

In one case the patient lost 11 lb. in weight in the course of the week preceding the coma.

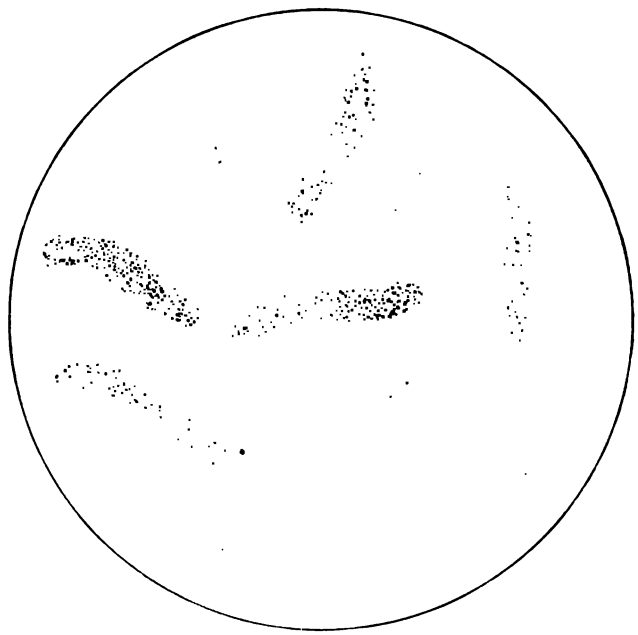

FIG. 18.—Granular casts in the urine in diabetic coma.

Convulsions did not occur in any of the twenty-six cases.

The knee-jerks were examined in twenty-one cases during coma; they were absent in eighteen, present in three; in one of these three cases, however, they became exceedingly feeble about two hours before death; but in one they were obtained distinctly half an hour before death.

The degree of coma varied. In some of the cases the patients were quite unconscious, and could not be roused for many hours before death. In other cases they were drowsy or semiconscious

for many hours, but only became totally unconscious for a short time before death. In some cases, though the patients passed into a semiconscious state, they could be roused to answer questions or to take medicine right up to the last hour of life. In one case the patient, though she was semiconscious and did not recognise her mother, was yet able to take her medicine ten minutes before death.

The duration of definite symptoms of diabetic coma was generally twenty-four to forty-eight hours; but in one case, five days elapsed between the onset of marked dyspnœa and death.

PATHOLOGY OF DIABETIC COMA.—The pathological changes met with in cases terminating in diabetic coma are not characteristic. The most constant are the changes in the epithelium of the kidney, described on p. 220, namely, the hyaline degeneration of Cantani, fatty degeneration, necrosis of epithelium (Ebstein), and the glycogenic degeneration of the epithelium of Henle's loop. The changes found in other organs are varied—they are generally due to complications—and cannot be regarded as important.

The literature relating to the pathology of diabetic coma is very extensive, but it will only be possible to refer to the more important views.

Fat emboli.—In some cases of diabetic coma there is an excess of fat in the blood (see p. 188); and Sanders and Hamilton (8) have detected fat emboli in the minute arteries and capillaries of the lungs, to a less extent in the kidney and other organs. They put forward the view that diabetic coma is the result of fat embolism. But this view is now rejected by almost all authorities.

As Dreschfeld (9) has pointed out, (1) in the majority of cases of diabetic coma, fat emboli are not found; (2) fat emboli have been found in the kidneys and lungs, in the most varied diseased conditions, and yet during life no symptoms thereof have been observed; (3) experiments on animals have shown that, unless very large quantities of fat be injected, no bad results follow, since the fat is gradually eliminated by the kidneys. Hence we may certainly conclude that in most cases of diabetic coma the symptoms are not due to fat embolism.

Cardiac failure.—In one variety of coma—the third form described as diabetic collapse—the symptoms are in all prob-

ability the result of cardiac failure, as suggested by Frerichs, Dreschfeld, and others.

Schmitz ([10]) points out that in advanced cases, just as the muscles of the extremities and trunk become greatly enfeebled, so also the cardiac muscles become weak and degenerated, and death may occur from cardiac failure, with symptoms of collapse.

But in the variety of diabetic coma first described (the most common form), some other explanation is probable.

The symptoms in this variety so strongly resemble those of some forms of intoxication, that there can be little doubt that in most cases the condition is the result of the action of some poison or poisons developed in the organism of the diabetic subject.

The facts that the blood and urine of diabetic patients contain a large quantity of grape sugar, that during coma the urine contains acetone, diacetic acid, and β-oxybutyric acid, and that the breath and the urine in diabetic coma have a peculiar chloroform-like smell, all seem to point to a poisoning of the organism.

Uræmia.—In diabetic coma, albumin in small or moderate amount is probably always present in the urine; also casts are probably always present, even though but a few days previously both were absent. Changes are frequently found in the renal epithelium, as above described. Nevertheless the symptoms of diabetic coma differ very much from those of uræmia, and it is not probable that there is the same toxic condition in the two affections.

Acetonæmia.—In many severe cases of diabetes and in diabetic coma the breath of the patient has a peculiar smell like chloroform, and has been shown to contain acetone. The urine has the same smell, and it also contains acetone (probably constantly). Acetone has been obtained from the blood in diabetic coma by some observers, but others have failed to obtain any evidence thereof. Hence the symptoms of diabetic coma have been attributed to the toxic effects of acetone in the system.

But Frerichs and Dreschfeld have shown that acetone can be taken in large doses by healthy men, without any symptoms of importance being produced. The expired air contained acetone, but only traces of this body were found in the urine. The late Dr. Linderman of Manchester tried the effect of sub-

cutaneous injection on himself. He found that the injection of 50 minims produced no bad effect. But acetone was present in the urine for twelve hours after the last injection.

Dreschfeld found that large quantities of sugar together with acetone could be taken without producing any toxic symptoms. When given to diabetic patients also, no definite symptoms were produced.

Subcutaneous injections of 5 to 10 minims of acetone, at long intervals, produced no symptoms in rabbits, beyond slight drowsiness; but if five or six doses of 10 minims each were given at short intervals, the rabbits became drowsy and comatose.

Acetone is found in the urine of diabetic patients, often for weeks or months before any comatose symptoms occur; also acetone appears in the urine of healthy persons when carbohydrates are cut off from the food entirely; and it is found in the urine in other diseases in which no symptoms of coma occur.

Aceto-acetic acid—diacetic acid.—Much the same results have been obtained in experiments with aceto-acetic acid, which has been thought to be the toxic agent in diabetic coma, and which is generally regarded as the substance giving the perchloride of iron reaction in the urine. Many observers—Dreschfeld, Frerichs, and others—have found that aceto-acetic acid can be taken in large doses by healthy persons without any toxic symptoms being produced; also the acetone odour of the breath has been detected, and the dark brown-red coloration with perchloride of iron has been obtained in the urine, in many diseased conditions besides diabetic coma (see p. 181).

The perchloride of iron reaction in the urine is often obtained for weeks or months, in severe cases of diabetes, without any comatose symptoms occurring.

Aceto-acetic ether given to healthy persons and to diabetic patients in large doses has also produced no results.

Acid intoxication.—Walter ([11]) has shown that large doses of dilute acids (hydrochloric and phosphoric) given to rabbits produce dyspnœa—the separate respiration being deep and laboured. At this stage there is no evidence of cardiac failure, and the blood pressure is not diminished. The dyspnœa is therefore not due to cardiac changes. Walter believes that these acids give rise first to a stimulation and then to a paralysis of the respiratory centre, followed by fatal collapse. He attributes

the symptoms to a diminished alkalinity of the blood, since they subside when sodium carbonate is injected into the blood.

These symptoms, produced in animals by acids, have some resemblance to those of diabetic coma in man, and Stadelmann ([12]) believes that the latter condition is really due to an acid intoxication. He attributes diabetic coma to a diminished alkalinity of the blood, owing to the presence of an organic acid. Minkowski ([13]) and others have supported this view. The symptoms have been referred to the presence of crotonic acid or to β-oxybutyric acid in the blood.

Vaughan Harley ([14]) has found that by injecting grape sugar into the jugular vein of dogs, symptoms resembling diabetic coma were produced, providing the ureters were ligatured so as to prevent any of the sugar or its products being eliminated by the kidneys. The result was: (1) a stage of nervous irritation, followed by (2) a comatose stage, varying from a few hours' drowsiness, up to deep coma, ending in death. Harley believes the coma to be, in part, the result of poisoning by substances produced by the decomposition of sugar. He thinks, however, that coma is principally due to a diminution of the alkalinity of the blood, owing to the production of acids by the splitting up of the sugar molecule.

Intestinal auto-intoxication.—Schmitz regards diabetic coma as the result of an auto-intoxication, due to the formation of toxic substances, by the putrefactive decomposition of albumins in the intestine. A great amount of nitrogenous food is taken, and, owing to the marked constipation, it remains long in the intestinal tract; decomposition occurs, toxic substances are formed, and, being absorbed, they give rise to diabetic coma. Schmitz states that by the use of purgatives (as castor-oil) he has caused the symptoms of diabetic coma to disappear, when the treatment has been commenced early.

It is very probable that constipation predisposes to coma (as pointed out on p. 273); but, on the other hand, constipation occurs to a marked degree in many affections without giving rise to any symptoms of coma; further, the bowels are often constipated in diabetes for long periods without any symptoms of coma developing; and, finally, in some cases of diabetic coma (though rarely) diarrhœa is present. Hence it appears more probable that constipation is merely an exciting cause of diabetic coma, and not the essential factor.

Rogue, Devic, and Hugounenq ([15]) have made some interesting observations on the toxic condition of the blood in a case of diabetic coma. They found that the alkalinity of the blood (estimated by sulphuric acid) was about half that of normal blood. To 30 c.c. of blood serum from a diabetic patient, a dilute solution of sodium bicarbonate was added, until the alkalinity of the mixture was the same as that of normal blood serum. In this way these observers were able to obtain two samples of serum from the same diabetic blood, of similar composition, except that one was twice as alkaline as the other. In order to determine whether the toxic action of the blood was the result of its low alkalinity, experiments were made on rabbits. It was found that 8 c.c. of serum of blood from the diabetic patient were sufficient to cause death; but, on using the diabetic serum, the alkalinity of which had been raised to the normal standard by adding sodium bicarbonate solution, it was found that 23 c.c. were required to give a fatal result. Hence these observers conclude that the toxic properties of diabetic blood are greatly reduced by the addition of alkalies.

Klemperer ([16]) and v. Noorden ([17]) are of opinion that in diabetic coma some toxic substances are produced in the organism, which, acting on the brain, produce coma, and which also cause destruction of protoplasm of the organism, and as a result thereof oxybutyric acid is produced. Coma on the one hand, and the formation of oxybutyric acid and the diminution of the alkalinity of the blood on the other, are the result of the action of some toxic substance formed in the diabetic organism.

The presence in the urine of acetone (in quantity), and of the substance giving rise to the brownish red coloration with perchloride of iron, are indications of a severe and serious nutritional change in the organism of the diabetic patient; and the continued excretion of β-oxybutyric acid in considerable quantity in the urine renders the onset of coma very probable.

In spite of the numerous researches and observations with regard to the pathology of diabetic coma, the exact cause still remains to be determined. Evidently some toxic substance or substances are formed in the system, which by their action produce the symptoms that have been described above.

Whatever the exact poison may be, as a rule, acetone, aceto-acetic acid, and β-oxybutyric acid are found in the urine coincident with this intoxication. It has not been proved,

however, that the presence of these substances in the blood cause diabetic coma; and in fact it appears more probable that they are produced in the system by the action of some unknown poison.

As already pointed out, in diabetic coma a small amount of albumin and numerous casts are generally present in the urine—probably they are always present—and very frequently changes are found in the epithelium of the uriniferous tubules. Hence it seems probable that failure of the renal function occurs, that some poison ceases to be eliminated, and as a result the symptoms of diabetic coma follow. Now, Vaughan Harley has shown (see p. 290) that similar symptoms can be produced in dogs by injecting grape sugar into the jugular vein, and preventing elimination by ligaturing the ureters. The two facts appear to me to throw much light on the pathology of diabetic coma.

DIAGNOSIS.—The diagnosis of diabetic coma is generally easy, when the patient has been under observation for some time and is known to be suffering from diabetes.

Important indications of commencing coma are: (1) Epigastric pain and nausea; (2) rapidity of the pulse; (3) dyspnœa (see case, p. 282); (4) drowsy mental condition, often with restlessness; (5) the appearance at the bottom of the urine glass of a small, opaque, greyish white deposit, which on microscopical examination is found to consist of enormous numbers of casts. The appearance of this deposit is generally, but not quite invariably, followed by coma, terminating fatally.

These indications are especially important if the patient is young and wasted, if the bowels are markedly constipated, and if the urine contains a small amount of albumin, and gives Gerhardt's reaction with perchloride of iron and the tests for acetone.

When the patient is seen for the first time in a comatose condition, the diagnosis is, of course, much more difficult. The differential diagnosis from other diseases may then generally be settled by an examination of the urine, which in the case of diabetic coma will have the characters mentioned above—namely, it will contain sugar in considerable quantity, albumin in small quantity, and almost invariably granular casts in enormous numbers; it will nearly always give a dark brownish red coloration with perchloride of iron and the chemical test for

acetone. It is stated that sugar occasionally disappears from the urine in diabetic coma; certainly, if this is ever the case, it happens exceedingly rarely. I have never met with such a case myself. In a few rare cases the perchloride of iron reaction is slight or absent.

If no urine is passed by the patient, it can generally be withdrawn from the bladder by the catheter; but if the bladder should be empty, then the blood examination for the methylene reaction described on p. 191, would be found of service in diagnosis.

Uræmia, opium poisoning, alcoholic intoxication, and coma from cerebral lesions of various kinds, are all liable to be mistaken for diabetic coma.

Uræmia.—Apart from the history, which of course cannot always be obtained from the friends of comatose patients, the following points in the symptomatology, during the stage of unconsciousness, would be of importance:—

In Favour of Uræmia.	In Favour of Diabetic Coma.
Œdema of face, legs, or genitals.	Patient generally much wasted.
Anæmia.	Slight cyanosis of face and limbs.
Pulse slow; when convulsions occur, pulse small and frequent.	Pulse small and rapid.
Cardiac hypertrophy present in many cases.	Cardiac hypertrophy very rare in severe forms of diabetes associated with great wasting.
Convulsions common.	Convulsions very rare indeed; knee-jerks generally absent; chloroform smell of breath.
Urine: Sugar absent, albumin present, often in large quantities.	Urine: Sugar present in large or considerable amount; albumin present, but only in small quantities.
	Methylene blue reaction with blood.

Blood examination.—The methylene blue reaction (see p. 171) would distinguish diabetic coma from other forms of coma.

Opium poisoning.—In favour of opium poisoning would be the smell of opium in the breath, the contracted pupils, and the absence of wasting. In favour of diabetic coma, the "acetone" smell of the breath, the above mentioned condition of the urine, and the methylene blue reaction of the blood.

Alcoholic intoxication.—As mentioned on p. 281, in diabetic coma sometimes the mental excitement is so great at the early stage, that cases have been mistaken for alcoholic intoxication.

In alcoholic intoxication there is the alcoholic smell of the breath, though this is not a sign of much importance, the peculiar dyspnœa of diabetic coma is absent, and the urine and blood do not present the signs characteristic of diabetic coma.

In cases of coma from *cerebral hæmorrhage* and other *cerebral affections*, it has been stated that occasionally sugar is found in the urine; but certainly this is very rare, and when sugar is present, only a trace is usually found, and diacetic acid and acetone are absent. Any evidence of unilateral paralysis or paresis of the limbs, such as indications of the limbs being more flaccid on one side than the other, or any unilateral affection of the cranial nerves, would be in favour of a gross cerebral lesion. In diabetic coma there are no indications of unilateral paralysis or paresis, and the urine and blood have the characters already described. In the coma of cerebral hæmorrhage, and sometimes in other cerebral lesions, the pulse is slow and full, whereas in diabetic coma it is quick and feeble, often almost too rapid to be counted. The presence of optic neuritis would exclude diabetes and point to tumour, abscess, or meningitis. If the urine cannot be obtained, or if its reactions are doubtful, I believe the blood test with methylene blue will be of great service in diagnosis. The difficulty in diagnosis is well illustrated by the case of a patient admitted into the Manchester Royal Infirmary a short time ago, under the care of Dr. Steell. A man, æt. about 28, had been found unconscious in the hold of a ship (on the Ship Canal) early on the morning of 9th January 1897. He had done his work all right on 8th January, and no history of accident or previous illness could be obtained. When first examined he was quite comatose. The limbs were flaccid, but there were no signs of unilateral paralysis. The pupils were equal. The urine was drawn away by a catheter, and found to give an abundant reduction of Fehling's solution. This roused suspicions of diabetic coma, since the reduction of Fehling's

solution indicated more than a trace or small quantity of sugar. Nevertheless one could definitely reject the diagnosis of diabetic coma, since the following symptoms and signs contra-indicated that condition. The specific gravity of the urine was low, 1011. There was no acetone smell of the urine or breath, and the urine gave no brown-red coloration with perchloride of iron. The pulse was not increased in frequency (70 per minute), and the tension was high. The peculiar dyspnœa of diabetic coma was absent, and the breathing was of the Cheyne-Stokes character. There was no wasting, and no cyanosis. Though no indications of external injury could be detected, still post-mortem examination showed that the case was one of fracture of the skull, the fracture involving the squamous part of the temporal bone, and running into the middle fossa. Between the dura mater and the skull was a large clot of blood, compressing the anterior part of the left cerebral hemisphere.

Prognosis.—The *prognosis* in diabetic coma is exceedingly grave; death usually occurs in from twenty-four to forty-eight hours. When once the patient has become unconscious, the case may be regarded as hopeless; but sometimes the early symptoms, such as dyspnœa, drowsiness, epigastric pain, and nausea appear for a day or two, and then subside without the patient passing into a comatose state. According to Hirschfeld, such abortive symptoms are not rare.

In an advanced case of diabetes seen in private practice, these symptoms—dyspnœa, epigastric pain, nausea, and drowsiness—became well marked; the urine gave a deep brownish red coloration with perchloride of iron, a trace of albumin was present, and there was an abundant deposit of casts. The patient was a man æt. 24; he was much wasted, and the symptoms pointed to the onset of diabetic coma. But large doses of alkalies were prescribed, the symptoms of commencing coma subsided, and the casts disappeared from the urine. The patient lived for six weeks longer without any comatose symptoms returning.

In another patient, æt. 29, who had been under my care on several occasions for two and a half years, the general symptoms increased rapidly; he became very weak and wasted; the urine presented a white deposit, which, microscopically, was found to consist of hyaline casts; drowsiness developed, and the patient appeared to be passing into a state of diabetic coma; but improvement

occurred in the general condition, the drowsiness passed off, and casts disappeared from the urine. Death occurred a few weeks later, without the symptoms of diabetic coma reappearing. In a third case (which has come under my observation at the Manchester Royal Infirmary), marked dyspnœa, epigastric pain and drowsiness had developed; but by treatment with very large doses of potassium citrate, prescribed by Dr. Reynolds, who was then the resident medical officer, recovery occurred, and the patient lived for twelve months, and finally died of phthisis. The case was under the care of Dr. Leech, and has been reported by Dr. E. S. Reynolds ([18]).

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CHAPTER XII.

PATHOLOGICAL ANATOMY.

NUMEROUS and varied pathological changes have been described in diabetes mellitus, yet, strictly speaking, the disease has no pathological anatomy. In various cases pathological changes have been found in every organ of the body; but they are general secondary, or due to complications. On the other hand, there is no organ which has not been found frequently normal on pathological examination. In the absence of any information as to the clinical history, or the examination of the urine or blood, a pathologist would be unable to diagnose diabetes mellitus by the macroscopical or microscopical changes found on post-mortem examination.

It is somewhat remarkable that the negative or indefinite nature of the pathological changes has not given rise to difficulties medico-legally. It is quite possible that a few of the numerous cases of death from unknown causes, in which post-mortem examination has failed to furnish any satisfactory explanation, have been due to diabetes mellitus—cases, for example, which are occasionally attributed to "serous" apoplexy, or to sunstroke, if the weather happens to have been warm.

Unless a specimen of urine be obtained from the bladder post-mortem, and sugar detected, or unless the blood be proved to contain an excess of sugar, the pathologist would not be able to decide as to the cause of death, providing nothing was known about the patient's symptoms during life. Also it is important to remember that the sugar in the blood diminishes markedly after death.

The pathological changes in the various organs are neither constant nor characteristic; they are chiefly secondary in nature, and have already been described in connection with the various complications, and in the chapter on etiology and etiological relation.

1. In the medulla, vagus nerves, and other parts of the base

of the brain, definite macroscopical or microscopical changes are occasionally met with, which are probably the *cause* of the disease, but such cases are rare, and often the brain is normal or only presents unimportant changes. The changes in the brain have been described and discussed on pp. 125–40. Those found in the spinal cord, the sympathetic and peripheral nerves, are described on pp. 129, 242, 131, 264.

2. The pancreas in many cases presents changes which are probably the cause of the disease, but in many cases this gland is normal or only presents slight and unimportant abnormalities. The pathological changes in the pancreas and their relation to diabetes have been discussed in Chapter VIII.

3. The liver presents no characteristic changes: its condition has been described on pp. 116–21.

4. The changes in the other organs are all secondary in nature. Those met with in the heart and vessels have been described on p. 216; those in the lungs on pp. 207–14; those in the alimentary canal on pp. 205, 206.

It is said that the most constant pathological change in diabetes is the glycogenic degeneration of the epithelial cells of Henle's loop of the tubules of the kidneys; but this change is of course secondary in nature. The abnormalities met with in the kidneys have been described on p. 219. The spleen is frequently reported to be normal, and when changes have been found they have been unimportant. The condition of the blood has been described in Chapter IX.

Pathogenesis.

We have now surveyed the chief facts which are known respecting the etiology, etiological relations, symptoms, and pathological anatomy of diabetes, and some of the more important experimental work in connection with the disease has been referred to. The question remains, What is the exact cause of diabetes mellitus in man? why do certain individuals become diabetic? The true nature of the disease still remains very obscure, and it is quite impossible to refer to all of the numerous theories that have been advanced. None of these are satisfactory, however, and in spite of the very extensive literature respecting diabetes, and the great amount of experimental and pathological research in connection with the disease, the riddle still remains unsolved, and will probably long remain so.

As stated above in Chapter II., in health the urine is either free from sugar, or it only contains minute traces, which cannot be detected by the usual clinical tests.

Why does the urine contain a large quantity of sugar in diabetes mellitus? In this disease, do the kidneys simply allow the sugar normally present in the blood to pass away into the urine? *i.e.* does the normal glucose simply separate itself from the other constituents of the blood, and leak through the urinary tubules into the urine? Or is the large amount of sugar in the urine due to an excess of sugar in the blood? The former supposition is certainly not correct, since the blood would then contain no sugar, or less sugar than in health, but chemical examination shows the reverse; the blood sugar is usually greatly increased in amount.

Hence we may conclude that sugar appears in the urine, because there is an excess of sugar in the blood, and the symptoms of diabetes are also owing to the same cause. This statement is certainly true with reference to the majority of cases of diabetes; and Bernard, Pavy, and most observers believe that glycosuria is always the result of an excess of sugar in the blood (glycæmia). But Seegen (1), whilst admitting that the above explanation holds good in the majority of cases, believes that in a few of the milder forms, glycosuria is not simply the result of an excess of sugar in the blood. In some of the latter cases he has found that the blood sugar has scarcely exceeded the normal limits. Putting aside these rare and disputed cases, there can be no doubt that in a very large majority, if not in all cases of diabetes, the glycosuria is due to the excess of sugar in the blood. The cause of this excess is the question which requires to be answered. Some authors have attributed it to (1) an excessive formation of sugar in the system; some have attributed it to (2) a diminished sugar destruction; whilst others believe (3) that in certain forms there is an excessive sugar formation, but in other forms a diminished sugar destruction. Now it is quite impossible, in a work devoted chiefly to the clinical aspect of diabetes, to mention all the more important arguments which have been advanced in support of each of these views, and only a few can be briefly referred to.

With respect to the theory of excessive sugar formation, Bunge (2) has pointed out the following objections: the great excess of sugar could not be derived from the carbohydrates

of the food, since these are normally converted into sugar, and then transformed into other substances. If the excess of sugar in diabetes had its origin in these carbohydrates, it would be owing to a diminished destruction and not to an increased formation. Neither has the excess of sugar its origin in fats, since diabetic patients can digest and assimilate them in large quantities. As to the proteids, assuming that a diabetic patient could consume 300 grms. in a day, this amount of albumin would not form more than about 200 grms. of sugar. And even if 200 grms. of sugar reached the blood daily, it would not cause diabetes, so long as the decomposition of sugar remained normal. A person whose power of sugar destruction was not impaired, would be able to decompose daily 600 to 1000 grms. of sugar (derived from starchy food), without glycosuria occurring. Hence Bunge thinks that increased sugar formation cannot account for the excess of blood sugar.

As regards excessive formation, in the strict sense of the term, Bunge's objections undoubtedly hold good with reference to the origin of sugar from foodstuffs, but do not apply to the possible formation of sugar from the albumins of the tissues.

On the other hand, Kaufmann (3) brings forward evidence in favour of the view that the excess of sugar in the blood in diabetes is always due to an increase in the sugar formation, and not to a diminished sugar destruction in the capillaries. He believes that in the normal condition the destruction of sugar in the blood is always compensated by an equivalent sugar formation by the liver, and that any modification of the destruction of sugar in the tissues reacts at once on the liver by the nervous paths or by the blood, and impresses on the sugar formation an activity in direct relation to the destruction.

Kaufmann has isolated the liver by tying all its vessels in a healthy dog, and also in another dog which had been rendered diabetic by extirpation of the pancreas. The sugar in the blood gradually became diminished during its circulation in other parts of the body. But an hour after the isolation of the liver, the blood had lost the same proportion of sugar both in the healthy and in the diabetic animals. After having determined the diminution of sugar, Kaufmann re-established the circulation in the liver by removing the ligatures placed on the vessels. He found that the sugar in the blood soon regained its previous percentage. Hence he concludes that sugar destruction pro-

ceeds with the same activity in dogs rendered diabetic by pancreas extirpation, as in the normal condition, and that the excess of sugar in the blood is due to increased sugar formation by the liver. Kaufmann believes that increased sugar formation, and not diminished destruction in the capillaries, is the cause of the excess of sugar in the blood in the diabetes produced by pancreas extirpation, by lesions of the medulla, and in all other ways.

Many authors, however, probably the majority, believe that diabetes mellitus in man is usually due to diminished sugar destruction.

As already mentioned, in the mild form of diabetes the removal of carbohydrates from the diet causes the glycosuria to cease. Now, in such cases the sugar appears to be derived in some way from the carbohydrates of the food. It may be that the sugar produced by the digestion of carbohydrates is absorbed into the portal system, and then conveyed into the general circulation, without being transformed into glycogen or other substances. Or it may be, that the sugar is converted into glycogen, but the hepatic glycogen is transformed into sugar again in an abnormal manner.

Seegen (4) believes that the cause of the mild form, which he terms the "hepatogenic," is the inability of the liver cells to assimilate the carbohydrates in a normal manner. But it has been shown by Ehrlich, Külz, and v. Mering that glycogen may be present in the liver in considerable quantity in diabetes mellitus. Also, pathological anatomy has failed to reveal any macroscopic changes in the liver associated with diabetes. Further, serious diseases giving rise to destruction of liver tissue—cancer, acute yellow atrophy, cirrhosis, etc.—are not associated with glycosuria.

According to Pavy (see p. 67), the two lines of defence —intestinal villi and the liver—are inadequate to accomplish their function of synthesising the carbohydrates. Hence the latter reach the general circulation in excessive quantity, and appear as sugar in the urine.

In the severe forms of diabetes, the sugar in the urine is evidently not dependent simply on the carbohydrates of the food, since the glycosuria persists when the diet consists only of fat and nitrogenous substances, and even during starvation.

Pavy thinks that in these severe forms the sugar eliminated

is derived not only from the food, but also from the tissues. He believes that the proteids of the body have a glucoside constitution, and that in diabetes of the severe form a carbohydrate is cleaved off from these proteids by the action of some ferment which he supposes to be present in the system.

According to Seegen, in the severe forms the cells and tissues of the organism have lost their function of destroying the sugar in the blood.

If we accept the views that the cells of the liver are at fault in diabetes, and in severe cases also the tissues of the organism, the question arises: Why do these tissues behave abnormally ?

Pavy believes that, as regards the liver, there is a vasomotor paralysis and dilatation of the small arterioles. As a result thereof, the blood passes through the capillaries too readily, and the contents of the small veins are not sufficiently de-arterialised. He has shown that a hyperoxygenated state of the blood favours the passage of carbohydrate matter into glucose. The vasomotor paralysis Pavy refers to changes in the nervous system.

Seegen points out that Pavy was able to produce diabetes experimentally, by injury to the nervous system after ligature of the hepatic artery, and he asks how vasomotor paralysis can be regarded as the explanation, if this be true.

According to Ebstein (5), the amount of carbonic acid formed in the tissues in diabetes is diminished. He believes that, owing to some abnormal state of the protoplasm, there is an altered condition of the internal respiration, with insufficient formation of carbonic acid. Glycogen is present in the tissues in greater quantity in diabetes than in health, and it is found in unusual positions. Ebstein also believes that in the tissues there is a diastatic ferment, and that the action of this ferment on glycogen is hindered by carbonic acid. He believes that in diabetes the diastatic ferment is present in normal quantity, but, owing to the deficient amount of carbonic acid the inhibitory action of the latter is less than normal. Hence an excess of sugar is produced; the sugar in the blood is increased, and glycosuria follows. Ebstein's views are in part based on the experiments of Pettenkofer and Voit, which appeared to show that the excretion of carbonic acid was diminished in diabetes; but these results have been disputed by Leo (6) and others.

According to Leo, the excretion of carbonic acid in diabetes is quite normal; and Ebstein's views have not been accepted by most pathologists and physicians.

As pointed out on in Chapter VIII., section *D*, there is strong evidence that some change in the nervous system is the starting-point of the disease in many cases.

Also, pathological observations and the results of experiments on animals render it very probable that in some cases of diabetes pancreatic changes are the cause of the disease (see Chapter VIII., section *E*).

It was pointed out on p. 156 that atheroma might act as the starting-point of diabetes, by producing changes in the nervous system or in the pancreas, and it is probable that a few cases of diabetes originate in this way.

Diabetes has been attributed by some authors to disease of the muscles. Bunge states that "as the bulk of the sugar is normally decomposed in the muscles, it seems probable that diabetes may fundamentally be due to a disturbance of the chemical processes in muscle." In stout diabetics a change from a sedentary to an active life has occasionally caused the glycosuria to cease, and a few cases of diabetes have been successfully treated by systematic muscular exercise. Bunge points out that the chemical processes in muscles are subject to the influence of the nervous system, and that numerous observations tend to show that the symptoms in diabetes are sometimes caused by disturbances which originate in the central nervous system.

The opinion appears to be gradually gaining ground, that diabetes is not a pathological entity, but rather a group of symptoms which may be produced by various morbid changes in the system. Just as fever is the result of many diseased processes, so it is quite possible, even probable, that diabetes is not always due to the same primary pathological condition, and that sometimes the starting-point of the disease is in the nervous system, sometimes in the pancreas, occasionally in disease of the arteries (arterio-sclerosis), possibly in the muscles sometimes, and possibly it is due to various other causes and to endogenous or inherited morbid conditions.

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CHAPTER XIII.

FORMS OF DIABETES—TERMINATION—PROGNOSIS.

Forms of Diabetes Mellitus and Glycosuria.

There are two chief forms of the disease, severe and mild, besides several other subvarieties. The main features of the two more important forms of the disease may be here repeated.

1. In the *severe* form, the symptoms—thirst, hunger, and diuresis—are well marked. The amount of sugar excreted is large, and does not cease, though it may be diminished considerably, when carbohydrates are rigidly excluded from the diet. There is often rapid loss of strength and marked wasting (hence the French term *diabète maigre*). This form of diabetes is met with chiefly in young persons or in persons under middle life. Often the patients are poor hard-working people, and a large proportion of the cases of diabetes seen in hospital practice belong to this class. The urine often contains acetone, and gives a dark reddish brown coloration with perchloride of iron (diacetic acid). According to Schmitz, the urine excreted during the night may contain a greater amount of sugar than that excreted during the day, even though carbohydrates be taken in the food (see p. 307). The sugar excreted is therefore not simply derived from the carbohydrates of the food. These cases frequently run a comparatively rapid course, and are often fatal in one to three years, death generally occurring from coma or phthisis.

But occasionally cases are met with which run a *very acute course*. The patients are often children or young people, under the age of 30, though acute cases may occur later in life. The disease may terminate fatally in a few weeks after the symptoms are first noticed. In one patient at the Manchester Royal Infirmary, who was 18 years of age, the symptoms were first

noticed only two weeks before death occurred; in two cases the symptoms were first noted only four weeks before the fatal termination; and in two other cases death occurred at the end of six weeks and eight weeks respectively after the symptoms first attracted attention. Death occurred from diabetic coma in all of the cases. Of course it is possible that in some of these cases the disease may have been present for a short time before the symptoms attracted the patient's attention; but others are on record, in which the urine had been examined and found free from sugar shortly before the diabetic symptoms appeared. Thus in Wallach's case, referred to on p. 166, the duration of the disease was under two weeks, as shown by the urine examinations.

2. In the *mild form* of the disease the sugar disappears from the urine on withdrawing carbohydrates from the food; generally thirst and diuresis are not so marked as in the severe forms; and dryness of the skin is often absent or slight. The patients are often old or middle-aged persons, and frequently stout. (To this form the term *diabète gras* is applied by French writers, and the term chronic glycosuria by certain English authors.) Not infrequently the patient also suffers from gout; and sometimes the urine contains a great excess of uric acid, but usually acetone and diacetic acid are absent. At an advanced stage, especially if the patient has been kept on an injudicious diet, marked wasting may occur. In this mild form of diabetes the night urine contains less sugar than that excreted during the day; in fact, the night urine may be quite free from sugar. The sugar in the urine appears to be derived from the carbohydrates of the food.

The onset of the disease is usually very gradual; frequently the patient seeks advice on account of some complication, such as carbuncles, gangrene, etc., and on testing the urine in a routine examination sugar is detected.

The mild form of diabetes generally runs a chronic course. Sometimes the disease is associated with kidney mischief—chronic parenchymatous or interstitial nephritis.

Some authors regard the mild and severe forms of diabetes as two different diseased conditions, but others believe that the mild form is simply an early stage of the severe variety. There can be no doubt, however, that many of the severe forms of diabetes have the characters of the severe variety from the onset,

and many of the cases of the mild form do not develop into the severe form. On the other hand, cases are sometimes met with in which at first the sugar excretion is very small, the diuresis slight, and the symptoms are those of the mild variety, but at a later date, months or years afterwards, the sugar excretion and diuresis increase, and all the symptoms of the severe form develop. Several cases of this kind have come under my own observation (see p. 166). There are, therefore, besides the mild and severe forms, *transitional* and *intermediate* varieties.

The following are examples of the differences in the quantity of sugar excreted in the day urine and in the night urine, in the mild and the severe forms of diabetes.

In a case of diabetes of the mild form in a very stout patient, æt. 49 (who came under treatment for eczema of the vulva), the specific gravity of the urine was 1029; and the total quantity of sugar excreted in twenty-four hours was 270 grs., the diet being unrestricted. When the diet was limited to flesh meat, fish, milk (2 pints daily), beef-tea, green vegetables, and a little bread, the sugar excretion diminished to 78 grs. daily. On three occasions the night urine, passed between 1 A.M. and 8 A.M., was collected and kept separate from the rest of the urine. It was found quite free from sugar. In other cases of the mild form of diabetes I have found sugar absent from the night urine, but present in the day urine.

In severe forms of diabetes I have never found the night urine free from sugar. Sometimes I have found that more sugar was excreted during the night than during the day; at other times the quantities have been about the same; sometimes the sugar excreted during the night has been a little less than that excreted during the day.

Thus in the case of a boy, æt. 19, who was suffering from a severe form of diabetes, the sugar excreted during the night was either more than that excreted during the day, or it was only a little less in amount.

The amount of urine from 8 A.M. to 9 P.M. was 102 oz. Total quantity of sugar excreted during the day was 3769 grs. The night urine from 9 P.M. to 8 A.M. was 106 oz. Total quantity of sugar excreted during the *night*, 4223 grs.

The patient had breakfast at 8 A.M., dinner at 1, tea at 4.30, and a little milk at 7 P.M. No food was taken afterwards.

In some of the mild forms of diabetes no sugar appears in the urine, even when a limited quantity of carbohydrate food is taken; but when the amount of carbohydrates in the food passes beyond a certain quantity, glycosuria occurs. There is thus a tolerance of a certain amount of carbohydrate food; but if this limit be exceeded, sugar is found in the urine. In other cases the urine only remains free from sugar when all carbohydrate food is withdrawn.

In some of the mildest cases the quantity of urine excreted is normal, or almost normal, whilst the specific gravity is high; thirst and other diabetic symptoms may be absent. Such cases have been described by the term *diabetes decipiens*.

In a case of the kind which I have followed for some time, the urine has a specific gravity of 1040–42; the amount is about 50 oz.; the sugar varies from 5 to 7 per cent. There is no thirst, no loss of flesh, and the patient (a young adult) appears and feels in perfect health.

In another variety of the mildest form, the symptoms may disappear from time to time; this is known as *intermittent* diabetes. Cases are sometimes met with in which the sugar excretion ceases, and for a time the patient is quite well; then some indiscretion as regards mode of life, etc., causes the glycosuria and other symptoms to return. The sugar may disappear on several occasions and return again, and finally the disease may terminate fatally.

Thus, for example, a gentleman æt. 56 consulted me on account of diabetes. He complained chiefly of dryness in the mouth; his urine had a specific gravity of 1035, and was loaded with sugar. The patient was stout, and for five or six years sugar had been found in his urine by his medical attendant; but the glycosuria had been intermittent, and sometimes had been absent for four to six weeks at a time.

Symptomatic glycosuria, in which the sugar excretion can be referred to some primary affection of the nervous system, or to other disease, has already been mentioned on p. 91. The symptoms are often slight, and frequently temporary.

Diabetes with pigmentation of the skin—Diabète bronzé (Hanot [1]).—In 1882, Hanot and Chauffard ([2]) described a disease characterised by the association of symptoms of diabetes mellitus with hypertrophic cirrhosis of the liver and pigmentation of the skin. To this disease Hanot gave the name of *diabète bronzé*.

In his second series of cases the liver was of normal size, but the other symptoms were present.

The disease has since been described by Letulle (4), Brault and Gaillard (5), Barth, Gonzalez Hernandez (6), Palma, Mossé (7), de Massary and Potier (8), and Marie (9).

The following is Hanot's clinical description of the disease :—

"The symptoms consist of general signs of diabetes, with abundant glycosuria; of melanoderma, most marked upon the face, the limbs, and the genital organs; general symptoms of hypertrophic cirrhosis, hypertrophy of the liver and of the spleen, with slight ascites and distension of the abdominal cutaneous veins.

"The onset is frequently sudden. Wasting, diarrhœa, œdema of the lower limbs, soon appear; loss of strength rapidly ensues, and death supervenes, either during coma, or from septic pneumonia following diabetic gangrene. Although the pathogenesis is not yet definitely proved, it appears to me that *diabète bronzé* is a distinct morbid entity.

"In different cases the liver weighed from 1800 to 3500 grms.

"The density of the tissue is considerable, and its reddish brown coloration recalls that of rust, or of old untanned leather. The surface is smooth, and the biliary ducts are, as a rule, unaffected.

"The intestinal glands are slaty-black in colour. The ascites is generally moderate in amount, from 2 to 9 litres. The spleen is increased in volume, indurated, and presenting a reddish brown colour, somewhat resembling that of the liver. The mesenteric and mediastinal glands have somewhat the same rusty colour as the liver. The ochre-coloured pigment, which infiltrates most of the organs and the Malpighian layer of the skin, is an iron-containing pigment, as is proved by its reaction with ammonic-hydric sulphate and potassium ferrocyanide. Brault has insisted upon the properties which distinguish the yellow pigment from the other ones, the melanin pigment and the pigment of Addison's disease, which have no reaction for iron. The pigment contained in melanotic sarcomas is soluble in potash; and if one places a fragment of a melanotic sarcoma in a tube containing potash, the pigment is entirely dissolved out, and the liquid in the tube takes the colour of port wine. The ochre-coloured pigment does not, on the other hand, dissolve.

"In the liver, the pigment, which in Dr. Lapicque's experience appears to be a 'salt of iron,' is found between the connective tissue fibres, in the fibres themselves, and in the hepatic cells. The cells sometimes contain a few granules only, and sometimes appear to be loaded with pigment, having lost their nuclei, and becoming transformed into yellowish masses."

Hanot and Chauffard regarded the pigmentary cirrhosis as the result of the diabetic condition. They believed that the pigment was developed in the liver, and then became diffused in the form of minute emboli through the whole organism.

Letulle does not think the pigment found in the various organs is formed originally in the liver, but believes it arises in various parts from the hæmoglobin of blood or muscle.

Gonzalez and Reiner have found that the pigment contains iron. Mossé believes that the evidence is in favour of its origin from altered hæmoglobin, and Massary and Potier think that the pigment is separated from the blood in the organs themselves.

According to Marie, *diabète bronzé* is neither a pigmentary cirrhosis in diabetes mellitus, nor a *cachexie bronzé*, but a true clinical and pathological entity; in fact, a new disease. Hanot's observations lead him to agree with this view.

Phosphatic diabetes ([10]) is the name which has been given to a somewhat indefinite group of cases, in which the excretion of phosphate of lime is excessive. There is great nervous irritability, derangement of digestion, great emaciation, and severe aching pain in the back and loins. As the disease advances, the amount of urine increases, and symptoms appear which are somewhat analogous to those of diabetes, especially the insipid form. Hence the name phosphate diabetes. The urine is usually free from sugar, but Osler ([11]) states that in some instances sugar has been present, and in others it has subsequently appeared.

Termination.

(*a*) *Recovery.*—According to Cantani ([12]), by a rigid diet, a cure is not infrequently obtained in mild forms. But many physicians, who have had a large experience of the disease, state that they have never met with any case of true diabetes in which permanent recovery has occurred. I have seen a number of cases of symptomatic glycosuria, associated with cerebral lesions, etc., in which the sugar excretion has ceased, but I have

never seen true recovery from a severe form of diabetes. In the milder forms, by restricted diet, the sugar may disappear from the urine entirely or partially; but when a less rigid diet is taken, the glycosuria returns. Patients suffering from the mild form may, by following a restricted diet, live for years without a return of the symptoms, or may live for years without any symptoms beyond the presence of a small amount of sugar in the urine. The urine of one of my patients—an old man of 72, who suffers from a mild form of diabetes—has contained sugar for seventeen years, but the other symptoms have been slight. In some of these cases, after the diet has been restricted for some time, the system is able to tolerate a certain amount of carbohydrates. A small quantity of starchy food may then be added without the appearance of sugar in the urine. Occasionally the symptoms of diabetes in its mildest form (or chronic glycosuria) disappear temporarily, or, very rarely, permanently. In mild forms of diabetes in women, occurring about the climacteric period, recovery sometimes takes place.

In a case which has recently come under my care, a female, æt. 20, began to suffer from thirst and diuresis. Six to eight pints of water were drunk daily, in addition to the usual quantity of fluids at meals. The thirst and diuresis continued two or three weeks, and then rapidly diminished. The urine was examined, and found to reduce Fehling's solution. The specific gravity was at one time as high as 1042. The diet was restricted, and the thirst and diuresis completely disappeared, and the reducing substance in the urine became less. Three months after the symptoms had first commenced, I found that the urine contained a very small quantity of sugar when the patient was on a restricted diet; but by allowing bread in considerable amount, the sugar reached 3 per cent. The quantity of urine was not increased, 36, 40, 44, 45 oz. being the amounts of urine for four consecutive days. The specific gravity varied from 1018 to 1032. That the reducing substance was sugar was shown by the fermentation test, and the reaction with phenyl-hydrazin. There was no thirst at the time, and the patient felt quite well. One week later every trace of sugar disappeared from the urine, and all diabetic symptoms were absent, but one month afterwards the glycosuria returned.

A case has come under my observation in which the patient,

a woman æt. 52, had suffered from very great thirst and very great diuresis for six months during pregnancy. The urine was at that time examined by her medical attendant, and diabetes diagnosed. After the birth of the baby, the thirst and diuresis disappeared at once, and did not return for fifteen years. She then began to suffer from slight thirst about once a week; this increased, and three years later she presented the symptoms of a severe form of diabetes, which terminated fatally. For nine years she had had much mental anxiety, worry, and overwork, owing to her husband having become a helpless paralytic.

In another case which has come under my observation, a female æt. 60 had suffered from great thirst, and had passed a large quantity of urine. She had lost flesh, and had suffered from pain in the limbs. After these symptoms had been present for nine months, the urine had been examined by a medical man, and diabetes diagnosed. The sugar gradually diminished, and all the diabetic symptoms disappeared, except pain in the legs. Twelve months after the onset of thirst, the urine had a specific gravity of 1014. Albumin was absent. A small quantity of sugar was present, as indicated by Fehling's solution, by the phenyl-hydrazin test, and by Seegen's test, after filtration through animal charcoal. The amount of urine varied from 39 to 43 oz. One week later the urine was free from the slightest trace of sugar, and remained so during the three weeks the patient remained under observation.

When diabetes is associated with phthisis or other serious complications, shortly before death the glycosuria and other diabetic symptoms have occasionally disappeared, and only those of phthisis or the complications have remained.

(*b*) *Termination in other diseases.*—1. Albumin may appear in the urine, and occasionally symptoms of chronic parenchymatous or interstitial nephritis develop. In these cases sometimes the kidney symptoms gradually advance, whilst the glycosuria diminishes; and, finally, the sugar excretion ceases, and only the symptoms of nephritis remain.

2. Occasionally the symptoms of diabetes mellitus give place to those of diabetes insipidus, and the sugar then disappears from the urine. A few of such cases are on record in which, finally, the polyuria has disappeared, and complete recovery occurred. The relation of the two diseases has recently been carefully discussed by Senator ([13]) (see p. 115).

(*c*) *Fatal termination.*—Diabetes may terminate fatally in the following ways:—

1. By diabetic coma. This is the most frequent termination.
2. By tubercular phthisis. This is a termination met with chiefly in young patients suffering from the severe form of the disease. As already stated, if phthisis becomes advanced, death does not generally occur from coma (though there are exceptions to the rule).
3. By other lung complications, such as pneumonia, pulmonary gangrene, non-tubercular phthisis, etc.; but these terminations are rare.
4. By exhaustion and marasmus.
5. By nephritis.
6. By cerebral hæmorrhage or softening.
7. By carbuncle or gangrene.

The following is the mode of termination in the last forty-two fatal cases of diabetes which have come under my observation:—

	Cases.
Diabetic coma	29
Asthenia from phthisis and lung disease (six tubercular, one non-tubercular)	7
Cardiac failure	2
Asthenia from cirrhosis of the liver	1
Pyæmic condition (multiple abscesses of the liver)	1
Acute pneumonia	1
Gangrene	1
	42

Duration.

In some severe cases the duration of the disease may be very short—two, four, or six weeks; but these cases are rare, and a duration of six months to three years or longer is much more frequent; whilst in the mildest forms the disease may run a very chronic course of five, ten, fifteen, or even twenty years. In one case, an old man of 72, the disease had been detected over seventeen years before he came under my treatment.

Prognosis.

Before giving a prognosis, it is important to place the patient on a restricted diet (taking the precautions mentioned

on p. 322), in order to decide to which form of the disease the case belongs. The prognosis depends chiefly on the form of the disease, and on the age of the patient.

The following are *unfavourable prognostic indications*:—

1. A severe form of the disease, when the most rigid exclusion of carbohydrates from the diet fails to remove sugar from the urine.

2. Early age. The younger the patient the more unfavourable the prognosis as a general rule, the prognosis being especially bad in children, and patients under 30. (In twenty-eight cases of diabetes in children, collected by Wegeli, the duration of the disease was very short, often some months only. The longest duration was four and a half years.)

3. Marked wasting, great loss of weight and loss of strength, especially when the disease is of short duration.

4. The occurrence of pulmonary tuberculosis as a complication.

5. Severe general symptoms and marked digestive disturbance.

6. The occurrence of gangrene.

7. A history of other members of the family having suffered from a severe form of diabetes.

8. Unfavourable conditions of life. Amongst poor people often the disease is not recognised until a late stage; also the treatment cannot be carried out so carefully. Mental anxiety and worry often hasten the fatal termination.

9. The presence of a well-marked brownish red coloration of the urine with perchloride of iron.

10. The sudden occurrence of a greyish white urinary deposit consisting of casts.

11. A high degree of acetonuria or a marked increase in the amount thereof (9, 10, and 11 indicate the approach of diabetic coma).

12. The appearance of other symptoms indicating the onset of coma.

13. The occurrence of symptoms of nephritis, especially if the glycosuria gradually disappears and is replaced by albuminuria.

It is to be remembered that in severe cases diminution in the amount of sugar in the urine is not always a favourable sign. Sometimes, as the glycosuria diminishes, the wasting

increases, the patient loses weight rapidly, and the general condition becomes worse; and this is especially liable to occur when phthisis is a complication. In such cases, sugar may disappear finally, and death occurs from the asthenia of phthisis.

Favourable indications.—1. A mild form of the disease; the sugar being removed from the urine by the withdrawal of carbohydrates from the diet.

2. Advanced age. The older the patient the better the prognosis as a rule.

3. The association of diabetes with obesity, gout, or the uric acid diathesis.

4. A long duration of the disease without the occurrence of complications, of much wasting, or of loss of weight.

5. A history of a mild form of diabetes in other members of the family.

6. Favourable conditions of life; absence of mental worry and anxiety; good social position and greater likelihood of early recognition and careful treatment of the disease.

7. The onset of the disease about the climacteric period in females.

8. The transition of diabetes mellitus into diabetes insipidus.

Diagnosis.

Usually the diagnosis of diabetes is very easy, but (1) the disease may be overlooked and the patient treated simply for one of the complications; or (2) various reducing bodies in the urine may be mistaken for sugar; or (3) a temporary glycosuria may be mistaken for a true diabetes.

When the patient complains of thirst and diuresis, when the urine is found to be pale and straw-coloured, of high specific gravity 1024 to 1040 or more, and when a well-marked reaction is obtained with Fehling's solution, there can be no doubt about the diagnosis. But difficulty arises chiefly, if the patient should complain only of wasting or weakness, or of some of the complications, and should make no mention of thirst or diuresis. The emaciation often rouses suspicions of phthisis, and if the urine be not examined, diabetes is perhaps never thought of. It is important, of course, to examine the urine in all cases, as a matter of routine, before making an exact diagnosis; but this is especially necessary in all cases of wasting. The urine ought

also to be examined for sugar in all cases of pruritus or eczema of the genitals, boils, carbuncles, gangrene, cataract.

It is important to remember, as pointed out on p. 10, that Fehling's solution is reduced by other bodies besides glucose —by glycuronic acid, lactose, alkapton, etc. Especially when the quantity of oxide of copper thrown down is small, or when other diabetic symptoms are absent, there is often considerable difficulty in diagnosis. It is then necessary to decide definitely whether the reducing substance is or is not grape sugar. (The detection of small quantities of grape sugar with certainty has been considered in the chapter on "Urine Testing," p. 35.)

Having determined that the urine does contain grape sugar, it is necessary to ascertain the quantity roughly if not exactly. Then the question arises, Does the patient suffer from diabetes? It is important to remember that the presence of grape sugar in a specimen of urine does not necessarily, *per se*, indicate diabetes mellitus. The patient may be suffering from—

1. Temporary glycosuria:

(*a*) physiological—alimentary glycosuria (rare), or

(*b*) pathological, and secondary to some other disease.

In these cases (*a* and *b*) the sugar is generally small in quantity; it soon disappears, and the urine is not increased, or only slightly increased, in amount.

2. The glycosuria may be *permanent*, and the patient may be suffering from

(*a*) the mild form of diabetes or chronic glycosuria, in which sugar is removed by a restricted diet; or

(*b*) the severe form of the disease, in which the glycosuria is not removed by a restricted diet.

It is important, therefore, to watch the case for a little time, to see if the glycosuria is persistent, and to determine the quantity of urine and the amount of sugar. The duration and the amount of the sugar are the points of greatest importance in the diagnosis, and are not simply of theoretical interest. Thus, for example, it is important not to pronounce the patient to be suffering from diabetes simply because the urine contains sugar. It is necessary to decide to which of the above groups the case belongs. Great harm may be done to a patient who suffers from a temporary glycosuria (physiological or pathological) by a mistaken diagnosis of diabetes. The mental shock might be great, especially if any relative of the patient had

died of diabetes. Thus a case has been recorded, in which the mental shock produced by the discovery of a small amount of sugar in the urine gave rise to Graves' disease, which terminated fatally (Grube). The case should be therefore carefully investigated, so that, if possible, the patient may be reassured, at the same time that he is informed of the presence of sugar, that he is suffering from a temporary or mild glycosuria and not a true diabetes. Then, again, if it be found that the patient suffers from true diabetes, the variety should be determined, so that, in case it is very mild, a favourable prognosis may be given. When the form is severe, the medical man ought to use the greatest discretion in informing the patient so as to cause as little mental shock as possible, and the patient ought also to be cheered by pointing out any favourable features of his case, if such exist.

In the severe form of the disease, an abrupt and hasty statement of an unfavourable prognosis might do much to hasten the fatal termination.

Then it is also important, for another reason, that the medical man should decide to which of the above classes the case of glycosuria belongs. His reputation may suffer considerably from the hasty diagnosis of diabetes, when the case is really one of mild or temporary glycosuria, from which the patient may recover in a short time. Even when all the above precautions are taken, there are still cases in which it is occasionally difficult to say whether the patient is suffering from temporary glycosuria or from the earliest stage of diabetes. Occasionally, only a guarded diagnosis can be given, and the case watched.

There are various mild forms of the disease of long duration, in which the quantity of urine is normal or only slightly increased, that are better described as chronic glycosuria than true diabetes.

Having decided that the case is one of diabetes or chronic glycosuria, it is important to try and determine if it is secondary to any other disease, as, for example, lesions of the brain, or pancreas, atheroma, gout, obesity, etc., but at present this is possible in a few cases only.

Occasionally, though very rarely, locomotor ataxia is complicated with glycosuria or diabetes. The knee-jerks are frequently lost in diabetes; often there are pains in the legs, tenderness of the calf muscles, and other slight symptoms of

peripheral neuritis. Hence a difficulty occasionally, though very rarely, arises in diagnosing between an early stage of locomotor ataxia with secondary glycosuria, and diabetes with loss of knee-jerks and early symptoms of a secondary peripheral neuritis, particularly if the latter be of the ataxic form. Again, a patient may come under treatment for a perforating ulcer of the foot; on examination, the knee-jerks may be absent, and pains in the legs may be troublesome. Such cases are also liable to be mistaken for locomotor ataxia, especially if the diabetic symptoms be slight.

A careful examination of the urine, and a consideration of the symptoms and general history of the case, are usually sufficient to enable a decision to be arrived at easily. Also the Argyll Robertson pupil, the sharp shooting nature of the pains, and a girdle sensation would be in favour of locomotor ataxia. Grube ([14]) thinks, however, that even the failure of the pupillary reaction is not always diagnostic, but believes that the presence of bladder symptoms is important. Sudden and involuntary discharge of urine or other slight bladder symptoms are frequently present in locomotor ataxia, but do not occur in diabetes with peripheral neuritis.

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CHAPTER XIV.

THE TREATMENT OF DIABETES.

UNTIL more light has been thrown upon the exact pathogenesis of diabetes mellitus, the treatment of many cases will remain unsatisfactory. In the milder cases much can be done, and often excellent results are obtained; but in the more severe forms the indications for treatment are less clear, and the results unsatisfactory. In the latter cases treatment can only be empirical, but it need not necessarily be unscientific.

PROPHYLAXIS OF DIABETES.

It has been shown that in healthy individuals the sugar-destroying power of the organism is not unlimited. According to v. Noorden, when more than 180 to 250 grms. of grape sugar are taken, even in health, temporary glycosuria is produced. The figures indicate the average quantities only, and in different healthy individuals the limit varies somewhat. v. Noorden [1] found that in four out of fifteen obese persons temporary glycosuria was produced by the administration of only 100 grms. of pure grape sugar. Of these four persons, two became diabetic some years later, and in the other two the lapse of time has been too short to exclude the possibility of diabetes developing. v. Noorden suggests that a large quantity of grape sugar should be given, by way of experiment, in the case of persons who have a family history of diabetes, or who are obese or gouty, in order to ascertain how much sugar they can assimilate. If a temporary glycosuria be produced by an amount of sugar which is much below the average above stated, then these individuals may be regarded as suspicious persons with regard to the possibility of the development of diabetes, and they ought to observe great caution with respect to amount of carbohydrates (especially sugar) in their diet. v. Noorden would limit the amount of beer

also in these cases. In this way it is possible that the development of the disease may be prevented in some obese and gouty persons, and in persons who have a family history of diabetes.

Management of a Case of Diabetes.

After a diagnosis of diabetes has been made, it is important to note carefully a number of points before commencing the treatment. The *general condition* of the patient should be carefully observed—whether he is well nourished or badly nourished. The patient's weight should be ascertained, and whilst he is under treatment he should be weighed once a week. It is important to keep a sharp outlook on these two points. Even though the sugar excretion and other symptoms should be diminished by any form of treatment, this must be regarded as unsatisfactory if the patient at the same time loses weight, and if the general condition deteriorates. Hence a weekly or monthly record of the patient's weight is perhaps more important in severe cases of diabetes than the daily record of the amount of sugar excreted.

Inquiries ought to be made with respect to the condition of the *bowels*. This is especially necessary in the case of patients just admitted to the wards of a hospital, since the confinement to bed and the altered condition of life are alone sufficient in many cases to produce obstinate constipation; and if the bowels have been previously constipated for a long period, the onset of diabetic coma will be thereby favoured. Hence, means should be taken to relieve severe constipation, if this symptom be present.

A routine examination of the patient should be made, and complications should be noted. The lungs should be carefully examined, especially in wasted patients, for signs of phthisis, since this is one of the two most serious complications which may arise. Diabetics, especially hospital patients, are very liable to develop tubercular disease; hence precautions should be taken, particularly if wasting be present, to avoid the risks of tubercular infection, and to prevent the development of this complication.

It is important to ascertain whether the urine gives the dark brownish red coloration with perchloride of iron (Gerhardt's reaction), since this reaction points to a severe form of the

disease, and is an indication that a rigid diet should not be prescribed.

In hospital patients the amount of sugar in the urine should be estimated daily, and this is done most readily by the fermentation test. A chart should be kept, showing in a tabular form the daily quantity of fluid taken, the amount of urine, the specific gravity of non-fermented and of fermented urine, the total daily excretion of sugar, the weight of the patient, and the treatment. In private practice, the amount of sugar can only be estimated periodically, as a rule. It is also of advantage to estimate from time to time the amount of urea excreted, in order to obtain an indication of the nitrogenous waste.

After admission to the hospital, the patient should be kept on a diet which is not much restricted for a few days before any observations are commenced with respect to the effect of any special diet or treatment. Very frequently there is a considerable diminution of the sugar excretion during the first three or four days after admission to the hospital, apart from any special form of treatment or restriction of diet. Hence it is well to wait until this equilibrium has been attained, before commencing any observations as to the effect of treatment. To this general rule there are exceptions, however. The patient's condition may make it necessary to restrict the diet at once, in certain cases, when the treatment has been greatly neglected before admission to the hospital, or when complications have arisen which demand prompt anti-diabetic diet. Then, again, if the patient has been on a very rigid diet at home, if an ordinary diet be allowed suddenly, the rapid change might lead to serious symptoms in advanced cases of diabetes. Diabetic coma has been known to follow such a sudden change in diet.

The figures respecting the sugar excretion for the first two or three days ought not to be taken into consideration in drawing any conclusions as to the effects of drugs.

The diet should, then, be restricted, but it is important to make the change gradually. Caution is especially necessary when the urine gives a deep red coloration with perchloride of iron, and in these cases it is also important that the diet should not be rigid for a long period.

Potatoes should be excluded from the diet first, then bread, and gradually all carbohydrates should be cut off. In the place of bread, the aleuronat and cocoa-nut cakes mentioned

on p. 357 may be given. It is then noted whether the sugar has disappeared from the urine; if so, the patient is suffering from a mild form of the disease. If sugar be still present, the case belongs to the severe form of diabetes.

If glycosuria disappears when the patient is on a rigid diet, then in course of time a little bread should be allowed, and the amount gradually increased. It should be carefully observed how much carbohydrate can be allowed before sugar reappears in the urine. This amount is an indication of the quantity of carbohydrates the patient can tolerate.

If exclusion of carbohydrates does not cause the glycosuria to disappear, a very rigid diet must not be maintained, especially if the urine give the dark brownish red coloration with perchloride of iron.

The effects of various drugs or other forms of treatment may be tried with or without restriction of diet.

The urine ought to be examined frequently for albumin and casts, in advanced cases of the severe form of the disease, as the appearance of the latter is often, but not always, a forerunner of diabetic coma.

General Principles of Treatment.

There is no routine treatment for diabetes. Each case must be separately considered, and the treatment varied according to the form of the disease.

The chief objects to be aimed at in the treatment are—

1. To diminish the amount of sugar in the urine and blood; to diminish the amount of urine, and to relieve thirst.

2. To increase the weight, or at least to maintain it (except in those mild cases in which the disease is accompanied by obesity), and to improve the general condition.

3. To treat the various complications.

In mild cases of diabetes, the first object may be attained by removal of the carbohydrates from the diet.

Leo (2) has pointed out that in the majority of severe cases of diabetes there is a great increase of the nitrogenous metabolism, and, as a result, a great loss of strength. The aim of treatment in these cases ought to be to diminish not only the excretion of sugar, but also the nitrogenous metabolism.

Careful observations have shown that sometimes improvement occurs, and the patient gains in weight, in severe cases of

diabetes, when a little carbohydrate food is allowed, even though the amount of sugar may be increased in the urine. If the patient be losing weight, and the general condition be deteriorating, then a diminution of sugar is of no avail.

In the slight cases, and in cases of medium severity, the diminution or disappearance of sugar is a most favourable sign; but in the advanced and severe cases, accompanied by great wasting, I have not infrequently found that a diminution of sugar has been associated with an unfavourable course of the disease, and has been accompanied by loss of flesh and deterioration of the general condition. The sugar has become less and less, and has occasionally disappeared shortly before the fatal issue.

It ought to be our aim to make thin diabetics stout, as in patients who are well nourished the prognosis is always much better.

Those who are engaged in general practice amongst people in good circumstances are apt to look upon the treatment of diabetes as often fairly satisfactory; whilst those who see much of the disease in the hospitals of our large towns, or of diabetes amongst the poor, will have been struck by the want of success in treatment.

Much depends on the *form* of the disease. The results of treatment in the mild form are very good, whilst in the severe form they are often very unsatisfactory. In the former, by treatment, the sugar may be removed from the urine, and the symptoms disappear, so long as the patient follows the treatment prescribed; or, if the sugar does not entirely disappear, it is diminished greatly, general improvement occurs, and very frequently treatment enables the patient to live with a fair amount of comfort and security. Life may be sometimes prolonged for ten or twenty years, or up to the natural limit.

The earlier the treatment is commenced the better; it is often very unsuccessful amongst the poor, because no attention is paid to the disease until a late stage. Moreover, there are very acute cases which sink rapidly, in spite of all treatment. All these points ought to be borne in mind, in considering the effects of treatment in any particular instance.

Dietetic Treatment.

It is well known that in certain parts of the world man

lives in perfect health on a diet from which carbohydrates are almost absent. A mixed diet is no doubt most suited for sustaining human life under the conditions of modern civilisation, but a review of the dietetic customs in different parts of the world (such as that given by Dr. Pavy in his "Treatise on Food and Dietetics," London, 1874, p. 427), shows that many races live almost entirely on food derived from the animal kingdom. Thus in the Arctic regions the Esquimaux live chiefly on animal food—on flesh and large quantities of fat. The Pampas Indians, who pass the greater part of their lives on horseback, are said to live entirely on animal food—"the flesh of their mares"—and to have neither bread, fruit, nor vegetables. The Guachos, the inhabitants of the Pampas in the Argentine Republic, who also spend the greater part of their time on horseback, are said "to live entirely on roast beef, with a little salt, scarcely ever tasting farinaceous or other vegetable food," and their sole beverage is stated to be maté taken without sugar.

Ever since Rollo published his book on diabetes in 1797, and pointed out the value of restriction of the carbohydrates in the food, it has been acknowledged that of all forms and methods of treatment this dietetic one is the most important.

In undertaking the dietetic treatment of any case of diabetes, it is necessary to give direction (1) as to the *nature* of the food, (2) as to the *quantity*. But there is no hard-and-fast rule on these points, and each case must be treated according to the form of the disease to which it belongs.

What has already been pointed out with respect to the varieties of the disease may be repeated, since different dietetic treatment is required in each case. Diabetic cases may be divided into two chief forms, mild and severe; of each of these forms Minkowski[3] recognises two varieties.

1. *The mild form* occurs chiefly in persons past middle life—especially in obese or gouty persons. *The removal of carbohydrates from the diet is followed by the disappearance of glycosuria.* Food increases the sugar excretion, which is therefore less during the night than during the day.

Varieties—(*a*) Slight cases in which *limitation* of the carbohydrates (without complete withdrawal) is sufficient to remove the glycosuria.

(*b*) More severe cases, in which complete withdrawal of

carbohydrates from the diet is necessary before the glycosuria disappears.

2. *The severe form* is met with more frequently in persons under the age of 45, and often amongst the poor and hard-working people, and amongst hospital patients in large towns. *The withdrawal of carbohydrates from the food does not cause the glycosuria to disappear.* Wasting is a marked symptom, and the urine often gives a dark reddish-brown coloration with perchloride of iron. As pointed out by Schmitz, the urine passed during the day may contain less sugar than that passed during the night.

Varieties—(*c*) In the milder cases of the severe form, sugar is still excreted in the urine when the diet is free from carbohydrates, but contains a very large quantity of albumin; if, however, the albumin in the food be *restricted*, the carbohydrates being withdrawn, the glycosuria sometimes disappears.

(*d*) In the most severe form, neither withdrawal of carbohydrates from the diet, nor restriction of the amount of albumin, suffices to remove the sugar from the urine. Hence, in these cases, sugar must be formed from the albumins of the organism.

Many cases, even when first seen, belong to the severe form of the disease; sometimes, however, cases which at first present the characteristic features of the mild form, at a later date pass into the severe form. By good dietetic treatment, occasionally a severe case may be transformed into a mild case; frequently, however, the case remains mild or severe from first to last.

The following are the indications for dietetic treatment in the various forms of the disease (4):—

1. In the *mild* forms it is generally acknowledged that by a restricted diet, *i.e.* by the withdrawal of carbohydrates from the food, the greatest benefit is derived.

In the mildest variety of the mild form (form *a*, in which limitation in the amount of carbohydrates in the food is sufficient to remove sugar from the urine), the carbohydrates should be withdrawn from the diet for a few weeks. Then a little bread may be allowed, and if no sugar is excreted in the urine a little more carbohydrate food may be given after two weeks. It is often found that in time the patient will be able to take a fair amount of carbohydrates without glycosuria occurring, but even in these mild cases it is best

to avoid excess of carbohydrates. Sugar and articles containing sugar ought to be permanently excluded from the diet; and potatoes, bread, and beer ought to be limited.

In the more severe cases of the mild form (group *b*), carbohydrates should be excluded from the diet for six or eight weeks. Sometimes it is then found that a little carbohydrate food can be tolerated, *i.e.* that the case has been converted into one of the variety (*a*). But in very many cases the urine can only be kept free from sugar by a diet from which carbohydrates have been completely withdrawn. Such a rigid diet cannot as a rule be continued for a very long period, and hence, after a time, a small amount of carbohydrates must be allowed, and we must be content if by a fairly restricted diet we can limit the sugar excretion to 500 or 600 grs. daily.

Whilst some authors hold that the diet ought to be as rigid as possible, others believe that even in the mild form patients do better on a moderately restricted but not absolutely rigid diet. A rigid or fairly restricted diet may be allowed in mild forms of the disease in stout persons, so long as the patient feels well on such a diet, and so long as definite wasting, albuminuria, acetonuria, and diacetonuria (as indicated by the ferric perchloride reaction) are absent.

In the mild form of the disease (as in all forms), fatty food is of great value as a substitute for bread, when the patient is placed temporarily on a rigid diet for diagnostic purposes, or when a rigid diet is prescribed as a means of treatment. Cakes of aleuronat and cocoa-nut (see p. 357) will be found very useful.

In the mild forms of diabetes, if the patient be stout, a reduction of the total quantity of food, and especially a reduction of the amount of nitrogenous food, is often of great service; but if the patient be wasted, no reduction of the amount of food should be attempted.

Life can be prolonged in many mild cases of diabetes to an advanced age, by careful dieting. Cantani states that he has cured many patients (in Italy) by absolute flesh and fatty diet; but in England and Germany a cure of diabetes in the true sense is certainly very rare, for if the glycosuria disappears when the patient is on a rigid diet, it returns when carbohydrates are taken (see p. 308). Occasionally glycosuria

which has persisted for some time disappears, but frequently it returns at a later date.

2. In the *severe* forms of the disease the opinion has gradually been gaining ground for some years, that a very strict diet (*i.e.* complete withdrawal of the carbohydrates) is injurious. In fact, it might almost be said that the milder the form of the disease, the more rigid the diet indicated, as regards withdrawal of carbohydrates; and the more severe the form, the more injurious a rigid diet will be.

As already mentioned, Leo (²) has pointed out that in the majority of severe cases of diabetes there is a great increase of the nitrogenous metabolism, and, as a result, great loss of strength. Marked wasting is a prominent symptom, and the aim of treatment ought to be to diminish not only the excretion of sugar, but also the nitrogenous waste.

Fatty food is said to diminish the nitrogenous metabolism (though this has been recently disputed by Dunlop), and Leo has shown that carbohydrates have a similar action (*i.e.* albumin-sparing influence). Leo has shown that the nitrogenous excretion in the urine and fæces was less in two cases of diabetes when the patients were taking a diet rich in albumin, *together with* a certain amount of carbohydrate food, than when they were taking the same diet *without* the carbohydrates. Careful observations have shown that in severe cases of diabetes improvement may occur, and the patient gain weight, when a moderate quantity of carbohydrates is allowed, even though the amount of sugar in the urine may be increased.

Hence, in these cases, not only should the sugar excretion be estimated daily, but also the general condition of the patient, and the weight, and the urea excretion should be carefully watched. A diet rich in albumin and deficient in carbohydrates is prescribed frequently to reduce obesity. A similar diet would therefore appear little suited for a weak, emaciated, diabetic patient. Then again, it is important to remember that in many of these severe cases phthisis develops, and death may occur from this complication. Hence it is necessary to prescribe a diet on which the patient can maintain his weight, even if the sugar excretion be somewhat increased thereby. On this account, also, a rigid diet is unsuitable for these severe cases.

When the urine of a diabetic patient gives the dark brownish red coloration (Gerhardt's reaction) with perchloride

of iron, the withdrawal of all carbohydrates from the diet is especially dangerous. This has been pointed out long ago by Ebstein (4) and many other writers.

When this reaction is obtained, there is even great danger in *suddenly* placing the patient on a rigid diet temporarily, for the purpose of ascertaining whether he is suffering from a mild or a severe form of the disease. Such a sudden change might lead to diabetic coma. Hence, if it is desired to ascertain the effect of a rigid diet on the amount of sugar excreted, the restriction should be effected very *gradually*, and only continued a very short time.

Hirschfeld (5) and others have shown (as previously mentioned) that acetonuria can be produced in healthy persons by a diet consisting of albumin and fat only; but the addition of carbohydrates to the food causes it to disappear. If carbohydrates are no longer burnt up in the system (as occurs in diabetes), acetone is often found in the urine, in spite of the carbohydrates in the food; and when acetone is present in large quantities, diacetic acid is also found. But, in the severe forms, when the diet has been rigid for a long period, if the carbohydrates of the food are increased, or if glycerin is added, the acetone and diacetic acid in the urine diminish.

When the urine gives a marked reaction with perchloride of iron, there appears to be good evidence that the rigid exclusion of carbohydrates from the food has often a tendency to bring on diabetic coma (Ebstein,[4] Hirschfeld,[5] Grube,[6] Schmitz[7]). Considerable evidence has been furnished that these cases often improve, and the threatening diabetic coma is arrested, by adding starchy food, potatoes, and bread in small quantities to the diet. Schmitz has also drawn attention to the value of a moderate amount of starch-containing foods in the most severe form of diabetes; he regards their complete withdrawal as injurious. The quantity he would allow is never great, however, and he regards saccharine carbohydrates as always decidedly injurious.

Ebstein has pointed out that the appearance of acetone and diacetic acid in the urine is an indication for *diminishing the albumin*, as well as for increasing the carbohydrates in the diet.

Minkowski states that a rigid diet increases the formation of organic acids in the system, and thus predisposes to coma.

Schmitz (7) has drawn attention to the danger of a very large amount of animal food in diabetes, since it passes into the intestine undigested; putrefaction occurs; toxic substances are formed and absorbed into the blood; and he believes that the absorption of these toxic substances leads to the development of the coma. But Seegen (8) and others oppose this view.

All authors agree as to the great value of fat in the severe forms of diabetes; and, in addition to fatty food, cod-liver oil, lipanin, and other fats may be given.

In the severe forms of diabetes no attempt should be made to restrict the total amount of food.

In certain cases of diabetes, for diagnostic purposes, the effect of temporary and gradual withdrawal of carbohydrates from the food, together with the *reduction of the amount of nitrogenous* food, may be tried. If a diet restricted in *both these* respects causes the sugar to disappear, then the cases belong to the variety (*c*), p. 326. But even in these cases a diet so restricted is not advisable for any length of time. Any signs of increasing weakness or loss of weight would be an indication to increase both carbohydrates and nitrogenous food at once.

Briefly, then, in diabetes of the severe form, *fatty food* should be given in large quantities, and a little alcohol taken to aid the digestion thereof; nitrogenous food should only be given in moderate quantities. Of the carbohydrates, saccharine food should be excluded; a certain quantity of starchy food, however, is of advantage in the form of *bread*, but of course a *great quantity ought not to be allowed.* Cream is of great service, and milk in moderate quantities may be allowed.

Articles of Diet.

1. Animal and Nitrogenous Food.

Most articles of food from the animal kingdom may be taken freely by diabetic patients. Butchers' meat and flesh meat of various kinds, poultry, game, and fish, may be taken in any form. But in the cooking thereof flour or bread crumbs should not be used, if a very strict diet is indicated; aleuronat may be used in place of flour, however (see p. 355), and butter and fats may be freely employed.

The following articles may also be allowed freely:—Tongue,

ham, bacon, potted beef, and chicken, preserved meats of various kinds, sardines, tinned and preserved fish, beef-extracts, beef-tea, meat juices, broth, soups, and jellies (when prepared without the addition of any saccharine or starchy materials).

Eggs in various forms are most useful articles of diet. An egg weighing about 600 grs. contains about 90 grs. of albumin and 75 grs. of fatty material. When hard boiled they can be taken with comparatively large quantities of butter. The "buttered" egg or omelette is a useful form.

Custard made of eggs and milk, and sweetened with saccharine or saxin, may be taken by diabetics; it is a useful substitute for rice and farinaceous puddings.

A kind of light fluid custard (commonly called "Samson" in some parts of the north of England) is very suitable for diabetic persons:—

> Take one egg, beat up well; make a mixture of cream and water, and boil; gradually add the boiled cream and water (whilst hot) to the egg, stirring the mixture with a spoon. Then place the mixture in a pan over the fire, and continue to stir with a spoon until it becomes thick; then pour into a glass. It is important that the mixture should *not* be heated too much (*i.e.* should not be boiled) as the albumin would be coagulated thereby. Flavour with cinnamon, and sweeten with saccharine or saxin if desired.

Eggs are also useful in the preparation of bread, pancakes, and various articles of diet for diabetic patients, as will be pointed out in another section.

Liver, which contains a considerable amount of sugar, and of substances capable of conversion into sugar in the alimentary canal, ought to be avoided, but other organs, such as brain, kidney, pancreas, thymus, lung, are harmless.

Oysters, cockles, mussels, and other mollusca are to be avoided, on account of the great amount of glycogen contained in their large livers. The interior of crabs and lobsters are also unsuitable articles of diet. Honey, of course, ought never to be taken. Butter, cheese, and cream may be allowed in large quantities.

With respect to *milk*, considerable caution is necessary. This article of diet, so useful in health and in disease, contains 4–4·82 per cent. of sugar in the form of lactose, which for the diabetic, of course, is an objectionable constituent. But milk

also contains large quantities of fatty and albuminous materials, which are most desirable.

According to Blyth (9), the following is the composition of cow's milk:—

Milk fat	3·5 per cent.
Casein	3·98 ,,
Albumin	0·77 ,,
Milk sugar	4·00 ,,
Water	86·87 ,,

Experiments made by various observers have shown that, in some cases of diabetes, when milk is added to the diet in considerable quantity, the amount of sugar in the urine is not increased. The lactose of the milk is therefore utilised in the system. In other cases, however, the glycosuria has been increased by this addition of milk to the diet; but in these cases the patient has nevertheless sometimes gained weight and improved in general condition.

In the milder forms of diabetes, if the addition of milk to the diet does not increase the glycosuria, it may be allowed; but when the glycosuria is increased thereby, milk is better avoided. When large quantities of milk have been employed in the treatment, as in the so-called "milk cure," often bad results have followed. If, however, the digestion is feeble, and other foods are digested with difficulty, milk may be generally allowed. In the most severe forms of diabetes, when a very rigid diet is not indicated, milk may also be allowed in moderate quantities; indeed, some physicians recommend large quantities (3½ pints) daily in these cases.

Skimmed milk contains less albumin and fat, and a greater percentage of carbohydrates, than ordinary milk. It has been recommended, however, by Dr. Donkin. In his method of treating diabetes he prescribes six to eight pints of skimmed milk daily; but most physicians who have tried this method of treatment record bad results.

If a simple and easy method could be found for removing the lactose, milk would then be a most valuable article of diet for *all* diabetic patients, on account of the great percentage of albumin and fat which it contains.

Wright (10) has suggested a method for making an artificial milk for diabetic patients. A quantity of milk is diluted with

three or four volumes of water, to which 1 to 2 parts per 1000 of acetic acid have been added (℥iss–℥iii of acid acet. fort. of the B.P. to a pint of water). This produces a precipitation of all the casein and fat of the milk. The precipitate is allowed to settle for a few minutes, and then strained through a piece of calico. It is washed and redissolved in a 1 per cent. solution of the following mixture:—

Sodium chloride .	11·5 parts.	Dimagnesium phosphate	4·0 parts.
Potassium chloride .	9·9 ,,	Magnesium citrate .	4·4 ,,
Monopotassium phosphate . . .	13·8 ,,	Dicalcium phosphate .	8·0 ,,
Dipotassium phosphate	10·0 ,,	Tricalcium phosphate .	9·6 ,,
Citrate of potassium .	5·9 ,,	Calcium citrate . .	25·5 ,,
		Calcium oxide . .	5·5 ,,
		Sodium carbonate .	40·0 ,,

A trace of saccharine may be used to sweeten the milk. The salt solution is best used at about blood temperature, and the casein and fat precipitate is to be mixed up with it, as in making cocoa, to the desired thickness. By this method a fairly palatable and entirely sugarless milk is obtained.

Ringer ([11]) has also described a method of preparing milk for diabetic patients:—Add to a pint and a half of milk about 90 c.c. of a 10 per cent. solution of acetic acid. This precipitates a curd caseinogen. It should be allowed to settle, and the clear fluid siphoned off and distilled water added. After standing for a time, the water should be decantered or siphoned off, and the curd should be filtered and well washed with distilled water. It is then rubbed up in a mortar with some calcium carbonate, and water added; all the caseinogen becomes dissolved, the calcium carbonate soon settles, and the milky fluid can be decanted. The dissolved caseinogen forms a substitute for milk.

(Martindale and Lee advise that the milk be diluted with an equal quantity of water, and that the filtration and washing of the caseinogen should be performed on a calico filter instead of filter paper.) On the addition of 2 per cent. of glycerin to the mixture of caseinogen, a not unpalatable form of milk is produced. Another plan proposed by Ringer is the following:—

"Milk is heated in a hot-water bath, then poured into tubular parchment dialysing paper, and the whole placed in a vessel filled with tap water; the water being kept running by

means of a tube connected with a tap, the tube ending in a piece of glass tubing, long enough to reach the bottom of the vessel, so that it is supplied from the bottom." In three days the milk sugar is reduced to one-sixth of the original quantity.

Both these methods can be carried out easily in the laboratory, but for the average private patient, and especially for the poorer classes of patients, they appear to be a little too complicated. I have found that a very palatable drink, closely resembling milk, can, however, be prepared from cream in the simplest manner possible. Now cream contains milk sugar (3·54 per cent., König; 2·8 per cent., Letheby); and though it is allowed to diabetics, still, if taken in very large quantities, this percentage of sugar would theoretically be objectionable, especially when a strict diet is indicated. But cream contains also 25·72 per cent. of fat (König), which is of the greatest value to the diabetic patient, and by the following exceedingly simple method a palatable drink can be easily made. To about a pint of water, placed in a large drinking-pot or tall vessel, three or four tablespoonfuls of fresh cream are added and well mixed. The mixture is allowed to stand for twelve to twenty-four hours, when most of the fatty matter of the cream floats to the top; it can be skimmed off with a teaspoon easily, and on examination it will be found practically free from sugar. This fatty matter thus separated is placed in a glass and mixed with water. Then the *white* of an egg is added, and the mixture well stirred. The water and white of the egg are added in sufficient quantities to make a mixture which has the exact colour and consistence of ordinary milk. If a little salt and a trace of saccharine be added, a palatable drink, practically free from milk sugar, is produced, which has almost the same taste as milk, and which contains a large amount of fatty material. With very little practice the right proportions can be easily guessed, and of course much larger quantities can be employed than those mentioned above. A drink may thus be prepared, which contains a large amount of fat, and which can be taken *ad libitum* by diabetic patients, even if the most rigid diet be deemed necessary. Devonshire cream, which has the consistence of a soft paste, contains only 1·72 per cent. of milk sugar, and hence may be used with advantage, in the place of ordinary cream, in preparing milk as above described.

Cream contains much less lactose than milk, but seven times

the amount of fat. Owing to this large percentage of fat in a form easily digested, cream is a most valuable article of diet for diabetic patients. It may be taken in considerable quantities with coffee or tea, or in other ways. With a little care, three-fourths of a pint of cream can be taken daily by a diabetic patient, and in the severe forms of the disease it is most useful. The following table shows the composition of cream and milk:—

	Milk.		Cream.	
	König.	Blyth.	König.	Pavy.
Water	87·40	86·87	66·40	66·0
Albumin	3·40	4·75	3·70	2·7
Fat.	3·66	3·50	25·72	26·7
Milk sugar	4·82	4·00	3·54	2·8

Devonshire cream is a white, soft paste, and "is produced by keeping the milk in large pans at a gentle heat for many hours. The temperature is always far under the boiling point. This application of a moderate heat during a lengthened time causes the fat to coalesce and rise more rapidly than the ordinary method."

Blyth ([12]) gives the following composition of Devonshire cream:—

	Per cent.
Milk fat	65·011
Casein	3·530
Albumin	0·521
Peptones	0·050
Milk sugar	1·723
Water	28·675
Ash	0·490

Owing to the small percentage of lactose, Devonshire cream is particularly suitable for diabetic patients.

Butter-milk contains less sugar than ordinary milk, part of the lactose having been decomposed. It still contains 3·38 per cent. of lactose, however, along with lactic acid. It is therefore a little more suitable than ordinary milk, but the taste is objectionable to many patients.

Koumiss.—Lactose does not ferment under the influence of the ordinary yeast fungus, but certain of the schizomycetes have

the power of decomposing it, alcohol and lactic acid being formed. The Tartar drink, koumiss, is fermented mare's milk; it can also be manufactured from cow's milk. Koumiss contains less lactose than ordinary milk, and is in this respect more suited for the diabetic patient. The Aylesbury Dairy Co. have kindly supplied me with samples of their diabetic koumiss, and a rough examination shows clearly that it contains very much less lactose than ordinary milk. The following is the analysis furnished by the Aylesbury Co. :—

	Koumiss.		
	One Day old.	Eight Days old.	Twenty-two Days old.
Water	92·24	92·38	92·55
Alcohol	·28	·35	·57
Fat	·51	·52	·51
Casein	2·19	2·13	2·05
Albumin.	·30	·25	·18
Albumose	·36	·48	·65
Lactic acid	·75	·86	1·22
Sugar	2·78	2·42	1·64
Ash	·59	·61	·63

In their "diabetic koumiss with glycerin," 10 per cent. of glycerin is added.

The great objection to koumiss is the taste, which many patients find disagreeable.

Koumiss has been recommended on theoretical grounds by several writers, but I am not aware that it has been much used in the treatment of diabetes in this country; it appears worthy of trial, however.

Stange ([13]) gives the table on p. 337, showing the composition of koumiss after fermentation for varying periods.

Kephir, a Caucasian beverage, is really milk, in which the lactose has been partly converted into alcohol, carbonic acid, and lactic acid, by the action of a ferment; the fatty elements are almost unaltered, and the fluid is said to contain only about 1·5 per cent. of lactose.

	Mare's Milk.	Koumiss, after Six Hours' Fermentation.	Koumiss, after Eighteen Hours' Fermentation.	Koumiss, after Thirty Hours' Fermentation.	Koumiss, after Four Days' Fermentation.
Carbonic acid .	...	3·8	6·0	7·0	11·0
Alcohol . .	...	18·5	19·5	30·0	30·0
Lactic acid . .	...	3·9	5·6	6·4	6·4
Milk sugar . .	51	18·8	16·3	...	...
Albumin . .	23	22·5	22·6	20·0	16·0
Fat . . .	19	18·9	20·0	19·0	19·0
Salts . . .	5	4·5	4·0	4·0	4·0

The Caucasian ferment has been found to consist of a mixture of yeast (*Saccharomyces cerevisiæ*) and a short bacillus, which has been named *Dispora Caucasica*. From this Caucasian ferment Dr. Lehmann has prepared a more reliable kephir ferment. By its action on milk, it is stated that home made kephir of an agreeable taste can be easily prepared.

(The ferment can be obtained in small quantities, with directions for use, from Dr. M. Lehmann, Berlin, C. Heiligegeiststrasse, 43–44.)

2. FATTY FOOD.

Fats, both animal and vegetable, are the most valuable articles of diet for diabetic patients, especially for those who suffer from the severe forms of the disease, and may be allowed in large quantities.

The more important articles of diet, containing a large quantity of fat, are butter, cream, bacon, cheese, eggs, suet.

Butter contains 82 to 87 per cent. of fat; ordinary cream, 25 to 26 per cent.; and Devonshire cream, 65 per cent. Cheese contains from 10 to 30 per cent. of fat, and is also rich in albumin.

Analysis of butter.—König (quoted by Blyth) gives the following as the mean of eighty-nine analyses:—

	Mean.
Fat	83·11
Curd	·86
Ash	1·19
Water	14·14
Milk sugar	·70

Analysis of several Varieties of Cheese (Blyth [14]).

	Water.	Ash.	Fat.	Nitrogen.
Cheddar cheese	28·1	3·34	22·5	7·3
Cheshire cheese	44·6	4·61	30·7	4·6
Cream cheese	63·1	1·4	6·5	2·76
Dutch cheese	39·6	6·4	11·5	4·8

The yolks of eggs contain a large amount of fat. An egg of ordinary size (600 grs.) contains 75 grs. of fat and 90 of albumin.

Cod-liver oil is of considerable service, especially in the severe forms of diabetes, and deserves to be more frequently used when there is much wasting or loss of strength. Schmitz speaks strongly in its favour. It is well to begin with a small dose, 1 drachm daily, and to increase it up to ½ oz. once or twice a-day after food. Lipanin may be employed, if the patient objects very much to the taste of cod-liver oil.

Vegetable oils, salad oil, and olive oil may also be taken freely with the food. Olive oil is largely used in the preparation of food in Italy, but is not suited to the taste of the inhabitants of Northern Europe.

Peach kernel oil (free from prussic acid) may be used in place of cod-liver oil. Mr. Kirkby (of Messrs. Jewsbury & Brown, Manchester) has prepared for me a very palatable emulsion of peach kernel oil (50 per cent. by volume) with the yolk of egg, saccharine elixir, spirits of chloroform, and essences of almond and cinnamon.

Petroleum emulsion and pancreatic emulsion are also worthy of a trial in cases accompanied by severe wasting.

Of all the fatty articles of food, butter and cream, in spite of the small amount of milk sugar which both contain, are the most suitable forms in which large quantities of fat can be taken.

Ebstein records the case of a young diabetic lady, who took 225 grms. of butter daily, along with other fats and nitrogenous food. The patient had become greatly wasted, but on this diet the wasting disappeared, and she gained in weight; the sugar excretion was less, acetone and aceto-acetic acid dis-

appeared from the urine, and the general condition was good.

Suet may be largely used in the preparation of puddings and various articles of diet.

Fatty food is generally digested well by diabetics, and often large quantities can be taken (half-a-pound or more) without digestive disturbances occurring. Sometimes excess of fatty food causes dyspepsia, but if a little alcohol (in the form of brandy or non-saccharine wine) be taken after a diet rich in fat, digestion is greatly aided; and in this way the diabetic is enabled to take large quantities of fatty food. The patient may be allowed to take an unlimited amount of fat, so long as digestive troubles are not produced thereby.

In the few cases, however, in which there is steatorrhœa (probably owing to severe disease of the pancreas), large quantities of fat cannot be digested.

If diarrhœa should be produced by a diet rich in fat, opium, bismuth, and calcium carbonate will be found useful in the treatment thereof.

3. VEGETABLE FOOD—CARBOHYDRATES.

As already mentioned, the withdrawal or limitation of the carbohydrates in the diet is the most important method of treatment, and this is especially the case in the milder forms. The caution necessary in the severe forms has been pointed out on p. 328. Articles containing a large quantity of sugar must always be avoided, and starchy food must be withdrawn, or restricted, according to the nature of the case. The carbohydrates are not equally injurious, however.

Starch is less injurious than sugar; according to Schmitz [15] sugar is ten times more injurious than starch; and the withdrawal of sugar is much better borne than the withdrawal of starch, especially in the severe forms of the disease.

Inulin is an amylose which replaces starch in the roots of many species of the compositæ. It occurs in dahlia tubers, in the Jerusalem artichoke, and in several other roots; and it has been often recommended as a carbohydrate for diabetic patients. Külz found that when inulin was taken by diabetic patients the sugar excretion was not increased, and the inulin was therefore utilised in the system. He gives directions for the pre-

paration of biscuit from inulin (see p. 360). Hale White concludes, from his recent observations, that in moderate amount, in the form of dahlia tubers, it does no harm to diabetic patients.

Lichenin, a carbohydrate contained in Iceland moss, has been recommended as a suitable carbohydrate in diabetes. In Iceland, bread is made from this moss, after the bitter principle has been removed.

Of the *sugar* group of carbohydrates, *glucose* is the most injurious, *milk* sugar and *cane* sugar rank next. *Lævulose* is least injurious.

In many cases milk sugar causes an increase in the sugar excretion, but not to the same extent as does grape sugar. It has been pointed out by Külz, Voit, Minkowski, and others, that *lævulose* and levorotatory carbohydrates may be utilised in the system. Much, however, depends on the nature of the case and the quantity of lævulose taken.

Minkowski found that in the diabetes following pancreas extirpation, the levorotatory carbohydrates were still burnt up in the organism; but he points out that after the use of lævulose in *large* quantities an increased excretion of dextrose may occur. In human diabetes a small dose of lævulose is almost completely used up in the organism, and only a very slight quantity of this sugar appears in the urine; but a large quantity of lævulose causes a most decided increase of the glucose eliminated, the greater portion of lævulose at the same time passes off unchanged by the urine.

Minkowski ([16]) has shown that—(1) Levorotatory carbohydrates are partially destroyed in the system; (2) partially converted into dextrose and eliminated as such by the urine; (3) but when large quantities of lævulose are given, a portion passes off unchanged.

Haycraft ([17]), by experiments on animals and by observations on three diabetic patients, has shown that—(1) In a case of chronic diabetes in an old person, all the lævulose taken (50 grms. daily) was utilised in the organism, and there was no increase of the glucose excreted. (2) In some acute cases, a part of the lævulose taken with the food was excreted as such, a part was utilised in the body, and a part was transformed into glucose. (3) In rabbits, glycogen is formed from the lævulose taken, and is stored up in the liver.

Hale White (18) has made a number of observations on the action of lævulose. He found that if large amounts of lævulose were taken, some appeared in the urine. In none of the cases did it have the pernicious effect (often produced by ordinary carbohydrates) of increasing the output of sugar beyond the extra quantity given. The excretion of sugar was usually increased when lævulose was given, but it was sometimes diminished. In most of the cases, after giving lævulose, much less sugar was passed in the urine than would have been excreted if the previous excretion of sugar had remained stationary, and all the lævulose had appeared in the urine. This result seems to indicate that, in these cases, a portion of the lævulose taken was retained and destroyed in the body.

Some of Hale White's cases show that lævulose can be utilised better than dextrose. None of the patients felt worse after taking lævulose; some felt better, and gained in weight.

Grube (19) concludes that lævulose can be given in moderate quantities, in the *mild forms of diabetes*, without any injurious results as regards sugar excretion, state of urine, etc. These patients appear to be able to utilise the lævulose in the system, though they are unable to utilise dextrose and cane sugar, which are excreted in the urine.

Bohland (20) has obtained similar results. In mild cases he found that lævulose was utilised in the system; in severe cases, the sugar excretion in the urine was increased when lævulose was given.

Pure lævulose is very expensive, too expensive for the majority of diabetic patients, but most of the sugar in many kinds of fruit consists chiefly of lævulose.

Mannite or manna sugar is not a true sugar, but a hexad-alcohol. It is the chief constituent of manna, and some fungi contain mannite, but little carbohydrate material. It does not increase the sugar excretion, and 30 grms. can be taken daily by diabetics without producing any digestive disturbances, but it has a slight purgative effect. It may be given with coffee.

Pentaglucose, *xylose*, *arbinose*, produce no bad effects in diabetes, but they pass out of the body undecomposed (Ebstein 21).

Lindemann and May (22) found that *rhamnose*, both in healthy and in diabetic persons, was partly utilised in the

system, whilst a portion passed off in the urine. In health a small percentage of rhamnose was excreted; in diabetes they found also a small proportion of rhamnose in the urine, along with an increase of the grape sugar excretion. Rhamnose was to some extent utilised in the system in diabetes, but not to the same extent as in health.

Inosite (or muscle sugar) is really a benzol product, and not a sugar. It is found in muscle tissue, is widely distributed in the animal kingdom, and is also present in young French beans. It is completely destroyed in the system in diabetes (Hirschfeld).

Saccharine, a coal tar product, having a very sweet taste, may be used in place of sugar to sweeten various articles of diet for diabetic patients.

Saxin,[1] another coal tar product, has recently been recommended for the same purpose. This substance is said to be six hundred times as sweet as sugar.

Tablets of both substances are prepared; a saxin tablet the size of a hypodermic morphia tablet is equivalent to a lump of sugar. The flavour of saxin is better than that of saccharine, and is almost exactly the same as sugar.

The great problem with respect to the dietetic treatment of diabetes is, to find a carbohydrate which is completely burnt up in the system, and which can be readily procured at a small cost.

Articles of Diet from the Vegetable Kingdom.

Fruits.—The most injurious constituent of fruit is sugar, but in many kinds of fruit a large percentage of the sugar is lævulose, which is utilised in small or moderate quantities in certain cases of diabetes.

There is a considerable difference of opinion with respect to the advisability of allowing a small quantity of fruit to diabetics. Many physicians advise fruit to be withdrawn from the diet entirely; others would allow a small quantity in certain cases. In any case of diabetes, if it has been shown that lævulose can be utilised in the system, *i.e.* that the glycosuria is not increased by its use, then a small quantity of a fruit in which the sugar is in the form of lævulose may be allowed. Otherwise, the complete withdrawal of fruit would appear the more reasonable,

especially in England, where fruit forms so small a portion of the diet of most people.

Peaches and apricots are regarded as the least objectionable kinds of fruit by Ebstein. Melons only contain 0·27 per cent. of sugar.

The patient may be allowed stewed *green* gooseberries and cream, sweetened with saxin, and a little soda-water may be taken afterwards to neutralise the acidity of the gooseberries.

Dates, figs, currants, raisins, dried prunes and plums, and other dried fruits which are rich in sugar, ought to be forbidden.

Nuts may be allowed, as a rule. Walnuts, almonds, filberts, hazel nuts, and Brazil nuts may be freely allowed. Chestnuts ought to be avoided, since they contain a large quantity of carbohydrates, including 2 per cent. of sugar.

Pickled walnuts may be allowed freely. Walnuts may be also boiled and used in the place of vegetables.

Place the walnuts (the shells having been removed) in boiling water, and continue to boil for thirty minutes; then drain away the water carefully, place on a plate and sprinkle well with aleuronat flour (see p. 355). Add salt, a little pepper, and butter also, if preferred. The pan used should be enamelled or well lined, as an iron pan turns the nuts black.

Cocoa-nuts contain a small quantity of sugar, but this may be removed easily, and cocoa-nut flour may be used for the preparation of biscuits (see p. 354). Almond flour is also largely used for the preparation of cakes and biscuits. A bread formed from pea-nut flour has recently been recommended. These preparations from nuts will be referred to later.

Vegetables.—As a general rule, it may be stated that green vegetables may be allowed, but white vegetables and root vegetables should be avoided.

The following may be allowed freely:—Salad (mustard and cress), water-cress, the green parts of cabbage and lettuce, Brussels sprouts, endives, broccoli, spinach, cucumber, mushrooms. Pickles—pickled cucumber, walnuts, and onions—may also be allowed. A considerable amount of carbohydrates is present in celery, onions, leeks, green French beans; by some they are forbidden, by others sanctioned, but when a very rigid diet is indicated they are better avoided.

The following ought to be avoided in a rigid diet:—Potatoes,

rice, sago, tapioca, groats, arrow-root, macaroni, peas, beans, turnips, carrots, parsnips, and beet-root.

Potatoes contain a less percentage of starch than the other articles just mentioned (only 15·5 per cent.). Sometimes the craving for potatoes is great, and in certain cases they may be allowed in small quantities, cooked in the form of potato chips. A single potato may then "be made to fill almost a whole dish." L. Brunton ([23]) gives the following directions:—

A large deep pan (not a frying-pan) 6 in. deep should be filled with oil, or grease or dripping. This is placed on the fire until it appears to boil. It is allowed to go on boiling, and all the water that is mixed with the dripping boils away; and finally, in place of a boiling liquid, there is a liquid with a perfectly smooth surface which is not boiling at all. This is the time for cooking the potatoes. They are cut into very thin shavings and thrown into the hot fat. They are then *quickly* boiled and kept in the fat until slightly brown. Under the influence of the great heat they have become firm and crisp upon the surface, and the fluid that they contain is boiled within these crisp surfaces by the fat, so that the chips are blown out, each little shaving of potato, which was originally as thick as a bit of cardboard, is now three-quarters of an inch thick.

Composition of various Articles of Diet from the Vegetable Kingdom.[1]

	Water.	Nitrogenous Substances.	Fat.	Starch, Sugar, Gum, etc.	Cellulose.	Ash.
CEREALIA.						
Wheat	13·56	12·42	1·70	67·89	2·66	1·79
Barley	13·78	11·16	2·12	65·51	4·80	2·63
Oats	12·92	11·73	6·04	55·43	10·83	3·05
Rice	13·23	7·81	0·69	76·40	0·78	1·09
LEGUMINOSÆ.						
Garden beans	13·60	23·12	2·28	53·63	3·84	3·53
Peas	14·31	22·63	1·72	53·24	5·45	2·65
Lentils	12·51	24·81	1·85	54·78	3·58	2·47

[1] v. Ziemssen's "Handbook of General Therapeutics," vol. i., Art. "On the Dietary of the Sick and Dietetic Methods of Treatment," by Bauer, Trans., London, 1885.

The mean composition of the *potato* (König) is as follows:—

Water	75·77
Nitrogenous matters	1·79
Fat	0·16
Starch	20·56
Cellulose	0·75
Ash	0·97

ROOTS (KÖNIG).

	Water.	Nitrogenous Substances.	Fat.	Sugar.	Non-nitrogenous Extracts other than Sugar.	Cellulose.	Ash.
Field carrots	87·05	1·04	0·21	6·74	2·60	1·40	0·90
Turnips	91·24	0·96	0·16	4·08	1·90	0·91	0·75
Beet-root	87·07	1·37	0·03	0·54	9·02	1·05	0·92
Celery	84·09	1·48	0·39	0·77	11·03	1·40	0·84
Horse radish	70·72	2·73	0·35	...	15·89	2·78	1·53
Radish	86·92	1·92	0·11	1·53	6·90	1·55	1·07
Onions	85·99	1·68	0·10	2·78	8·04	0·71	0·70

VEGETABLES (KÖNIG).

	Water.	Nitrogenous Substances.	Fat.	Sugar.	Other Non-nitrogenous Substances.	Cellulose.	Ash.
Cabbage	89·97	1·89	0·20	2·29	2·58	1·84	1·23
Cauliflower	90·39	2·53	0·38	1·27	3·74	0·87	0·82
Brussels sprouts	87·63	4·83	0·46	...	6·22	1·57	1·29
Spinach	90·26	3·15	0·54	0·08	3·26	0·77	1·94
Endive	94·13	1·76	0·13	0·76	1·82	0·62	0·78
Lettuce	94·33	1·41	0·31	...	2·19	0·73	1·03
Asparagus	93·32	1·98	0·28	0·40	2·34	1·14	0·54
French beans	88·36	2·77	0·14	1·20	6·82	1·14	0·57
Garden peas (unripe seeds)	80·49	5·75	0·50	...	10·86	1·60	0·80

FRUITS.

	Water.	Nitrogenous Matters.	Free Acids.	Sugar.	Other Non-nitrogenous Matters.	Cellulose + Kernel.	Ash.
Apple . .	83·58	0·39	0·84	7·73	5·17	1·98	0·31
Pear . . .	83·03	0·36	0·20	8·26	3·54	4·30	0·31
Plum . .	84·86	0·40	1·50	3·56	4·68	4·34	0·66
Greengage .	80·28	0·41	0·91	3·16	11·46	3·39	0·39
Peach . .	80·03	0·65	0·92	4·48	7·17	6·06	0·69
Apricot . .	81·22	0·49	1·16	4·69	6·35	5·27	0·82
Grape . .	78·18	0·59	0·79	24·36	1·96	3·60	0·53
Cherry . .	80·26	0·62	0·91	10·24	1·17	6·07	0·73
Strawberry .	87·66	1·07	0·93	6·28	0·48	2·32	0·81
Gooseberry .	85·74	0·47	1·42	7·03	1·40	3·52	0·42
Orange (without rind or pips)	89·01	0·73	2·44	4·59	0·95	1·79	0·49
Cucumber .	95·60	1·02	...	0·95	1·33	0·62	0·39
Melon . .	95·21	1·06	...	0·27	1·16	1·07	0·63

DRIED FRUITS.

	Raisins.	Figs.
Water	32·02	31·20
Nitrogenous matter . . .	2·42	4·01
Fat	0·59	1·41
Free acid	...	1·21
Sugar	54·16	49·79
Other non-nitrogenous matters .	7·48	4·51
Cellulose and seeds . . .	1·72	4·98
Ash	1·21	2·86

NUTS (KÖNIG).

	Water.	Nitrogenous Matter.	Fat.	Carbohydrate.	Cellulose.	Ash.
Sweet almond . .	5·39	24·18	53·68	7·23	6·56	2·96
Walnut . . .	4·68	16·37	62·86	7·89	6·17	2·03
Chestnut . . .	51·48	5·48	1·37	38·34	1·61	1·72

4. BREAD AND ITS SUBSTITUTES.

Bread is the article of diet with respect to which there is the greatest difficulty in the dietetic treatment of diabetes, since wheaten bread contains a large percentage of starch. The mean composition from a large number of analyses collected by Köing ([24]) is as follows:—

	Mean for Fine Bread.	Mean for Coarse Bread.
Water	38·51	41·02
Nitrogenous substances .	6·82	6·23
Fat	·77	·22
Sugar	2·37	2·13
Carbohydrates . .	49·97	48·69
Woody fibre . . .	·38	·62
Ash	1·18	1·09

It is therefore unsuitable, at least in the ordinary quantities, when a rigid diet is indicated.

Most patients, however, object to the withdrawal of bread for any length of time from the diet, since it is so difficult to find a satisfactory substitute.

In the most severe forms of diabetes, as previously mentioned, bread ought to be allowed in limited quantity, since a rigid diet is dangerous. In the mildest cases of the mild form of the diseases it is sometimes found, after keeping the patient on a rigid diet for a short time, that a small quantity of bread may be allowed, without any sugar reappearing in the urine, *i.e.* the patient is able to tolerate a small quantity of carbohydrate food. In these cases, of course, a little bread ought to be added to the diet, so long as it does not cause glycosuria. But in other cases, the more severe cases of the milder form (variety *b*, p. 325), the addition of bread to a rigid diet always causes sugar to appear in the urine. In such cases it is well to entirely replace bread by some other substitute, temporarily at least. In course of time, however, the patient's desire for bread often becomes so strong, that this article of diet can only be in part replaced by some of

the bread substitutes, and a small amount of ordinary bread must be allowed.

As already mentioned, for diagnostic purposes it is always well to place a patient on a rigid diet—from which bread has been withdrawn—for a short time, and then some bread substitute is necessary.

A number of bread substitutes have been from time to time advocated, but unfortunately a large proportion of these are useless. Many of them are exceedingly expensive, many are very unpalatable, and many contain a very large percentage of starch, as shown by analysis.

A large number of the specimens of diabetic bread and biscuits which I have examined, have been coloured deep blue-black by a drop of iodine and potassium-iodide solution, indicating the presence of a large percentage of starch. Hence it is not surprising that Schmitz, in writing of diabetic bread substitutes, should state that they are of service chiefly to the *baker*; and that Saundby should state that diabetic breads are often "neither more nor less than frauds." Some physicians, especially on the Continent, prefer always to allow the patient a small limited amount of ordinary white bread daily, rather than trust to expensive, unpalatable, and unreliable substitutes.

For my own part, I fail to see the advantage of diabetic foods, containing half as much starch as ordinary bread. Thus, for example, some preparations of diabetic bread contain nearly 25 per cent. of carbohydrates. Now, ordinary bread only contains about 50 per cent. of carbohydrates. Hence a patient taking 12 oz. of this diabetic bread daily would consume 3 oz. of carbohydrates, but he would only consume the same quantity of carbohydrates if he took 6 oz. of ordinary bread, and the latter he would find much less expensive, and much more palatable and satisfactory, than 12 oz. of certain diabetic breads.

All diabetic food preparations have not the above-mentioned defects, however, and a number of these articles, when properly prepared, are of great service in the cases indicated. I have had many diabetic foods prepared at my own house; as a rule, they can be made easily; and diabetic bread and cakes prepared at home are generally more satisfactory—more reliable, more palatable, and much less expensive—than those obtained from many firms.

Before recommending any bread substitute, it is well to test

a sample with a drop of a watery solution of iodine and potassium iodide. Any preparation which gives a *deep* blue-black coloration with this solution contains a large quantity of starch, and ought to be rejected; also samples of cocoa-nut or almond cakes ought to be tested for sugar (by the fermentation test).

The following are the most important substitutes for bread and farinaceous articles of diet, which have been employed in the treatment of diabetes:—

(1) "*Torrified*" *bread*, prepared by toasting thin slices of bread until they are dark brown or almost blackened, is often recommended for diabetic patients, in place of ordinary bread. It is supposed that the starch and gluten of the bread are in part decomposed by the heat. The patient is certainly not likely to eat any large quantity of this burnt bread, and this is probably its only advantage.

(2) *Gluten bread* is one of the oldest substitutes, and has been perhaps more largely used than any other. It was first introduced by Bouchardat, over fifty years ago, and has enjoyed great popularity in France. It is prepared from gluten flour, a substance obtained by washing away the starch from wheat flour. A large number of specimens of gluten bread which I have tested, have contained so much starch, however (indicated by the intense blue colour produced with a drop of iodine solution), as to be practically useless as bread substitutes. But all gluten breads are not of this kind. Some preparations of gluten flour contain only a small amount of starch and cellulose, 2 to 2·5 per cent., and are of great service to the diabetic patient.

Mr. R. O. Bischof (28 Hanging Ditch, Manchester, and 35 Brooke Street, Holborn, London, E.C.) supplies a gluten flour which has the following composition:—

Gluten, by direct extraction and drying . . .	82·70
Loss in washing, principally soluble albuminous matter	3·69
Moisture	10·34
Ash	1·05
Starch and cellulose	2·22
	100·00

From this gluten flour, bread can be easily prepared daily at the patient's house, and for a time it may answer as a bread substitute completely or partially.

Recipe for making gluten bread.

Mix one pound of gluten flour (Bischof) with three-quarters of a pint or one pint of water, at 85° F. (No yeast is required.) As soon as mixed, put the dough into the tins, and immediately place them in the oven, which should be about 430° F. Or the dough may be made into small dinner rolls, and baked on flat tins. The loaves in the tins take about an hour and a half to bake, and the rolls three-quarters of an hour. There is not the slightest difficulty in the making of either. The addition of a little salt improves the bread.

Gluten bread is light, dry, and crispy, and is improved by being well buttered. The gluten bread bought from various firms ought always to be tested with iodine and potassium iodide solution, in order to form a rough estimate of the amount of starch present.

By the use of a good gluten bread in the place of ordinary bread, of course a marked diminution of the sugar excretion may be produced. For example, a patient suffering from a mild form of diabetes, whose diet had been restricted for some time, was allowed ordinary white bread for two weeks, but no other kind of carbohydrate food. The average excretion of urine was 83 oz. per diem, and the sugar excretion averaged 35 grs. per oz. of urine. Then for two months the ordinary bread was replaced by gluten bread, the diet otherwise remaining the same. The quantity of urine averaged 54 oz. per diem, and the sugar 16 grs. per oz.

Gluten flour may also be used for the preparation of pancakes, puddings, etc.

Gluten *pudding* may be prepared as follows:—

A batter of eggs, cream, and gluten flour is prepared. This is flavoured with lemon or other essences, and baked.

Gluten *pancakes* are made by adding gluten flour to one or two eggs, and beating into a batter. The pancakes may be sweetened with saccharine or eaten with a little glycerin.

(3) *Bran cake.*—The husk or bran of wheat consists of leguin and an albuminoid substance; after washing, to free it from starch as much as possible, it may be made into bread with butter and eggs.

Camplin ([25]) long ago strongly recommended bran cake as a substitute for bread in diabetes. He found it necessary to have the bran very finely ground, otherwise it was hurried through the

intestines undigested, and diarrhœa was produced. When very finely ground this disadvantage was overcome.

The following are his directions for the preparation of bran cake:—"Take a sufficient quantity (say a quart) of wheat bran, boil it in two successive waters for a quarter of an hour, each time straining it through a sieve, then wash it well with cold water (on the sieve), until the water runs off perfectly clear; squeeze the bran in a cloth as dry as you can, then spread it thinly on a dish, and place it in a slow oven; if put in at night let it remain until the morning, when, if perfectly dry and crisp, it will be fit for grinding. The bran thus prepared must be ground in a fine mill and sifted through a wire sieve of such fineness as to require the use of a brush to pass it through; that which remains in the sieve must be ground again until it becomes quite soft and fine. Take of this bran powder 3 oz. (some patients use 4 oz.), the other ingredients as follows—three new-laid eggs, 1½ (or 2 oz. if desired) of butter, and about half a pint of milk.

"Mix the eggs with a little of the milk, and warm the butter with the other portion; then stir the whole well together, adding a little nutmeg and ginger, or any other agreeable spice. Bake in small tins (pattipans), which must be well buttered, in a rather quick oven for about half an hour. The cakes, when baked, should be a little thicker than a captain's biscuit; they may be eaten with meat or cheese for breakfast, dinner, and supper; at tea they require rather a free allowance of butter, or may be eaten with curd or any of the soft cheeses. It is important that the above directions as to washing and drying the bran should be exactly followed, in order that it may be freed from starch, and rendered more friable. In some seasons of the year, or if the cake has not been well prepared, it changes more speedily than is convenient—this may be prevented by placing the cake before the fire for five or ten minutes every day. Mr. Blatchley of 352 Oxford Street, London, makes the bran biscuits, and prepares the powder for those at a distance who have no mill."

Bran flour can be obtained from Mr. E. Blatchley, 167 Oxford Street, London, but Camplin recommends that the patient, if he does not prepare the flour, should at least have it baked at his own house, rather than purchase the dry hard biscuit of commerce.

(4) *Soya biscuits or bread.*—During the last seven years soya beans have been used in the preparation of bread and biscuits for diabetic patients. The soya or soja bean is used in Japan for preparing various articles of food. The Japanese give the name of daidsu to the plant from which the beans are derived, but various botanical names have been given to it, *Soja hispida*, *Glycine hispida*, etc. (H. White [20]).

In China an emulsion in water is made with the oil expressed from the beans, and is drunk in those districts in which the people are too poor to buy milk.

Dujardin-Beaumetz ([27]) recommended bread prepared from the soja beans for diabetic patients, at the Berlin International Congress in 1890, and since then it has been frequently employed.

It is stated that the soja beans contain a large quantity of nitrogenous matter and fatty material, and only a small percentage of starch; and for this reason they are recommended as a suitable article of diet for diabetic patients. But the various analyses published show great discrepancies. According to Dujardin-Beaumetz, soja bread contains less than 3 per cent. of starch or sugar, 9 per cent. of fat, 20 per cent. of proteids, and 45 per cent. of water. The *Lancet* for August 16, 1890, gives 2·72 as the percentage of starch in soja bread. *Guy's Hospital Gazette* (28th February 1891) gives 6·4 as the percentage of starch; Saundby, 23 per cent. in the bread, 46 per cent. in the biscuit, 45 in the flour ([28]). According to Professor Attfield, soja flour contains 30 per cent. of cellulose, starch, and sugar.

Soja bread does not keep well, but the biscuits can be kept for a long time. Most of the biscuits which I have tried have had an unpleasant taste—some of them a very unpleasant taste. One sample gave only a faint blue coloration with a drop of iodine solution; but several others, obtained at different times from the same makers, contained a large amount of starch, and gave a deep blue-black coloration with iodine solution. Hale White ([26]) and others have obtained good results from the use of soja preparations.

(5) *Almond cakes* were recommended long ago by Dr. Pavy as a substitute for bread. Ground almonds, in the form of a powder, can be obtained from many provision shops. The sweet almonds contain 3 to 5 per cent. of sugar, but this may be removed by pouring over the pulverised almonds boiling water acidified with tartaric acid (Pavy), or acidified with a few drops of acetic acid (Seegen). Almond flour washed in this manner is almost free from sugar.]

Composition of the Sweet Almond (König).

Water	5·39
Nitrogenous matters	24·18

Fat	53·68
Carbohydrates	7·23
Cellulose	6·56
Ash	2·96

The following are the directions given by Seegen ([29]) for the preparation of almond cakes :—

Break up about a quarter of a pound of sweet almonds as fine as possible in a stone mortar (or the almond flour may be used). Put the flour into a linen bag, which is then immersed for a quarter of an hour in boiling water, acidulated with a few drops of vinegar. This removes the small amount of sugar from the almonds. Mix intimately with 3 oz. of butter and two eggs. Then the yolks of three eggs and a little salt are added, and the whole stirred briskly for a long time. A fine froth is made by beating the whites of three eggs, and then added to the above mixture. The paste is made into biscuits, smeared with melted butter, and baked with a gentle fire.

Almond cakes have long been used with a certain amount of success, but, on account of the large quantity of fatty matter which they contain, they are somewhat difficult to digest, and are apt to give rise to dyspepsia. Their digestion is greatly aided, however, by a small quantity of wine, brandy, or some form of alcohol, taken with the biscuits, or directly afterwards.

Saundby gives the following direction for the preparation of *almond cakes* :—

One lb. of ground almonds, four eggs, two tablespoonfuls of milk, a pinch of salt. Beat up the eggs, and stir in the almond flour ; divide in twelve flat tins, and bake in a moderate oven for about fifteen minutes.

I have found cakes prepared according to these directions very palatable. They can be easily made at home.

I have also found *almond pudding*, prepared according to the following directions, very palatable and useful :—

Two eggs, ¼ lb. of almond flour, ¼ lb. of butter. Three tabloids of saccharine dissolved in an ounce of brandy, or a little saccharine solution, may be used to sweeten the mixture.

Warm the butter, beat in the yolks of the eggs and the almond flour ; add the saccharine.

Whisk the whites of the eggs into a froth, then mix all together, place in a mould, and bake in a quick oven.—Mrs. Hart ([30]).

(6) *Cocoa-nut.*—The edible part of cocoa-nut forms a useful addition to the diet of the diabetic. It may be purchased in desiccated powder, which can be easily made into biscuits. Cocoa-nut powder is very cheap, and costs only 4½d. to 6d. per lb. Cocoa-nut contains a small amount of sugar, but a large amount of fat (70 per cent.).

Almost all the samples of cocoa-nut powder which I have examined have contained a very small quantity of sugar, and sometimes it is adulterated with sugar; hence it is well to test the powder (by the fermentation test), to ascertain if there is any quantity of sugar present. It may also be tested for starch with iodine. A good sample contains, however, very little sugar; and specially prepared cocoa-nut powder can be obtained, which is stated to be free from sugar, but most of the samples which I have examined have contained a little, and it is somewhat expensive.

The trace of sugar can easily be removed from ordinary cocoa-nut powder, however, by adding a little yeast and water, and allowing the mixture to ferment before use.

Biscuits and cakes made of cocoa-nut may be prepared for diabetic patients. The following are directions for home-made cocoa-nut and cream cakes, which I have found to be very palatable:—

Three tablespoonfuls of cocoa-nut powder are mixed into a paste, with a little German yeast and water. The mixture is allowed to remain by the fire, or in a warm place, for about twenty minutes, until fermentation occurs, and it becomes "puffy." Then a little of a watery solution of saccharine is added.

One egg is beaten up, and this with two teaspoonfuls of cream and a little water are added to the cocoa-nut paste. The whole is well mixed, and dropped into small tins, and baked in an oven for about thirty minutes.

These cakes are excellent, but contain so much fatty material that in many persons they cause slight dyspepsia. This may easily be prevented by taking a little wine, or alcohol in some form, soon after eating the cakes.

Saundby gives the following directions for the preparation of cocoa-nut and almond cakes:—

Three-quarters of a lb. of the finest desiccated cocoa-nut powder, ¼ lb. of ground almonds, six eggs, half a teacupful of milk.

Beat up the eggs, and stir in the cocoa-nut and almond flour. Divide into sixteen flat tins, and bake twenty-five minutes in a moderate oven.

Cocoa-nut can also be made into *puddings*, which will supply the place of rice pudding. I have found the following useful:—

Take three tablespoonfuls of cocoa-nut powder, mix with a little German yeast and water, and keep for twenty minutes in a warm place, so as to decompose the small quantity of sugar present; add four tablespoonfuls of cream, one egg, a little salt, half a pint of water sweetened with saccharine.

Mix into a paste. Place in a dish greased with butter. Cook like rice pudding, in a slow oven, thirty minutes.

Cocoa-nut pancakes can also be prepared. I have had these made as follows:—

Take one egg; beat up in two tablespoonfuls of milk, or better, in a little cream and water. Add a pinch of salt.

Then add two tablespoonfuls of cocoa-nut powder (freed from sugar). Allow to stand five to ten minutes.

Add a little more cream and water.

Mix well, until it is a little thicker than ordinary pancake batter. Place a little lard in a frying-pan; heat until the lard is just melted; then drop in half of the above mixture.

Allow to remain over a moderate fire for a few minutes (five), until the under surface is brown; then turn the cake over, and heat for another five minutes.

The other half of the mixture may be used for a second pancake.

(7) *Aleuronat.*—Professor Ebstein ([31]) has drawn attention to the value of an albuminous substance, named aleuronat, in Germany (*ἄλευρον* = flour). This is a vegetable albumin, which Dr. Hundhausen prepares by a special process from wheat. It is a light yellowish brown powder, and contains 80 to 90 per cent. of albumin in the dry substance, and only 7 per cent. of carbohydrates. (It can be obtained from R. Hundhausen, Hamm, Westphalia, Germany, in parcels of 4½ kilos., for about seven shillings.) Aleuronat powder is thus a cheap form of albumin, and can be used as a substitute for ordinary flour in various ways, in cooking, in the preparation of soups, sauces, etc., and it can be baked into bread. But in the preparation of bread it is necessary to add a considerable amount of ordinary flour. Ebstein gives directions for the preparation of aleuronat breads containing 27·5 per cent. and 50 per cent. of albumin in the dry substance. The following are his directions for the preparation of bread containing 50 per cent. of albumin:—

About 6 or 7 oz. of ordinary white flour.
„ 6 or 7 oz. of aleuronat powder.
„ 5 oz. of butter (of the best quality).
One teaspoonful of salt.
Three-quarters of an ounce of baking powder.

The flour and aleuronat are mixed in a warm dish, and the melted butter and milk (made lukewarm) are gradually added, then the salt, and finally the baking powder (one part of sodium carbonate and two parts of cream of tartar). The dough is well mixed, then formed into loaves, and baked at a good heat.

I have had aleuronat bread prepared at my own house, and have prescribed it for diabetic patients. It forms a useful and fairly palatable brown bread; but, as will be seen from its composition, it contains a considerable amount of starch. A patient taking 16 oz. of this bread per day would consume as much starch as a patient taking 8 oz. of ordinary white bread, but the amount of albumin would be much greater in the former case. After a time most patients would much prefer the 8 oz. of ordinary bread to the 16 oz. of aleuronat bread. It has always appeared to me that half measures with regard to diabetic food preparations are somewhat unsatisfactory, and that it is better either to replace bread entirely by some substitute almost free from carbohydrates, or to allow a definite small amount of ordinary bread, with the addition of some starchless diabetic bread substitute.

Aleuronat and cocoa-nut cakes.—After a number of experiments, which I have had made at my own house, I have found that very satisfactory cakes and buns can be formed by a combination of aleuronat and cocoa-nut ([32]). Home-made preparations of these cakes are preferable; and at the Manchester Infirmary, for several years, excellent biscuits have been made by the cook, for diabetic patients, according to my directions. Of course the patient regards all bread substitutes as more or less objectionable after prolonged use. But I have found that most of the numerous private and hospital patients who have used these aleuronat and cocoa-nut cakes prefer them to any other kind of diabetic bread, and their composition is reliable.

Cocoa-nut powder contains a large quantity of fatty material, but a small quantity of sugar is also present; as already mentioned, the latter can be almost entirely removed by the action of yeast.

For the preparation of these cakes, 2 oz. of desiccated cocoa-nut powder are mixed with a little water containing a small quantity of German yeast. The mass is then formed into a kind of paste, and this is kept for half an hour or longer in a warm place. The small amount of sugar contained in the cocoa-nut is almost entirely decomposed by the fermentation produced by the yeast, and the cocoa-nut paste becomes spongy. Two oz. of aleuronat, one egg beaten up, and a small quantity of water, in which a little saccharine or saxin has been dissolved, are now added to the cocoa-nut, and the whole well mixed until a paste is formed. This is spread out on a tin and divided into cakes, which are baked in a hot oven for twenty or thirty minutes.

Messrs. Callard & Co. of Regent Street have kindly supplied me with a desiccated cocoa-nut powder, from which the small amount of sugar has been almost entirely removed. If this be employed, then the addition of the yeast is not necessary; 2 oz. of aleuronat, 2 oz. of cocoa-nut, 1 egg (beaten up), and a little water sweetened with saccharine, are simply mixed together, divided into cakes, and baked.

The cakes are most palatable when newly made. If they have been prepared more than twenty-four hours, the taste is greatly improved if they are slightly warmed before the fire. They are also improved by being buttered.

I have had excellent buns, about 1 inch in thickness, prepared from aleuronat and cocoa-nut powder. Two oz. of desiccated cocoa-nut powder are mixed with a little yeast and water, and kept in a warm place (by the fire) for fifteen to twenty minutes. Then 2 oz. of aleuronat are mixed well with one teaspoonful of baking powder and a little salt. After the action of the yeast, the cocoa-nut powder is added to the aleuronat, together with one egg, beaten up, and water (sweetened with saccharine or saxin, if preferred). The mixture is worked into a thin batter, and this is then placed in deep tins or tart dishes, which are put at once into a hot oven for twenty to thirty minutes. When half baked, the buns or rolls may be glazed with a little egg albumin, and then placed in the oven again until browned.

The above directions indicate the proportions of the substances, but of course large quantities can be employed.

The advantages of these cakes, buns, and rolls are—(1) A

diabetic patient can have them easily prepared at his own home. (2) If so prepared, they are cheap in comparison with most diabetic foods. (Aleuronat can be obtained from Germany, in parcels containing 4½ kilos. for 7s., that is, about 9¼d. per lb.; fine desiccated cocoa-nut powder at 4½d. per lb.) (3) They are much more palatable than most diabetic cakes; to many persons they are very palatable. (4) They contain a large quantity of vegetable albumin and fatty matter, and only a very small amount of carbohydrate. A solution of iodine gives no blue coloration with the cakes, and hence the starchy matter must be very small. When given to diabetic patients in place of ordinary bread, of course a great diminution of the quantity of sugar excreted in the urine is observed.

I have found these biscuits and buns useful as a bread substitute, when for diagnostic purposes a patient has been placed on a rigid diet. They are also of great service in the dietetic treatment of diabetes, to replace ordinary bread totally or in part when a rigid diet is indicated.

The table on p. 359 shows the diminution in the sugar excretion and diuresis produced in a diabetic patient by replacing ordinary bread by the same quantity of aleuronat and cocoa-nut biscuits —the diet otherwise being the same. The patient was put on a diet of meat, green vegetables, and bread, and 1 drm. of citrate of potassium given three times a day. The sugar was carefully estimated. As is usually the case, there was a diminution of the sugar excretion during the first three days, but an equilibrium was soon reached. Omitting the figures for the first week from consideration, for the next six days, when the patient was taking 14 oz. of ordinary bread daily, the sugar excretion was from 3520 to 4800 grs. per day; the amount of urine from 200 to 240 oz. daily. The urine gave no brown-red reaction with perchloride of iron, and no reaction for acetone. At the end of this time 14 oz. of aleuronat and cocoa-nut cakes were given in place of the 14 oz. of bread for five days. Otherwise the diet was kept exactly the same. The thirst became less, the diuresis and glycosuria diminished; the daily amount of urine being 112 to 159 oz., and the amount of sugar 1792 to 2850 grs. To make the observation complete, at the end of five days, 14 oz. of white bread were given in place of the aleuronat and cocoa-nut cakes, the diet otherwise remaining the same.

The thirst increased, and the diuresis and sugar excretion rose to their previous level. In this case the bread was carefully weighed daily. By replacing bread by the same quantity of aleuronat and cocoa-nut biscuit, the average quantity of urine excreted was thus reduced by 80 oz. daily, and the average amount of sugar excreted was reduced practically by 2000 grs. per diem.

	Ounces of Urine.	Sp. Gr. of Unfermented Urine.	Sp. Gr. of Fermented Urine.	Grains of Sugar excreted daily.	Diet.
I. (6 days)	230	1025	1007	4140	Chop; steak or fish; green vegetables; milk, 2 pints; tea; water; 14 oz. of bread; citrate of potash, 1 grm., three times a day.
	220	1023	1007	3520	
	225	1023	1007	3600	
	230	1023	1003	4600	
	240	1024	1004	4800	
	200	1024	1003	4200	
II. (5 days)	150	1023	1004	2850	Medicine and diet the same, except that the 14 oz. of white bread were replaced by 14 oz. of aleuronat and cocoa-nut cakes.
	112	1022	1006	1792	
	150	1021	1009	1800	
	150	1022	1006	2400	
	159	1023	1011	1908	
III. (4 days)	188	1024	1006	3384	The aleuronat and cocoa-nut cakes replaced by 14 oz. of white bread; diet otherwise the same.
	258	1024	1002	5676	
	220	1026	1004	4840	
	220	1026	1006	4400	

	Average amount of Urine daily.	Average amount of Sugar daily.
FIRST STAGE.		
14 oz. white bread . . .	224 oz.	4143 grs.
SECOND STAGE.		
14 oz. of aleuronat and cocoa-nut biscuits in place of bread	144 ,,	2150 ,,
THIRD STAGE.		
14 oz. of bread in place of biscuits	221 ,,	4585 ,,

I have also had cakes prepared from aleuronat and almond flour as follows:—

Three oz. of aleuronat; 3 oz. of almond flour; one egg beaten up; about two teaspoonfuls of cream, and a little water.

Moisten the aleuronat with a little water containing saccharine, for a few minutes; then add the almond flour, the egg and cream, and water

as required, just to make a light paste. Spread on to a tin. Cut into squares and bake in a moderate oven for twenty minutes.

Aleuronat may also be used in the following preparations:—

Aleuronat Pancake.

Take one egg; beat up in a little water and cream: take two tablespoonfuls of aleuronat powder; add half a teaspoonful of baking powder and a pinch of salt; mix well, then add gradually to the egg and cream, and beat into a batter; allow to stand five minutes. If too thick, add a little more cream and water.

Fry as an ordinary pancake in a frying-pan with a little lard. At the end of about eight minutes, when the under surface is browned, turn it over and continue to heat for about five minutes longer.

I have found that the following forms a useful, palatable, and cheap combination for diabetic patients:—

Aleuronat and Suet Pudding.

Take 2 oz. aleuronat flour, 2 oz. suet, one egg, a pinch of salt, half a teaspoonful of baking powder. Sprinkle a little aleuronat flour on a chopping-board. Chop the suet on this part of the board. Then mix all the aleuronat with the chopped suet in a basin. Add the salt and baking powder. Beat up the egg in about three tablespoonfuls of water, to which a little saccharine has been added. Then add the egg gradually to the mixed aleuronat and suet, stirring the whole mass well into a paste. The addition of a little more water may be necessary. Drop into a tin pudding mould, smeared with butter or lard, and float it in a pan of water, and boil for two hours, taking care that the water does not flow over into the pudding-mould; or, better still, the pudding may be baked in the oven. The addition of almonds ($\frac{1}{2}$ oz.) improves the taste. It can be eaten with a little red wine as a sauce.

(8) *Inulin biscuits.* — Inulin is assimilated by diabetic patients, and Külz ([33]) recommends inulin biscuits prepared according to the following directions:—

Fifty grms. of inulin are placed in a large porcelain basin, and, while standing over a water bath, are rubbed up with 30 c.c. of milk, and as much hot water as may be necessary, into a uniform dough, with which the yolk of four eggs and a little salt are mixed. To this the whites of the four eggs are added, having first been beaten to a foam, and carefully worked in. The dough is finally baked in tin moulds, previously smeared with butter. The taste of the biscuits may be improved by the addition of vanilla or other spices.

Inulin is so expensive, however, that this bread is not likely to be of much practical use.

(9) Bread prepared from *pea-nut flour* has been recommended by Stern. The kernel of the pea-nut (*Arachis hypogæ*) contains 29 per cent. of proteids, 49 per cent. of fat, and 14 per cent. of carbohydrates in the dry material. The oil is extracted and used for various purposes in trade. The meal contains 52 per cent. of proteids, 8 per cent. of fat, and 27 per cent. of carbohydrates. The pea-nut is one of the cheapest foodstuffs known.

The following are Stern's ([34]) directions for the preparation of a "diabetic pea-nut flour":—

> The pea-nut kernels are boiled in water for half-an-hour, to extract a portion of the oil which they contain. They are then dried and pounded into fine particles by a rolling-pin. The pounded kernels are then placed in boiling water, acidulated with tartaric acid or vinegar in order (1) to extract saccharine elements, (2) to overcome the smell and taste of the pea-nut, (3) to prevent emulsification of the remaining oil. After having undergone a thorough boiling with acidulated water, the ground kernels are subjected to dry heat, and then rolled into fine flour. The flour can be used in the form of porridge with milk; bread and biscuits can be baked from it; but it may be utilised in the form of the German pancake. As will be seen from the figures given above, it contains a considerable amount of carbohydrates, however.

(10) O'Donnell recommends the following as a home-made substitute for bread ([35]):—

> Six eggs are thoroughly beaten, then a teaspoonful of baking powder or its chemical equivalent and a quarter of a teaspoonful of salt are added, and again the eggs are beaten. This mixture poured into hot waffle irons, smeared with butter, is baked in a very hot oven. For variety pulverised nuts (almonds) may be added. They may be eaten hot with butter and cheese.

(11) *Iceland moss* is a lichen which is much used by the inhabitants of Iceland, Lapland, and the Arctic regions as an article of food. It contains a soluble gelatinous, carbohydrate substance, known as lichenin, and two bitter acids—cetraric and lichen-stearic. After the removal of these bitter substances by repeated washing (or washing with a solution of bicarbonate of potash), a bread may be formed from the moss, which is largely used in Iceland.

(12) *Meat bread and biscuits.*—A bread substitute composed chiefly of flesh meat has been recommended by Baron Luhdorf [36]. Also meat biscuit and cheese biscuit are prepared by some makers of diabetic foods, but naturally they have never been much used.

Beverages.

It is now generally acknowledged that it is unnecessary to restrict the quantity of fluid taken by diabetic patients, unless the thirst be exceedingly great. Restriction of the amount of fluids has been shown to be distinctly harmful; the volume of urine and the amount of sugar excreted daily may be temporarily reduced thereby, but the general distress increases. A diabetic patient ought not to be allowed either to hunger or thirst; but of course food and liquids must be taken in moderation. The greater the quantity of sugar excreted by any diabetic patient, the greater the thirst as a general rule, and *vice versâ*. If, by treatment, the sugar excretion is diminished, the thirst and diuresis are also diminished.

Prout has recommended that all liquids should be taken tepid, since the thirst is thereby relieved much better than when the liquids are cold. Of beverages, good drinking water is the best. Tea and coffee both contain a small quantity of carbohydrates, but the percentage is so very small (especially in the case of tea) that they may be allowed freely; of course they must not be sweetened with sugar; if a sweet taste is preferred, saccharine or saxin may be added. Maté or kola may also be allowed. Cocoa contains a considerable amount of carbohydrates, and hence ought to be forbidden. A preparation of cocoa, from which the carbohydrates have been removed, is sold in Neuenahr, and to this of course there is no objection. Chocolate should be forbidden, on account of the considerable percentage of carbohydrates which it contains. It has been already pointed out that milk contains 4 per cent. of lactose; whilst some patients take it without any bad effects, in others the sugar excretion is increased by its use. Unless, therefore, it has been proved that the case belongs to the former class, milk ought to be forbidden, or allowed only in limited quantities when a rigid diet is indicated. Cream is one of the most useful articles of diet, and the artificial milk prepared from cream

(see p. 334) may be taken freely. Diabetic koumiss (see p. 336) and kephir may also be allowed. Bouillon, beef-tea, meat-broths (to which no carbohydrate material has been added), eggs beaten up with cream and water, or with a little milk, and sweetened with saccharine or saxin, may be taken without restriction. Soda, potash, seltzer and Apollinaris waters, or the alkaline waters of Neuenahr, Carlsbad, or Vichy, may be allowed freely. But these carbonated alkaline waters should not be given at meals, as they impair digestion, especially the digestion of fats.

Alcohol does not increase the sugar excretion; and when taken in moderation and in a form unmixed with carbohydrates, it is of great service in some cases. It may be given in the form of brandy or cognac, or some of the wines which contain very little sugar. In the milder forms of diabetes, alcohol is unnecessary, but in the more severe forms it is very useful. Alcohol is of value chiefly as an aid to the digestion of fatty food. Fatty articles of food are of the greatest importance in the diet of diabetics, especially in the severe forms of the disease, but frequently these articles cause dyspepsia when taken in considerable amount. The patient is, however, often enabled to eat large quantities of fatty food, without nausea or indigestion, if he take a small amount of alcohol in the form of brandy or non-saccharine wine, with or just after the meal. It is also of some service in aiding the digestion of nitrogenous food. By its use, therefore, in the severe forms of the disease, a much larger quantity of fatty food can be taken, and this is a point of importance when there is much wasting, or when tubercular complications are present.

Hirschfeld attaches considerable importance to the use of alcohol in cases of commencing diabetic coma.

Wines and alcoholic beverages.—Of course, great caution is necessary with respect to alcoholic beverages, as the thirsty diabetic is very liable to take these to excess; certainly they ought only to be allowed with the meals. Some beverages are suitable, whilst others are very unsuitable. Wines which contain a large quantity of sugar must, of course, be avoided, but if the percentage of sugar be very small they may be permitted. Many old wines contain only a trace of sugar, and, as a rule, the older the wine the more suitable it is for diabetic patients; new wines should generally be avoided. The name of the

wine is not always a reliable guide as to its composition, and, before advising any wine or wines for frequent consumption, it is important to obtain information respecting the results of the chemical analysis. It is also to be remembered that wine is a drink and not a food; and large quantities ought not to be taken by diabetic patients. But in addition to their value in quenching thirst, and in aiding the digestion of fat (owing to the alcohol they contain), wines are probably of value, as Schmitz and others have pointed out, on account of the vegetable acid and mineral elements present, especially since the diabetic patient is to some extent deprived of these, through abstaining from fruit.

Bordeaux wines contain only about 0·2 per cent. of sugar; Rhine wines only 0·3 to 0·4 per cent. (König); Hock, Moselle, and Ahr wines contain very little; whilst some dry sherries are free from sugar.

Austrian and Hungarian table wines also contain only a very small quantity of sugar; and Hungarian Carlowitz is practically free from sugar. All these wines may therefore be permitted in moderation. A pleasant way of taking the very acid table wines is to dilute them with a little soda water. In this way there is less risk of "heart-burn" and colic from the strong acidity of these wines.

Wines which contain sugar in large or considerable quantities must be avoided. Must, Malaga, Port, Madeira, Tokai and the other sweet Hungarian wines, Malmsey, champagne, and many Spanish, Sicilian, and Greek wines, contain large quantities of sugar, and must therefore be avoided.

A champagne *sans sucre* can be obtained, however, by those diabetic patients with whom this wine is a favourite beverage.

Sweet ales, porter, rum, sweetened gin, and beer must also be forbidden. Brandy, cognac, or old whisky may be taken in small quantities.

In order *to relieve thirst*, it is important, of course, to try to diminish the sugar excretion by restricting the diet and by the use of drugs. As above stated, a reduction in the sugar excretion diminishes the thirst. But, in addition, there are other means of considerable service in relieving this troublesome symptom, such as acid drinks of various kinds. Sir William Roberts recommends bitartrate of potash water, of which the following

is a pleasant form. A drachm or a drachm and a half of cream of tartar is dissolved in a pint of boiling water, and flavoured with lemon peel and saccharine; when cold it may be taken in small quantities throughout the day.

The following forms a useful lemonade, which is often prescribed for the relief of thirst:—Citric acid, 10 grs.; glycerin, 4 drms.; water, one pint. This may be taken in small quantities during the twenty-four hours. Or a lemonade may be made from fresh lemons, and sweetened with saccharine or saxin.

Water containing a little dilute phosphoric acid or other dilute acids is also often prescribed.

Then there are several other means of relieving thirst. The patient may be allowed to suck ice, broken up into small fragments. Washing out the mouth frequently with cold water, with iced water, with acidulated water, or with weak brandy and water, sometimes gives considerable relief. Bouchardat recommends that the patient should be allowed to chew roasted coffee beans, and diabetics tell me that this is successful in relieving thirst to some extent.

Large quantities of fluid should not be taken immediately after meals; the chief potations should precede the meals.

MODE OF LIFE, HYGIENIC CONSIDERATIONS, ETC.

The mental condition.—In the section devoted to etiology it has been shown that not infrequently diabetes has followed some severe mental shock. It is also well known that the condition of a diabetic patient is often markedly affected by the mental state. Severe mental shock or nervous excitement is frequently followed by a decided advance of the symptoms, and sometimes by diabetic coma.

Hence it is important to relieve the patients from mental anxieties and worry as much as possible. Everything should be done to cheer them and to make them forget their business, professional, or family cares and anxieties. This is especially desirable when the patients suffer, as is so frequently the case, from great mental depression. A change of climate or residence, the removal from old associations, in some cases retirement from business or professional duties, may all be of great service by their good effect upon the mental condition of the patient.

No doubt a considerable share of the good results of a visit to Carlsbad or Neuenahr may be accounted for by the cheering effect on the mind, produced by the absence from the worries and anxieties of daily life. In fact, a visit to any health resort may be of service, through its beneficial effect on the mental condition, providing the patient is suffering from a mild form of the disease only, and that he is not in an advanced stage, and that there is no likelihood of coma being brought on by the journey.

A few years ago we heard much of the supposed value of music in therapeutics. Of course, nothing but slight improvement could ever be expected from the influence of music in any disease. But when we consider the undoubted influence of the mental state on the symptoms of diabetes, it would certainly appear that the effects of music are worthy of a trial, especially if the patient be suffering from much mental worry and anxiety.

Many intelligent diabetic patients keep a sharp look-out on the amount of sugar excreted daily, and are greatly alarmed if the number of grains increases even to a slight extent. Hence it is better, when the patient shows any anxiety about the amount of sugar excreted, to prevent him obtaining detailed information on this point. The instructive case recorded by Karl Grube is well worth bearing in mind. A patient, in whose urine a trifling amount of sugar had been discovered, was so alarmed on hearing thereof, that symptoms of acute Graves' disease developed, and rapidly proved fatal. This patient had lost a relative from diabetes, and at once concluded that the trace of sugar discovered in her own urine indicated an incurable and severe disease.

Marriage.—Women who suffer from diabetes, especially in its more severe forms, ought not to marry, as pregnancy is dangerous. Abortion frequently occurs, and either confinement or abortion has an injurious effect.

Cases of diabetes in males are sometimes met with, in which the symptoms have developed not long after marriage, and it is possible that sexual excess may have played some part as an exciting cause. It is advisable that males suffering from diabetes (especially in the more severe forms) should not marry; also all sexual excess should be avoided.

Clothing.—It is important that diabetic patients should be well protected from cold, and that they should wear warm

clothing; in winter, woollen clothing should be worn next to the skin. Camplin long ago pointed out that diabetics were worse in cold weather, and insisted on the importance of warm clothing.

Action of the skin.—Warm baths followed by cutaneous friction are of service in promoting the action of the skin, especially if the latter be excessively dry, but cold plunges or sea baths ought not to be taken.

Exercise.—Külz has shown that in dogs, by vigorous exercise the glycogen is made to disappear from the liver. He also made experiments on five diabetic patients in order to determine the effect of exercise. He found that exercise diminished the sugar excretion in two powerful muscular patients, whilst in the other three cases (patients who were badly nourished) the sugar excretion was unchanged in two, increased in one. Zimmer found that in well-nourished patients exercise diminished the sugar excretion, but in patients suffering from a very severe form of the disease, much exercise was useless or even injurious. Seegen has obtained good results from moderate exercise in the open air; and when the disease is not too advanced, he recommends the patient to spend the winter in a mild climate, such as that of the Riviera, where exercise in the open air can be taken frequently. Schmitz refers to the cases of eight soldiers who suffered from diabetes, and whose urine contained from 1 to 4 per cent. of sugar; in each case the exercise of a manœuvre caused the sugar to disappear. Frerichs mentions the case of an English medical man, whose diabetic symptoms ceased when he took vigorous exercise in the country, hunting with his brother. He also mentions the case of a landlord, whose glycosuria disappeared through free exercise in the open air. Brunton has drawn attention to the value of exercise in the glycosuria of gouty persons. The value of exercise appears to vary, therefore, according to the form of the disease. We have already seen that the diet which is most suitable for mild forms of diabetes is unsuitable for severe forms, and in like manner a difference ought to be made with respect to the amount of exercise recommended in the two varieties of the disease.

A considerable amount of exercise in the open air appears to be of great service in the mild forms of diabetes, when the patient's general condition is good, and especially in the case of obese or gouty patients; but over-exertion or undue strain must be avoided. In other forms of diabetes only gentle

exercise can be recommended; in severe cases it is especially important to avoid much exercise, since any unusual strain or vigorous muscular exercise would be liable to bring on diabetic coma.

Massage is worthy of a more careful trial in diabetes, especially when the patient is too stout, or too thin and weak, to take much exercise. In these cases it is recommended by Lauder Brunton, who points out that the flow of blood through the muscles takes place three times as quickly under the influence of massage. Brunton and Tunnicliffe (37) have also shown that the total blood pressure is diminished. Grube (38) has seen the best results from massage in cases of diabetes, associated with arterio-sclerosis, and in such cases he thinks it is specially indicated on account of its power of diminishing the blood pressure. Ralfe speaks favourably of massage, both general and over the abdominal viscera; he believes it improves assimilation and promotes metabolism; and when thoroughly carried out he has "seen it effect a wonderful improvement in the patient's general condition." But the most careful observations appear to have been made by Finkler eleven years ago (39). His results show that massage alone, without any restriction of diet or any medical treatment, is able to cause a great diminution in the sugar excretion and diabetic symptoms. Zander of Stockholm has employed regular Swedish gymnastics in the treatment of patients, and though no cure has been effected, considerable benefit is reported.

Treatment by Alkali Mineral Waters.

The mineral waters of certain continental spas have a great reputation in the treatment of diabetes mellitus, and every year these spas are visited by large numbers of diabetic patients from all parts of Europe. The spas most frequented are Carlsbad, Neuenahr, Vichy, Marienbad. The waters of Carlsbad and Marienbad may be briefly described as alkaline sulphate water; those of Vichy and Neuenahr as alkaline bicarbonate waters.

As to the value of a visit to these spas, and as to the value of the waters, there is much difference of opinion, and the statements found in the writings of various authors are somewhat conflicting. Whilst some writers state that it would be much better and infinitely cheaper for patients to stay at

home and have the water sent to them, others attribute any good effects to the visit to the spa and not to the waters. Whatever the explanation may be, there can be no doubt that a large number of diabetic patients *are greatly benefited* by a visit to Carlsbad and Neuenahr. Excluding the somewhat glowing statements of many of the resident practitioners, we find that many German and Austrian physicians, who have specially devoted their attention to the clinical study of diabetes, and who do not practise at any of these spas, testify as to the undoubted benefit which many diabetic patients derive from a *visit* to Carlsbad or Neuenahr.

Thus Frerichs (40) of Berlin stated that he had no doubt that through the use of these waters the diabetic symptoms diminish markedly, and sometimes disappear temporarily. Of course no permanent cure is obtained; but Frerichs stated that he had often observed that every trace of sugar had been absent for months, and then gradually returned. The beneficial influence he had seen mostly after the first visit. Then gradually the good results diminished, and finally ceased.

Minkowski (41) of Strassburg states that in the milder forms of the disease, frequently the sugar disappears from the urine of patients at these spas, by the use of a less rigid diet than would be necessary at home; that the patients bear a restricted diet better at the spas; and that after returning home there is frequently a greater tolerance for carbohydrates. Naunyn (42) of Strassburg also bears similar testimony to the value of a visit to Carlsbad in cases of slight or moderate severity, but admits that in severe cases little benefit is derived. Seegen of Vienna also speaks very highly of the value of Carlsbad waters.

Physicians such as Seegen and Kállay, who have had much experience of the treatment of diabetes both in Carlsbad and elsewhere, have obtained more successful results in Carlsbad.

Mode of action.—There are other factors besides the drinking of the waters which tend to improve the condition of the diabetic patient during a visit to these spas.

(1) The patient is removed from his usual routine of life, from the anxiety of business or professional cares; he has complete rest of mind as a rule; and he lives a quiet, peaceful, and regular life. It is well known, as has been pointed out on p. 365, that the disease is influenced by the mental condition.

(2) He is in the open air a large portion of the day. (3) He takes suitable bodily exercise. (4) His diet is carefully regulated, more carefully, as a rule, than when at home. (5) Further, as Minkowski points out, the waters may act, not on the diabetic state, but on the pathological condition which is at the bottom of it, such as disease of the liver or pancreas.

Many physicians and physiologists attribute the improvement in patients visiting Carlsbad and other spas *entirely* to the above mentioned factors, and not to the influence of the waters. Külz, Riess, and Griesinger, Senator, and others have tried the effect of Carlsbad water on patients in hospital, and have not been able to detect any improvement by their use; also Carlsbad salts have not been of service to diabetic patients at home.

Riess ([43]), from observations which he has made respecting the influence of Carlsbad waters, concludes that they are unable to diminish the sugar excretion, apart from a nitrogenous diet, in either slight or severe cases, and that in some cases they are directly injurious.

Leichtenstern ([44]) states, however, that from his own experiments he cannot agree with the conclusions of Riess.

On the other hand, Seegen ([45]) asserts that he has observed improvement in the mild forms of diabetes by the use of Carlsbad waters, even when drunk at a distance; and in the case of patients who cannot visit the continental spas, owing to the expense, or for other reasons, he advises that two or three times a year, for three or four weeks, the patient should take a bottle of warmed Carlsbad water daily.

Whilst there is, therefore, considerable *clinical* evidence that mild cases of diabetes *do* derive benefit from a visit to Carlsbad and other spas, it is disputed how much of the benefit is to be attributed to the waters, and how much to the altered conditions of life and diet, etc.

The patients that derive benefit from a visit to these spas are those who suffer from the milder form of the disease, especially the obese and gouty. The severe cases with wasting derive little or no benefit, but such cases do not derive much benefit from any kind of treatment. Also *a long journey* is often most injurious in the serious forms, and has frequently been the exciting cause of diabetic coma. It is well to remember this fact, and on no account to permit a patient suffering from

severe or *advanced* diabetes to take a long journey to Carlsbad, or Neuenahr, or other distant spa.

Carlsbad.—The chief salt in the Carlsbad waters is sodium sulphate, but the following are also present in smaller quantities: sodium bicarbonate, sodium chloride, carbonate of calcium and magnesium, etc. Seegen (45), who has had great experience of the use of these waters, points out the following results which he has observed in mild cases:—

1. Symptomatic improvement is soon obtained. The thirst and dryness of the mouth diminish, the urine becomes less, and therefore micturition during the night is less frequent, and the patient sleeps better and feels stronger. These results have been observed even when the sugar has not diminished.

2. In the majority of cases there is a real diminution of the sugar excreted. This is most marked in the mild cases, but even in many of the severe forms of the disease a diminution of the sugar excretion occurs.

3. In many cases there is an increase in the body weight; but in the severe cases it remains the same. Seegen has observed a diminution of body weight only in slight cases with marked obesity.

4. The simple symptomatic improvement, without sugar reduction, is never lasting, it disappears rapidly after the termination of the treatment with the Carlsbad waters; but in the majority of the cases in which the sugar excretion is diminished this improvement is more or less permanent.

5. Not infrequently, as a result of the Carlsbad treatment, a greater tolerance of carbohydrates is established.

6. The improvement occurs without any regard to apparent cause; it is noted when the symptoms point to a brain lesion, and also in cases in which there is a marked hereditary tendency.

Indications and contra-indications of Carlsbad waters.—The milder forms of the disease, especially in the obese and gouty, are most benefited by a visit to Carlsbad. The waters are unsuitable for the severe forms accompanied by great weakness and wasting, and in such cases there is great danger of producing diabetic coma by a long railway journey to Carlsbad. According to some authorities, cases associated with nephritis are also unsuitable. Seegen has seen improvement in cases complicated with tuberculosis.

Carlsbad salts, natural and artificial, can be obtained and taken at home very conveniently; but, apart from their useful purgative action, it has not been shown definitely that they are of service in diabetes.

Carlsbad is situated in a beautiful part of the north of Bohemia, and a visit may be made very enjoyable. But the expenses are somewhat high, and the journey from England is a long one. During the season, the little town is crowded with patients from all parts of Europe, most of whom show their faith in the waters by the great regularity with which they follow out the treatment, and there can be no doubt that many patients suffering from the milder forms of diabetes do return home much improved. After a recent visit to Carlsbad, I do not think that such improvement can be entirely attributed to the climate and the more favourable condition of life, etc. Carlsbad is situated in a valley, and is closely surrounded by high hills. In summer the climate is frequently so hot and relaxing, that most healthy persons are glad to leave after a short visit. Apart from the extra amount of time spent in the open air, certainly there does not appear to be anything specially favourable in the climate and conditions of life, and one can hardly help coming to the conclusion that the improvement in the patient's condition is partly due to the Carlsbad waters.

Neuenahr.—The waters of this spa are warm, and have the great advantage of tasting pleasant. There can be no doubt that they are of great value in relieving thirst. The chief solid constituent is bicarbonate of soda; they also contain a very small amount of magnesium and calcium carbonate, sulphate of soda, sodium chloride, minute quantities of oxide of iron, silica, aluminia, potassium, and lithium salts; they contain, in addition, free carbonic acid.

Indications and contra-indications.—R. Schmitz ([46]), who practised at Neuenahr for many years, points out that the waters of Neuenahr are of service chiefly in cases of glycosuria complicating gout, the alkaline waters acting on the gouty condition, to which it is probable that the glycosuria is secondary. In other cases of diabetes they are also of service, and often good results are obtained even when a strict diet is not prescribed. Schmitz points that contra-indications to treatment are considerable cardiac weakness, arterio-sclerosis with a tendency to hæmorrhages, which is not infrequently complicated

with glycosuria, and also great general weakness. He thinks that Carlsbad and Vichy waters, on account of the large amount of sulphate of soda contained in the former, and the large amount of alkaline bicarbonate in the latter, are less suitable than those of Neuenahr for weak patients.

Neuenahr is a beautiful little village situated in the valley of the Ahr, to the west of the Rhine, not very far from Bonn. It is more accessible than Carlsbad to patients from England and the north of Europe. Apart from the influence of the waters, the mode of life and surroundings are eminently calculated to improve the general health. The place is very quiet—for some patients it is too quiet; but diabetics whose illness has been brought on or aggravated by mental irritation and anxiety, will here be able to lead a regular life free from all excitement, in a healthy country village, with pleasant surroundings and good hygienic conditions.

With military punctuality, the patients visit the Kurgarten, and drink the water two or three times a day; and from the quantity which I saw drunk by the patients, during a visit to Neuenahr a few years ago, it was difficult to believe that such a large amount of bicarbonate of soda solution could be taken so regularly without some effect, either for good or evil.

Vichy is much frequented by gouty and diabetic patients. The water contains chiefly bicarbonate of soda, in addition to smaller quantities of sodium chloride, calcium carbonate, bicarbonate of potash, carbonate of magnesium, and sulphate of soda.

Vichy water may be taken at home (3 to 6 oz.), half an hour before each meal (Yeo).

The evidence in favour of the waters of the other spas is even less decided.

The arsenical waters of *La Bourboule* (Puy de Dôme, France) are said to be of service, and are recommended in the severe forms of diabetes. They can also be obtained at home, and a minute quantity of arseniate of sodium is their most important constituent; they contain also free carbonic acid gas, chlorides of sodium, potassium, lithium, and magnesium, with bicarbonates of calcium and sodium, and sulphate of soda.

Seegen recommends the use of the arsenical mineral water of Roncegus and Levico in the case of diabetes in children and young people.

Medical Treatment of Diabetes.

The drugs which have been employed in the treatment of diabetes mellitus are almost too numerous to mention, but only a few have been proved to have any real beneficial influence. Even in the cases in which the results have been most favourable, the action of the drugs has not been curative; marked improvement only has been produced. Nevertheless, to be able to produce any improvement in the patient's condition by drug treatment is of great importance.

When we consider that diabetes is generally a chronic disease, that apparently the symptoms are produced by an excess of sugar in the blood or by some toxic substance, and that the coma which so often terminates the disease is of the nature of an intoxication—in other words, that in diabetes there is a poisoning of the organism with chemical substances—treatment by drugs appears particularly suitable; yet the records of the past have been disappointing. Nevertheless it does not seem at all improbable that future research will lead to the discovery of some internal remedy of great service.

The records of medical literature present the greatest discrepancies as to the value of the various drugs which have been used in the treatment of diabetes. A few drugs are acknowledged by *most* writers to be of service; a large number are advocated by certain writers, but are stated to be useless by the majority of observers.

It has been already pointed out that success in the dietetic treatment of diabetes depends largely on the form of the disease, the age of the patient, etc., and this is equally true with respect to drug treatment. Too frequently these points have not been considered in drawing conclusions as to the value of various drugs. The records published in medical literature very often omit to state details as to the form and duration of the disease; too often the results are those produced by restricted diet plus the drug; and it is then, of course, impossible to say how much of the improvement is due to diet, and how much to the drug. To prove whether a certain drug will or will not *cure* diabetes in any form and at any stage, is an easy matter; there is generally no difficulty in obtaining negative evidence; but to prove whether this drug has or has not *any* beneficial influence is, as a rule, a most difficult task. Though

at first sight this might seem very simple, yet to anyone who takes the trouble to study the natural course of the disease, and the numerous sources of fallacy in drawing a conclusion, it will be evident how useless is most of the literature with respect to the drug treatment of diabetes.

The conclusions with respect to the action of many drugs are simply examples of the *post hoc propter hoc* fallacy. A number of drugs are stated by certain writers to have produced marked improvement, whilst others state that they are useless or injurious. Now, in many cases the change in the patient's condition, or in the sugar excretion, has been purely accidental, and due to variation in the diet, to altered surroundings, to the course of the disease or other circumstances, and not to the action of the drug.

It is important to remember, with respect to hospital patients, that there is generally a marked diminution of sugar excretion during the first three or four days after admission, even if no drugs be given and no special diet ordered.

Hence, in making *scientific* observations as to the action of any drug on hospital patients, it is necessary to wait until this equilibrium of sugar excretion has been produced before prescribing the drug, and to exclude the sugar excretion of the first four days from consideration.

Probably many of the discrepancies with regard to the action of various drugs may be owing to the fact that the observations have been made by some practitioners in mild forms or at early stages of the disease, and by others in severe forms or in late stages. Then again, it is probable that the pathological conditions at the foundation of the disease are not always the same. In one case it may be that diabetes is due to some change in the nervous system; in another, to a pancreas lesion, etc. If this be so, then these discrepancies in the results of treatment are only natural.

Hirschfeld ([47]) states that in a number of careful observations he has found that most of the drugs hitherto recommended cause a temporary diminution of the sugar excretion, but this diminution is not important, and seldom amounts to more than 25 per cent. Sometimes the diminution is followed by an increased excretion, and the same drugs which cause a diminution of the sugar in some patients cause an increase in others, whilst in a third group they have no influence.

The records of the daily sugar excretion in a large number of diabetic persons, who have been patients at the Manchester Royal Infirmary, bear out the above statements with respect to many of the drugs which have been employed in the treatment of the disease in that hospital. These patients, however, have generally been suffering from the most severe form of the disease, often at an advanced stage.

The following is a summary of the evidence with reference to the drugs which have been most frequently used in the treatment of diabetes.

Opium and its alkaloids.—Opium has been long employed. Dobson, in a paper published in 1779, mentioned amongst the drugs used in the treatment of the disease, Dover's powder and tincture thebaica. According to Dickinson, opium was first recommended in 1812 by Warren, who gave large doses of the drug with benefit. During the last fifty years it has been extensively used; and M'Gregor, Pavy, Seegen, Frerichs, and numerous other writers speak of the great value of this drug and its alkaloids. Years ago, Pavy ([48]) showed clearly how useful these drugs were in diminishing the sugar excretion. No one, of course, regards opium or its alkaloids as direct curative agents, except perhaps in the mildest form of the disease; but the evidence in their favour is greater than that in favour of any other drug. Sometimes, in the milder form of the disease, by this treatment, together with restricted diet, the glycosuria disappears temporarily, though diet alone is not sufficient to remove the sugar from the urine. But in most cases only a diminution of the symptoms is obtained.

The effects of opium and its alkaloids are—

1. To diminish thirst.
2. To diminish the appetite.
3. To reduce the quantity of urine.
4. To diminish the amount of sugar excreted in the urine.
5. Sometimes to increase the weight, and to improve the general condition of the patient.
6. To diminish nervous irritability.

Owing to the diminished excretion of urine, produced by the drug, sleep is undisturbed by frequent micturition.

In some cases, opium, like every other remedy, is useless; but in other cases benefit is obtained, even when the diet is not restricted. It is important to remember, however, that often

large doses of the drugs are necessary to produce good results. Diabetic patients are very tolerant of opium or its alkaloids, and can take large quantities without narcotism or any bad effects being produced; after a time, often 2, 4, or 5 grs. of opium can be taken thrice daily.

It is best to begin with half a grain of opium, or of the extract, three times a day, and then gradually to increase the quantity; or the compound soap pill of the pharmacopœia (grs. 5 = 1 gr. of opium) may be given twice a day, and gradually increased.

If the sugar can be removed from the urine completely by diet, it is, of course, not necessary to give opium; but when diet alone is insufficient to do this, then opium or its alkaloids ought to be tried.

Ralfe ([49]) has paid special attention to the treatment of diabetes by opium and its alkaloids. From his own observations he concludes that the most decided results are obtained when opium is administered by the mouth. With regard to the best time for administration—whether immediately before meals or during digestion—he has found that when taken about an hour after a meal it has a greater effect in restraining diuresis than when taken on an empty stomach; that not much difference is effected on the sugar secretion; but that the dose taken shortly after food has the advantage of not deranging the stomach or causing dyspeptic symptoms.

Ralfe prefers morphia to codeia, but states that the best results are obtained when some preparation of crude opium is added to either alkaloid. Thus liquor opii may be combined with acetate of morphia. Diabetic patients often exhibit individual peculiarities as regards the different preparations of opium. Ralfe mentions a case where codeine and morphine had to be given up on account of the headache and giddiness which they produced, whilst solid opium, in the form of compound soap pill, was taken without discomfort. In fixing the dose, it is important to remember that each patient has his own capacity for the drug. Ralfe thinks that as regards dose we err on the side of too much caution, and that as soon as the glycosuria ceases to be controlled by diet, opium should be given in doses that sensibly affect the excretion of sugar, and should be increased, until either it entirely controls the glycosuria, or until no further reduction in the amount of sugar is obtained on

increasing the dose. When this latter point is reached, then it is not wise to attempt to further increase the amount of opium. Ralfe points out the danger of suddenly reducing the dose, especially when opium has been administered for some time, in advanced cases. After opium has been administered for a long period, its good effects cease.

It is not known how opium acts in diminishing the diabetic symptoms. Minkowski thinks that perhaps it inhibits the formation of sugar from albumin. Sir William Roberts attributes the good influence of opium to its action in diminishing the appetite, and as a consequence less sugar is excreted in the urine. Also, it may produce good effects by inducing sleep and allaying painful sensations and irritability.

The effects of opium ought to be carefully watched, however. It is liable to cause obstinate constipation and dyspeptic troubles, the tongue may become thickly coated, and the patient may suffer from epigastric pains. It is sometimes necessary to discontinue its use on account of these symptoms. In cases in which coma is threatening, it is well to avoid the use of opium. In these cases, as a rule, there is constipation, which probably has some indirect connection with the development of coma, and by the use of opium the constipation is only made worse. Also, in cases complicated with nephritis, opium should be avoided or only given with caution.

As regards the form of the opium preparation, Frerichs, Sir William Roberts, Ralfe, Strümpell, and many others prefer crude opium; Bruce, Osler, and many observers prefer morphia, whilst Pavy is in favour of codeine.

Morphine.—Kratschmer ([50]), Mitchell Bruce ([51]), and others have clearly shown the value of morphine in reducing the amount of sugar in the urine in cases of diabetes. Bruce found that it acted much better when given by the mouth, than when injected hypodermically. In two cases he compared the action of acetate of morphine and phosphate of codeine, and found that the former was distinctly more powerful in reducing the glycosuria. Morphine is also much less expensive than codeine. In the cases reported by Bruce, the patient was put on a rigid diet, so that the results are due to the diet plus the drug.

If morphine be employed, it is well to begin with a small dose, one-sixth of a grain three times a day, and gradually to increase the amount. In course of time, diabetic patients are

often able to take 1 gr. three times a day, or even larger doses, without any bad effects.

Codeine.—Pavy and other observers prefer codeine to opium or morphine; but many think that it is inferior to both. Codeine should be given at first in small doses, half a grain three times a day, and gradually increased. In this way 4 or 5 grs. are often taken three times a day, without any bad effects. The advantages of codeine over morphine and opium are, that it causes less constipation, that it is less liable to derange digestion, and that it does not cause so much drowsiness. But against these advantages it is stated by Lauder Brunton, Bruce, and others, that morphia is more powerful in diminishing the amount of sugar excreted. Pavy, however, thinks that it is quite as efficacious as opium or morphia.

In a number of cases which have come under my observation, codeia has given fairly good results. I have obtained better results with opium or codeia than with any other drug.

Narcotine and narceine were found to be useless by Pavy.

Alkalies have long been used in the treatment of diabetes, and numerous cases have been recorded in which such treatment has appeared to be of service. Pavy, writing in 1862, stated that an alkaline treatment was that which had perhaps received most favour.

With reference to the alkaline treatment, it is interesting to note that the urine is generally markedly acid in diabetes, and that diabetic coma has been attributed to an intoxication with organic acids.

Alkalies may be given in the form of the mineral waters, which have been already referred to, or they may be given as medicine in the usual way. The salts which have been chiefly used are the bicarbonate, carbonate, or acetate of sodium, the bicarbonate, carbonate, tartrate, citrate, or acetate of potash, carbonate of ammonia, and carbonate of lithium. Good effects can only be expected when very large doses are given. The sodium salts are to be preferred, owing to the toxic action of potash salts in large doses, and bicarbonate of soda is the salt which has been most employed. If the patient be gouty, the carbonate or citrate of lithium will be more suitable. The dose of bicarbonate of soda ought to be large. Richardiere ([52]) recommends 60 to 150 grs. in the twenty-four hours, but some writers recommend very much larger doses.

In severe cases the alkaline treatment is useless. I have never seen improvement in this form of the disease which could be fairly attributed to alkaline treatment, except in cases of commencing coma (these cases will be referred to later). In mild forms of the disease there is a considerable difference of opinion as to the value of alkalies. Some writers believe that in these cases they have a distinct influence in diminishing the sugar excretion.

Richardiere has recently written strongly in favour of the alkaline treatment (sodium bicarbonate) in mild cases. He thinks it is better to give an alkaline course for two or three weeks every three or four months instead of continuous alkaline treatment. He believes that alkalies act by altering the general nutrition. Among contra-indications of the sodium bicarbonate treatment, he mentions pulmonary tuberculosis, cachexia, and an advanced stage of the disease.

Lime salts were employed long ago in the treatment of diabetes. Willis, writing in 1679, mentions a diabetic patient who recovered from the disease, and who was treated with lime-water, among other drugs. Quite recently, Karl Grube ([53]) has pointed out the value of calcium salts.

Robin also recommends glycero-phosphates of lime and magnesium to be given with the meals, in order to counteract the great loss of the phosphates of magnesium and calcium which occurs in diabetes (see p. 386).

Arsenic has frequently been given in diabetes during the last twenty years, and from time to time papers have been published drawing attention to its value. Experiments on animals have shown that the administration of arsenic, in sufficient doses and for an adequate time, will cause the glycogen to disappear from the liver, and puncture of the floor of the fourth vertricle is then no longer followed by diabetes. Hence there appears to be some theoretical evidence in favour of its use in diabetes; but whilst a number of observations have been published, recording improvement, a number have also been published showing negative results. Murray ([54]), a short time ago, drew attention to the value of arsenic. He believes that after the sugar has been reduced by diet and codeia, arsenic will often effect a cure. Murray's patients appear to have suffered from a mild form of the disease, however. Arsenic may be given in the form of liquor arsenicalis, and the dose gradually increased. Murray

recommends the doses to be increased until 10 minims of liquor arsenicalis are given three times a day.

Frerichs has tried hypodermic injection of arsenic, but has found it useless.

Clemens' solution, arsenite of bromine, has been largely employed in the treatment of diabetes, in doses of 3 to 5 minims once or twice a day after meals, but the evidence in its favour is not convincing. By many observers it has been found useless.

A combination of lithium and sodium arseniate, dissolved in aerated water, has been much used in France, especially in gouty cases. Dujardin-Beaumetz recommends 5 grs. of lithium carbonate, and 2 minims of Fowler's solution of arsenic in a glass of Vichy or other alkaline water. But extensive trial by others has failed to produce much evidence in favour of this treatment.

I have given arsenic a fair trial both in severe and mild forms of the disease, and have seen it tried in numerous cases at the Manchester Royal Infirmary, but cannot say much in its favour. Probably it is useless in the severe forms of the disease, but in the milder forms it is worthy of trial, after a restricted diet and opium preparations have been employed.

Jambul.—The seeds of *Syzygium jambolanum* have been recommended for diminishing the sugar excretion in diabetes, and a few years ago the drug was pretty extensively tried, but recently it appears to have been little used. It may be administered in powders, cachets, pills, or as a liquid extract. The dose of the latter is given as a half to 2 drms.; that of the powder, 5 to 30 grs.

In numerous cases the use of the drug has not been followed by any good results. In experimental pancreatic diabetes, Minkowski found that its administration did not produce any effect on the sugar excretion.

Lewaschew ([57]) states that, after giving a sufficient dose of 20·0 to 40·0 grms. daily (about 300 to 600 grs.), he has always found a decrease in the amount of urine and sugar, of the thirst and other diabetic symptoms. He thinks that the frequent failure of the drug is owing either to the dose being too small, or to the impure condition of the drug.

In a case, under the care of Dr. Steell, which I had the opportunity of watching for a long time in the Manchester Royal

Infirmary, the sugar excretion diminished markedly under the use of jambul, but the patient's general condition became gradually worse as the sugar diminished, and the case terminated fatally.

Antipyrin has been frequently employed in the treatment of diabetes during the last seven years. In doses of 30 to 60 grs. daily, according to Dujardin-Beaumetz ([58]), it diminishes the quantity of urine without increasing the percentage of sugar per litre. Robin ([59]) also employs antipyrin in his "alternating" treatment, which will be subsequently described. If the glycosuria be not modified in a few days, it is useless to continue the drug. The action of antipyrin is only temporary; it ought not to be administered for a long period, as it is liable to give rise to digestive troubles and temporary albuminuria. Many observers, however, have found antipyrin useless. I have found it apparently of service in relieving the pains in the limbs in diabetes, but have not been able to detect real improvement otherwise.

The evidence in favour of antipyrin is not therefore very conclusive. Still, it is one of the drugs which are worthy of a fair trial when diet and opium fail.

Sodium salicylate has been recommended, especially by Ebstein ([60]), and during the last ten years numerous instances of improvement, and diminution of sugar excretion under the use of this drug have been reported, whilst many cases have also been recorded in which it has appeared to be useless.

Ebstein states that its influence is greatest in recent cases. Often, however, as Fürbringer ([61]) has shown, it has no influence on the glycosuria, but it reduces the nitrogenous excretion, and in this way may be beneficial.

Ebstein recommends large doses, 75 to 150 grs. in the twenty-four hours. I have never given it or seen it given in such large doses, but in the usual doses, 10 to 20 grs. three times a day, I have not found any benefit in severe cases. Patients sometimes prefer the drug to other remedies, however, and state that they feel better when taking it.

Brunton and Ralfe think it is useful chiefly in the glycosuria of gouty persons.

It is important to remember that the urine of patients taking sodium salicylate gives a purplish brown coloration with perchloride of iron, which is liable to be mistaken for Gerhardt's so-called diacetic reaction (see p. 181).

Salicylate of bismuth.—Schmitz ([62]) of Neuenahr, who had great experience in the treatment of diabetes, has recorded four cases which show the value of salicylate of bismuth in causing the sugar to disappear from the urine in mild forms of the disease. He gives 5 decigrammes (about 7½ grs.) twice a day in powder. It is the only drug from which he has obtained marked results. I have given it a fair trial in a very mild form of diabetes, but without any good effect.

Potassium bromide is thought to be of service by v. Noorden, Osler, Saundby, and other physicians, in cases in which there is great nervous irritability or excitement. Owing to the depressing action of the potassium salt, in many cases it would be better to give sodium bromide, 15 to 20 grs. well diluted, or lithium bromide in 5-gr. doses. The bromides may be given alone or in combination with opium, in the class of cases mentioned.

Uranium nitrate.—Leconte long ago (in 1857) discovered that by the prolonged administration of this substance glycosuria was produced in animals. Hughes found that when given to diabetic patients the symptoms were diminished, but the drug does not appear to have had a fair trial, and its use was discontinued until 1895, when West ([63]) recorded three cases, and referred to others in which uranium nitrate apparently caused a marked diminution of the sugar excretion. He commences the treatment with a small dose, 1 to 2 grs. freely diluted with water, twice a day after meals. He increases the amount at intervals of a few days until its effects are produced. When given in this way no digestive disturbances are produced, and no albuminuria occurs, and the dose may be increased in some cases up to 15 or 20 grs. three times a day.

According to West, the effects of the drug are (1) to diminish thirst; (2) to reduce the amount of urine; (3) to reduce the percentage of sugar. He points out that in giving the drug it is well to discontinue it every three or four weeks, for a few days, and after that time to resume it. In 1896, West ([63]) reported five other cases in which favourable results were obtained. He concludes that we have in uranium nitrate a drug of considerable value in diabetes, though it cannot be relied upon to produce equally good results in all cases indiscriminately.

Quinine sulphates has often been given as a general tonic, but it has not been shown to have any other action. It is worthy of

careful trial when the symptoms have followed malaria, or when the patient has lived in a malarial district.

Iodide of potassium was carefully tried many years ago by Dickinson ([64]). He found that a remarkable diminution of the sugar excretion occurred when the drug caused loss of appetite and general depression, but when the appetite was scarcely affected there was very little change in the excretion of sugar or urea. He therefore concludes that the diminution of the sugar excretion which is sometimes produced by potassium iodide "is not the result of any mitigation of the disease, but of loss of appetite and general depression of function." He "has never found the saccharine diminution thus caused to be permanent, nor been able to trace to it any amelioration in the general condition of the patient."

Anti-syphilitic treatment.—It has been already pointed out that a history of acquired syphilis is not common in diabetes. Certainly, in the greater proportion of cases, acquired syphilis is not the cause of the disease, but it is probable that in a few rare instances syphilis may produce diabetes or glycosuria, either by giving rise to changes in the nervous system, by causing disease of the pancreas (see p. 113), or in some other way. When, therefore, a history of syphilis is obtained, and when there are indications of a syphilitic affection of the nervous system or of other organs, anti-syphilitic treatment ought to be prescribed. Iodide of potassium may be given in 10 gr. doses with aromatic spirits of ammonia, and mercurial inunctions should also be employed. A few cases are on record of the mild forms of diabetes, accompanied by syphilitic lesion of the nervous system, in which anti-syphilitic treatment caused great improvement. Feinburg ([65]) has reported such cases; and v. Noorden refers to twelve cases of diabetes preceded by syphilis, in two of which decided and permanent improvement was obtained by the use of mercury and potassium iodide; but in no case did complete recovery follow. v. Noorden ([66]) points out, however, that in several cases fatal complications occurred during the mercurial course—in one case, gangrene of the foot; in two, hæmoptysis and rapid progress of pulmonary tuberculosis. Hence the patient ought to be seen daily and carefully watched, as mercurial stomatitis and dysenteric intestinal catarrh are very liable to develop.

Iodoform has been strongly recommended by Moleschott,

and a number of cases have been reported which have improved under the use of this drug. Frerichs confirms the favourable reports; he has found a moderate temporary improvement. In mild cases the sugar disappeared, in severe cases it was diminished, but no actual cure was obtained, and the improvement was not permanent. On the other hand, it has often been found useless.

Oxygen inhalation has been highly spoken of, and in mild cases is said to have caused the sugar to disappear when the diet has been restricted, though diet alone and ordinary treatment have caused no improvement ([67]).

Purdy ([68]) recommends 3 to 5 gallons of oxygen to be inhaled twice daily, morning and afternoon, and has obtained "the best results" thereby—what the exact results were is not stated.

Lactic acid has been highly recommended by Cantani ([69]), but others have not found it of service. Cantani prescribed it in the form of lemonade; 5, 15, or 20 grms. of lactic acid are dissolved in 1 litre of water, and a little aromatic water, such as peppermint or anise, is added. The patient is allowed half a wine glassful of this mixture with ½ grm. of bicarbonate of soda every hour, or every two hours.

According to Cantani, pure lactic acid, given in water directly after a meal, aids the digestion of nitrogenous food, and enables the patient to take a rigid nitrogenous diet for a long period without the occurrence of the diarrhœa or gastro-intestinal disturbances which are so liable to be produced.

Benzosol has been highly spoken of, and appears worthy of further trial.

Methylene blue.—Recently Marie and Le Goff ([71 and 72]) have employed this substance in the treatment of three cases of diabetes. In two of the cases there was a gradual diminution of the sugar, and an improvement in the general condition.

Pilocarpine injections have apparently caused a diminution of urine and of the sugar excreted in some cases, but in other cases they have been found useless.

Numerous other drugs, in addition to those referred to, have been recommended from time to time by various physicians, but the evidence in favour of their use has often been simply of the *post hoc propter hoc* kind, and, on careful trial by others, generally no good results have been obtained. Amongst the drugs of this

class may be mentioned chloral, carbolic acid, sulphonal, tincture of iodine, phosphoric acid, benzoic acid, sodium benzoate, salol, belladonna, phosphorus, strychnine, valerian, Calabar bean, picric acid, sodium phosphate, peroxide of hydrogen, guaiacol, calcium sulphide, creasote, camphor, nitro-glycerine, salicin, sulpho-carbolate of soda, cocaine, ouabain, cannabis indica, ergot, etc.

Robin ([73]) has recommended an "alternating method" of treatment. (1) He first prescribes antipyrin in 15 gr. doses along with 7½ grs. of bicarbonate of soda in the form of a powder, to be taken twice a day—one hour before breakfast and dinner. He also prescribes cod-liver oil, and orders the bowels to be kept regular by the use of saline aperients. (2) On the fourth or fifth day he changes the medicine, and prescribes about 6 grs. of quinine sulphate at the mid-day meal. This is taken for six days, then discontinued for four days, and afterwards again taken for six days. Twice a day he also gives a cachet containing arseniate of soda, carbonate of lithium, and codeia. (3) After fifteen days the above treatment is discontinued, and valerian, opium, and belladonna are prescribed together in the form of a pill, or potassium bromide is given. Cod-liver oil is discontinued, and the patient is allowed a weak alkaline solution. To counteract the loss of phosphates of magnesium and calcium, he recommends the glycero-phosphates of lime and magnesium in cachets at each meal.

If sugar is still present in the urine, the course is commenced again, but, after the second course, diet only is trusted to.

Robin has treated 100 cases by this alternating method, in each of which the daily quantity of sugar excreted was 100 grms. or more. In twenty-four of these recovery has occurred, *i.e.* for six months at least after treatment there has been no reappearance of sugar in the urine. In twenty-five cases recovery is still doubtful. Sugar has disappeared under treatment, but has returned under the influence of unsuitable diet, mental excitement, etc. In thirty-three cases there has been considerable and permanent improvement. In eighteen cases the results have been negative.

Glycerine was recommended years ago by Schultzen, but it has not been found of any service by others.

Cod-liver oil is of service, especially in those cases in which the patient is wasted. Whilst it is often prescribed by some medical men, it is somewhat remarkable that its use has

not become more general in this class of cases. Lipanin may be given in place of cod-liver oil to those who object to the taste of the latter. Peach kernel oil (free from prussic acid) may also be used. It can be made into a pleasant emulsion with eggs, sweetened with saccharine, and flavoured with cinnamon. Petroleum emulsion is also worthy of a trial (see p. 338).

Pancreatic emulsion, 1 to 3 drms. in a little water and spirits, may be given once or twice a day, one or two hours after food, in cases in which there is much wasting.

Pepsin and rennet were fairly tried years ago, but were found to be useless by nearly all observers.

The action of *electricity* has been tried in diabetes, but without success.

Saccharine treatment.—Many years ago, it was believed by Piorry and others that the symptoms of diabetes were due to the loss of sugar by the kidneys, and it was thought that possibly relief might be obtained by increasing the amount of sugar in the diet in order to compensate for the loss. This method of treatment received a fair trial, and was found by nearly all observers to be injurious. The theory on which this treatment is based is of course erroneous, still nothing is more to be desired in the treatment of diabetes than the discovery of some form of sugar or other carbohydrate which the organism is capable of utilising, and which may therefore be given in place of the carbohydrates of food.

Lævulose and lactose in certain cases can be burnt up in the system, and may thus be used in moderation, in the diet of such diabetic patients, to replace the injurious carbohydrates (see p. 340).

Lepine's glycolytic ferment.—Lepine ([74]) has recorded the result of the treatment of four cases of diabetes mellitus with a glycolytic ferment prepared from the diastase of malt. In all four cases there was a distinct improvement. As regards the sugar excretion, in the first case, before treatment the mean quantity for the twenty-four hours was 140 grms., under the influence of the ferment it was 70 grms.; in the second case the sugar was reduced from 41 to 11 grms.; in the third case, from 116 to 80 grms.; in the fourth case, from 257 to 124 grms., but later only to 163 grms. The ferment is not diuretic, it has no injurious effects, but the improvement is only temporary.

Yeast is a very old remedy for diabetes, which was re-

commended many years ago, but it has not met with any definite success. Recently, I have seen a marked case with wasting in a young man, under the care of Dr. Steell, in which improvement occurred in the general condition when the usual opium treatment was discontinued and yeast taken. The dose was two dessert-spoonfuls of fresh barm, mixed with water to such a consistency that it could be easily drunk. The improvement was not permanent, however, and he finally died of coma.

I have heard of several other patients who have improved under the yeast treatment. The above dose can be readily taken, and is not particularly unpleasant. It is important to obtain fresh yeast, and to take only the frothy part; any fluid settling to the bottom of the vessel ought to be rejected. If the barm be not fresh, and if the fluid part be taken, severe diarrhœa may result.

Cassaet ([75]) a short time ago reported good results from the use of brewer's yeast.

Treatment by pancreatic preparations.—After the publication of the brilliant results of the experiments of Minkowski and v. Mering, de Dominicis, and others, on the relation of the pancreas to diabetes (see p. 73), it was only natural that those interested in the treatment of the disease should have had the best hopes that the knowledge acquired would be of great importance in therapeutics. The excellent results which have attended the use of thyroid extract and other thyroid preparation in the treatment of myxœdema, led to the trial of various pancreatic preparations in diabetes. Unfortunately the expectations have not been realised. In the first place, it was shown by the experiments of de Dominicis, Minkowski, Thiroloix, and others, that in the diabetes produced in dogs by the total extirpation of the pancreas, the sugar excretion in the urine was not diminished by injections of pancreatic infusion, whether the injections were subcutaneous, intravenous, or intraperitoneal. Also by feeding the animal on pancreas no benefit was derived.

Clinically, it has been found in most cases that pancreatic preparations have been quite useless; in a few cases some improvement has followed their administration, but whether it has been really due to the pancreatic preparations or to some other cause, remains to be decided by future observations.

Pancreatic juice has been given by Mansell Jones ([76]) and H.

Mackenzie ([77]), but there is no evidence that it caused any real improvement. Pancreatic extract has been tried with similar results by H. Mackenzie and P. Watson Williams ([78]).

Patients have been fed on raw pancreas, but the records published by Hale White ([79]) do not furnish any conclusive evidence in favour of this treatment. Liquor pancreaticus has been injected subcutaneously by Hale White, but no real benefit has followed.

Cerenville ([80]) has reported the results of the pancreatic treatment in five cases of diabetes. Four were fed on chopped sheep's pancreas in doses of 4 to 10 to 30 grms. daily. In three of these cases no improvement was detected; in one there was slight temporary improvement. The fifth case was treated with pancreas extract, injected hypodermically, but no improvement followed. Lightly cooked calf's pancreas was given by Ausset ([81]); marked improvement followed, but only one case is recorded. Bormenn ([82]) has given pancreatic preparations per rectum; the patient improved greatly, but again only one case is recorded. Various pancreatic preparations have been injected subcutaneously, and given in other ways, on the Continent, but, as a rule, without benefit. Experiments have shown that it is not the absence of pancreatic juice in the intestinal canal which causes diabetes in dogs after extirpation of the pancreas, hence it is not surprising that in most of the cases in which the pancreatic treatment has been tried clinically, the results have been negative. The prospects of success by injections of pancreatic extract appeared more promising theoretically, but clinical experience has shown them to be of no value.

Minkowski, Hédon, and others have shown that a graft of pancreatic tissue under the skin of the abdominal wall is able to prevent the occurrence of diabetes in dogs, when the whole of the pancreas has been removed from the abdominal cavity (see p. 76). In 1893 I suggested the possibility of treating diabetes successfully by grafting a piece of the pancreas of one of the lower animals under the skin of the abdominal wall in *pancreatic* diabetes in man ([83]). About that time I was treating a case of diabetes in a young man, and I was strongly inclined to try the effect of grafting a piece of sheep's pancreas under the patient's skin. A surgical friend promised to perform the operation, but I hesitated to advise it, (1) because I could not be certain that the diabetes had a

pancreatic origin in this case, and (2) I was afraid that the operation might lead to diabetic coma. The patient improved somewhat; he returned to his work, and after a few months discontinued all treatment, except that he avoided certain articles of diet. Eighteen months later he again came under my care, and finally died of asthenia and phthisis. I obtained permission to make a post-mortem examination at his home, and removed the pancreas. On examination, I found it normal macroscopically and microscopically.

Of course it is possible, but not probable, that a graft of pancreatic tissue under the skin might have been of service in this case, though no pathological changes were detected in the gland post-mortem; but when the pancreas is normal, the operation does not seem to be indicated.

The operation of grafting pancreatic tissue in man has since been performed, however. Williams ([84]) of Bristol had pieces of sheep's pancreas grafted under the skin of the breast and abdomen in a case of diabetes. Unfortunately, however, diabetic coma developed on the third day after the operation, and terminated fatally.

The two difficulties with respect to the treatment by subcutaneous pancreatic grafts are therefore (1) the absence of definite clinical indications which will enable us to diagnose with certainty when diabetes is associated with pancreatic disease; (2) the risk of producing diabetic coma by the operation.

The grafting of pieces of pancreas subcutaneously appears, however, to be the only form of pancreatic treatment from which success can be expected (judging from the results of experiments on animals); and it is possible that, in spite of the two difficulties above mentioned, the treatment may yet be found to be of service in certain selected cases of diabetes in man.

Hepatic extract.—Gilbert and Carnot ([85]) have recently tried the effect of hepatic extract prepared from pig's liver, and given per rectum as an enema. The results varied somewhat, but these observers conclude that it caused a diminution of the excretion of glucose.

The drugs, therapeutic agents, and methods of treatment which have been referred to, are those which have been chiefly used, or which have been found to be of most service. Numerous others have been recommended, but it is quite impossible to mention all. Neither is it possible to give more than a few

references to the various papers on the methods of treatment described. But since so many of these methods have not been attended with any benefit, the omission is scarcely to be regretted.

In the treatment of diabetes, attention to diet is the most important point, especially the careful regulation of the diet according to the form of the disease and condition of the patient. Attention to the general hygienic conditions is also of importance. If the patient be wealthy, if he be suffering from a mild form of the disease, and if he be in a condition suitable for travelling, a visit to Carlsbad or Neuenahr may be attended with some benefit, whatever may be the exact cause of the improvement. But the greatest caution should be observed in recommending a visit to these spas, and the cases should be very carefully selected.

As regards drugs, those which appear to be most deserving of trial are opium, codeia, morphia, arsenic, antipyrin, sodium salicylate, bismuth salicylate, jambul, uranium nitrate, cod-liver oil. Brewer's yeast also appears worthy of a trial.

From a review of the treatment of diabetes, it will be evident that what is required to enable us to combat the disease successfully is either—

1. Some new form of carbohydrate which diabetic patients can assimilate, and which can take the place of sugar and starch in the diet; or

2. Some internal remedy which will prevent the accumulation of sugar in the blood—a remedy which will enable the system to dispose of the carbohydrates in the normal manner.

Treatment of Complications and Troublesome Symptoms.

Thirst.—The relief of this troublesome symptom has been already considered on p. 362.

Carious teeth and inflammation of the gums.—For these common complications the use of a mouth wash several times a day will be found serviceable. A weak solution of boracic acid, or of borax in camphor water, may be used; or the following may be prescribed as a mouth wash:—

℞ Borax, ℥ij; boric acid, ℥i; potassium chlorate, ℥i; camphor water, ℥xx (Yeo).

A 3 per cent. solution of sodium bicarbonate is also a useful mouth wash. The teeth and gums should be kept clean by

the use of a tooth-brush; but it is very important that the brush should not be too hard, or mischief may be done by its use.

Dyspepsia is to be treated on general principles. A mixture of alkalies and hydrocyanic acid may be prescribed. I have also found frequent doses of bicarbonate of soda (10 grs.) in a teaspoonful of milk, of service. Sir William Roberts states that, when craving for food and a sense of sinking at the epigastrium are troublesome, 2 or 3 grs. of asafœtida in a pill two or three times a day often gives relief.

For gastric crises Grube recommends that the bowels should be kept regular, and an alcoholic extract of pancreas taken after the three principal meals.

Constipation.—For this troublesome symptom, Carlsbad salts, given in a tumblerful of lukewarm water before breakfast, are of service. Artificial effervescing Carlsbad salts act quite as well, and are much more pleasant to take. Other purgatives, such as castor-oil, confection of senna, aloes, or Friedrichshall or Hunyadi waters, may be employed.

For *flatulence and intestinal catarrh*, a pill containing creasote or thymol is suitable. For diarrhœa, salicylate of bismuth, 8 grs. in powder twice a day has been found very useful.

Phthisis is such a common and serious complication, especially in the severe forms of the disease, that it is most important that the diabetic patient should carefully avoid all risk of tubercular infection; and great attention should be paid to the ventilation of the rooms in which he lives and to other hygienic conditions. If phthisis should arise, then residence in a mild climate is to be preferred rather than at a high altitude. A large quantity of fatty food is especially to be recommended; and a small amount of alcohol should be given, in order to aid digestion. Creasote, cod-liver oil, and the usual drugs prescribed in phthisis may also be employed.

Itching of the skin.—Warm baths or frequent sponging with tepid water are of service in relieving this symptom. It is important also to keep the bowels regular. Potassium iodide has been recommended internally. Seegen thinks that potassium bromide is sometimes useful. When the symptom is very troublesome, the calcium chloride treatment recommended by Savill for general pruritus is worthy of trial—

℞ Calcii chloridi, 20 to 40 grs.; tinct. aurantii, ℥i; aquæ chloroformi, ʒi; t.d.s.

Pruritus and eczema of the vulva.—It has been already mentioned on p. 223, that both these conditions are due to the irritation of the saccharine urine, and often crusts containing fungus mycelia and spores are found on the external genital organs. To prevent the development of these troublesome symptoms, the patient ought to be advised to dry the external orifice of the urethra and surrounding parts with lint, or, better still, with absorbent wool, directly after each act of micturition. If eczema has actually developed, then the use of remedies which prevent the fermentation of sugar is found most beneficial. Boracic acid ointment is often of great service; or the parts may be washed with a warm, freshly made, saturated solution of boracic acid, and, after careful drying, zinc ointment should be applied (Saundby). A lotion containing sodium hyposulphite, 1 oz. to 40 oz. of water, is also a favourable remedy. Lawson Tait recommends an ointment composed of 10 grs. of potassa sulphurata to 1 oz. of benzoated lard. He has obtained the best results from this ointment along with opium internally.

Hebra's unguentum diachylum has been found useful in obstinate cases by Seegen.

Eczema of the prepuce.—To prevent this complication, the patient ought to dry the end of the penis after each act of micturition with lint or antiseptic wool. If eczema has actually developed, boracic acid ointment or boracic acid lotion may be employed.

Cystitis.—When this rare complication occurs, it may be treated in the usual way, by washing out the bladder with boracic acid solution (15 grs. to the oz.), or with a weak solution of sodium salicylate (30 grs. to the oz.), in each case the solution being made lukewarm by the addition of hot water before being used. Internally, sodium salicylate, salol, or boric acid may be given.

Boils and carbuncles.—In addition to the attempt to remove sugar from the urine by the dietetic and usual medicinal treatment, moist compresses of lint, soaked in a mild antiseptic such as boracic acid, should be applied locally; or an antiseptic poultice may be applied. The latter is made by adding 2 drms. of pure carbolic acid to 10 oz. of boiling water, and immediately afterwards stirring in linseed meal. Quinine in 3 gr. doses four times a day may be given internally.

Operative interference should be avoided, if possible, on account of the danger of exciting coma thereby; also, if chloroform be administered, there is the danger of the narcosis itself, owing to the depressing action on the heart. Hence, ether narcosis is to be preferred, if an operation should be necessary.

Gangrene.—The dietetic and medicinal treatment for diabetes ought always to be enforced. As regards the local treatment, König ([86]) and others point out that the chief indications are to make the gangrenous parts dry and aseptic, if possible. All moist dressings are to be avoided. The parts are to be dressed with iodoform and wool, and access of air allowed. If cellulitis be present, free incisions should be made. König points out that amputation may be necessary in diabetic gangrene in two conditions—(1) when, in spite of energetic antiseptic treatment, the cellulitis increases, and fever continues; (2) when the glycosuria persists in spite of anti-diabetic treatment, and coma is threatening.

Godlee ([87]) points out that, when diabetic gangrene is associated with extensive atheroma, the arterial changes will probably extend as high as the knee. In these cases, if the gangrene should be progressing rapidly, he advises amputation, but not lower than the knee; when the gangrene is due to neuritis (see p. 226), he does not advise amputation, or, if amputation be performed, it should be below the knee.

Corns.—Unless it is absolutely necessary, corns ought not to be cut, since any skin irritation or wound produced might lead to the formation of troublesome trophic ulcers, perforating ulcers, or to superficial gangrene.

All operative treatment should, as a general rule, be avoided, or should only be performed when absolutely necessary, since wounds heal badly, gangrene is liable to occur, and there is the danger of the operation being followed by diabetic coma. The operation for diabetic cataract is an exception to the above statement.

For *sleeplessness*, sulphonal, chloralamide, opium, etc., may be given. When there is much nervous excitement, potassium bromide is very useful.

In the rare cases in which *œdema* of the legs or other regions occurs, apart from the presence of any kidney complications, rest in bed is very successful in removing the

anasarca. Internally, perchloride of iron may be prescribed (Dickinson).

For the troublesome gnawing pains in the legs I have found antipyrin useful (10 grs. in 1 oz. or ½ oz. of peppermint water, three times a day).

For neuralgia and sciatica the usual remedies may be employed.

If diabetes is associated with very marked arterio-sclerosis, iodide of sodium should be given internally, and the bowels kept quite regular by frequent purgatives.

When *nephritis* (parenchymatous or interstitial) occurs as a complication, then a rigid nitrogenous anti-diabetic diet must not be prescribed. Only a medium quantity of nitrogenous food should be allowed; milk in large quantities is indicated; fatty food may be taken freely. All saccharine food must be avoided, but a limited amount of carbohydrate in the form of bread may be allowed. Ordinary drinking water and alkaline mineral waters may be taken freely. Opium, morphia, or codeia ought not to be prescribed. An alkaline treatment with potassium or sodium citrate appears the most suitable. The bowels should be kept freely open.

Treatment of Diabetic Coma.

The exciting causes of diabetic coma have already been pointed out (p. 272), and by bearing them in mind we obtain several hints as to the mode of life, etc., best calculated to prevent the onset of this complication.

When the urine gives a marked reaction with perchloride of iron, especially if the patient be wasted, and under the age of thirty, there is a great risk of coma developing; and, as already pointed out on p. 273, in such cases the diet ought not to be too rigid. A sudden complete withdrawal of carbohydrates might lead to coma; also a *sudden* change from a rigid diet to an ordinary diet sometimes has the same effect. Hence any change in either direction ought to be gradual.

The danger of a long railway journey and of over-exertion has been pointed out (see p. 273).

Prolonged constipation ought also to be avoided, since it is probable that it acts as an exciting cause.

When the earliest symptoms of diabetic coma have made

their appearance, the patient should, of course, be confined to bed. It is advisable to increase the carbohydrates in the food if the diet has been rigid previously. Schmitz ([88]), Grube ([98]), and others have pointed out that sometimes, in cases presenting symptoms of early coma, an increase in the amount of carbohydrate food—by the addition of a moderate amount of white bread and a small quantity of potatoes to the diet—has been followed by the disappearance of these symptoms. The quantity of flesh meat, eggs, and other forms of nitrogenous food ought to be diminished. Fatty food is especially indicated, and cream in large quantities is the best article of diet. Milk may also be allowed in moderate quantities.

A considerable amount of alcohol, given in small quantities at a time, is advisable, not only as a stimulant, but also as an aid to the digestion of fatty food.

Hirschfeld ([90]) recommends glycerine (100 to 150 grms.) daily, in black coffee, in order to diminish the acetone formation.

v. Noorden thinks that, when the patient has been taking *large* quantities of carbohydrates before the onset of coma, they ought to be diminished and replaced in part by albuminous and fatty food.

If constipation is present,—and this is usually the case,—it is important to relieve the bowels, but drastic purgatives ought to be avoided (see p. 273). Mild purgatives and enemata are best. Schmitz prefers castor-oil; if this should prove useless, calomel or compound jalap powder may be given. Schmitz has recorded cases which appear to demonstrate the importance of the relief of constipation (by castor-oil) in the treatment of diabetic coma. In some of his cases, the early symptoms disappeared after the constipation had been relieved.

Cardiac stimulants are indicated when the heart is failing: they are of most service in the third form of diabetic coma, which appears to be due to degeneration of the cardiac muscle (see p. 281). Ether, ammonia, digitalis, and alcohol are useful in such cases.

The patient ought to be allowed to drink large quantities of water, in order to wash out the tubules of the kidneys.

The inhalation of oxygen appears to be worthy of trial, and several cases have been reported in which it has apparently been of slight service. In one case it is stated that consciousness was restored by the inhalation of oxygen for

five minutes, and the patient lived for two months afterwards.

It has already been pointed out that many observers are of opinion that diabetic coma is due to an acid intoxication, and to counteract the effects thereof, alkalies have been often recommended. There appears to be some evidence in their favour, and as we know of no more satisfactory treatment, it is advisable to give alkalies a fair trial in all cases. The alkalies most suitable are the bicarbonate and citrate of soda and citrate of potash. Of these the sodium salts are to be preferred, since very large doses can be given without any risk of toxic effects.

In a case of diabetes of the most severe form, which was under my care twelve months ago, alkalies appeared to be of service. The patient was twenty-four years of age; he was very much wasted; and the urine was loaded with sugar (3000 to 4200 grs. being excreted daily). Four months after the onset of his symptoms he rapidly became much weaker, the urine gave a dark brownish red coloration with perchloride of iron, and a small quantity of albumin was present. He began to suffer from nausea and vomiting, a deposit of casts appeared in the urine, he became drowsy, and the breathing became deep and laboured. The symptoms pointed to the onset of diabetic coma. I prescribed 30 grs. of bicarbonate of soda every three hours (to be taken in a little milk), and 100 grs. of citrate of potash three times a day. The nausea and vomiting ceased, and the drowsiness passed away; the casts disappeared from the urine; the patient improved, and lived for one month after the disappearance of these early symptoms of diabetic coma.

In a case which I had the opportunity of observing at the Manchester Infirmary under the care of Dr. Leech, large doses of citrate of potash were prescribed by Dr. Reynolds ([91]), who was then resident medical officer, with the result that the early symptoms of coma, drowsiness, and dyspnœa passed away, and the patient lived for twelve months longer.

Huchard ([92]) records a case in which premonitory symptoms of diabetic coma had appeared, but after the administration of large doses of bicarbonate of soda (10 drms. daily) the symptoms disappeared.

Cases similar to those just referred to have been recorded from time to time. It is impossible, of course, to definitely prove that fatal coma would have followed if the alkalies had

not been prescribed; but such cases indicate the desirability of giving alkalies a trial. Unfortunately, however, the comatose symptoms usually advance to a fatal termination in spite of similar alkaline treatment.

Huchard recommends sodium bicarbonate (2 to 10 drms. daily), especially when hyperacidity of the stomach contents is present. v. Noorden recommends 90 to 120 grs. of sodium bicarbonate daily, to be taken in one or two bottles of Vichy or Neuenahr mineral water. If there should not be any marked hyperacidity of the stomach contents, probably the formula given by Yeo is as satisfactory as any—4 drms. of sodium bicarbonate, 2 drms. of citric acid, 5 oz. of water flavoured with a little saccharine and essence of lemon. The whole of this mixture should be taken once or twice daily in frequent doses.

Intravenous injections.—During the last ten years, intravenous injections of alkaline fluids have been often recommended in diabetic coma, especially by those physicians who believe that the condition is due to the presence of an abnormal acid in the blood (acid intoxication). Others have recommended the injection of a solution of sodium chloride and phosphate, or even of sodium chloride alone. The treatment by intravenous injections has now had a fair trial, and from the records in medical literature, and from what I have seen of the method at the Manchester Royal Infirmary, I think there is evidence (1) that when properly performed, intravenous injections have often a decided beneficial effect; but (2) that these results are only temporary, and that the fatal termination is not prevented. After an intravenous injection the pulse often improves, the colour of the face is better, the slight cyanosis disappears, the coma is less, and the patient can be more readily roused. Often, when the patient is quite comatose and collapsed, and a speedily fatal termination has appeared imminent, an intravenous injection has caused decided improvement, and life has been prolonged for twenty-four hours, though the patient has not recovered consciousness. Occasionally a patient who has been quite unconscious before, has recovered consciousness after the injection, and remained conscious for several hours. But even in the most successful cases, in the course of a few hours the coma again becomes profound, and death occurs. Osler (93) states with respect to the results of intravenous injections, that "of seventeen cases collected by Chadbourne, in only one was it

successful; in seven there was temporary improvement." It is not stated whether the coma disappeared permanently in the one case. I am not acquainted with the record of any case in which there was permanent recovery from deep coma after intravenous injections. Nevertheless it may be sometimes very desirable, for various reasons, that a return of consciousness should be produced for a few hours, if possible, and in such cases intravenous injections are advisable.

In one case which I have seen, the patient had become quite unconscious, but after an intravenous injection of 3 pints of 0·75 per cent. solution of sodium chloride there was a distinct improvement in the pulse and general condition. The profound coma disappeared, and though the patient was in a drowsy condition she was able to answer questions intelligently for twelve hours, then she became quite comatose, and death occurred. In another case there was improvement in the pulse and general condition, but no recovery of consciousness, after an intravenous injection of a similar salt solution. In a third case an injection of a solution of sodium carbonate, chloride, and phosphate was followed simply by slight improvement of the pulse. In a fourth case there was no improvement after an injection of salt solution. The solution injected consisted of 4 drms. of sodium chloride dissolved in two pints of water. This is mixed with an equal quantity of warm water immediately before being injected.

Fagge (94) records a case in which an intravenous injection of 26 oz. of a solution of sodium phosphate and chloride, having a specific gravity of 1020, was followed by return of consciousness, but thirty-two hours later the patient again became drowsy, and death occurred. v. Noorden (95) mentions a case in which very marked improvement followed the intravenous injection of 1 litre of an 0·6 per cent. sodium chloride solution (four times 250 c.c., at intervals of three hours); the patient regained consciousness, and marked diuresis was produced. The improvement was only temporary, however. Dickinson has observed a return of consciousness after the intravenous injection of 456 oz. of a solution of potassium chloride, sodium carbonate, sodium phosphate, and sodium sulphate.

The intravenous injection of a 3 per cent. sodium bicarbonate solution has also been used. Hesse (96) has recorded a case of diabetic coma in which decided improvement followed the intravenous injection of a 4 per cent. solution of sodium carbonate.

The patient relapsed, however, into a state of coma, but was again relieved by a second injection; after twenty-four hours he became comatose and died.

Lépine (97) records the results of intravenous saline injections in a case of diabetic coma. The patient regained consciousness for several hours. Before the onset of coma the urine gave a marked reaction with perchloride of iron; no albumin was present; 9 to 10 litres of urine were passed daily, and the amount of sugar was 48 to 55 grms. per litre. The first symptom of coma was deep respiration. Sodium bicarbonate (25 grms. in the twenty-four hours) was prescribed. Next day the patient felt much worse; coma developed, and became complete. The eyes were closed, the pupils very contracted; the respirations were 28 per minute, and very deep. The breath had the characteristic odour of acetone. The pulse was very feeble, and the pulse-beats 124 per minute. The temperature was subnormal. A solution was prepared, consisting of 7 grms. of chloride of sodium and 10 grms. of bicarbonate of soda, dissolved in 1 litre of sterilised water. Two litres of this solution, at a temperature of 38° C., were injected into a vein of the arm in less than a quarter of an hour. Whilst the fluid was being injected the pulse became stronger, and the respiration less deep; at last the patient opened his eyes, and asked to drink; 50 grms. of bicarbonate of soda dissolved in water and wine were given to him in the course of a few hours. Four hours after the injection the patient still remained conscious. The urine was very acid, pale, and scanty. Three hours afterwards the patient became unconscious. After the coma had continued eight hours, death occurred. In the case recorded, the patient took altogether 90 grms. of bicarbonate of soda by the mouth, and 20 grms. were given by intravenous injection. The urine remained very acid in spite of the great quantity of alkali introduced into the system. In another communication Lépine (98) states that he has never known any case of diabetic coma recover. In order to have any prospect of success, he thinks that the injection of alkaline fluids ought to be made before the patient becomes comatose, that is, when the prodromal dyspnœa first appears. He records two cases in which early injections were made. The first case was that of a boy, æt. 16, who suffered from a very severe form of diabetes. The urine gave an intense reaction with perchloride of iron. Large doses of bicarbonate of soda internally (30

grms. daily) produced no effect. As the condition was becoming worse, 2 litres of a solution containing 7 grms. of sodium chloride and 10 grms. of bicarbonate of soda per litre, were injected subcutaneously—under the skin of the abdomen. The condition of the urine remained practically the same; no improvement occurred; symptoms of commencing coma appeared, and the patient was removed from the hospital by his parents. The second case was that of a man, æt. 37, who also suffered from a severe form of the disease. Whilst under treatment, aceto-acetic acid appeared in the urine, and the general condition became much worse. He became restless, and a marked augmentation of the respiratory movements was noticed. An intravenous injection of 2 litres of the above solution was made. After the injection the quantity of urine increased slightly, and at least three times the quantity of acetone, aceto-acetic acid, and oxybutyric acid was excreted. Thus the injection caused abundant elimination of these toxic substances. Next day there was improvement of the general condition and diminution of the quantity of urine excreted. Twenty-nine days later the patient was shown at the Lyon Medical Society, the improvement having continued.

The small operation of intravenous injection can be easily performed, just in the same way as transfusion of salt solution in cases of hæmorrhage, etc. All the apparatus necessary is a funnel and piece of india-rubber tubing with clips and cannula. One of the veins in front of the elbow is exposed, and the cannula inserted. It is important that the fluid used should not be cold. The solution of sodium chloride or sodium bicarbonate is mixed with an equal quantity of warm water just before being transfused. Lépine recommends that the fluid injected should have a temperature of 38° C. The fluid is apt to become cold if kept for a long time in the funnel whilst the vein is being exposed. Hence it is better to expose the vein first, before placing the warm fluid in the funnel and tubing. In place of a funnel a vessel may be used which has a cover, the fluid flowing from the lower part. [For details respecting the operation of transfusion, see surgical works, and article by Jennings, *Brit. Med. Journ.*, London, February 8, 1896.]

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APPENDIX.

In Chapter XIV. the dietetic treatment of diabetes has been discussed, and the class of cases pointed out in which a rigid diet is contra-indicated. The following is a list of articles of diet and beverages, arranged in a tabular form, which ought to be sanctioned or forbidden, when for diagnostic or therapeutical purposes a very strict diet is desirable:—

Articles of Food in Diabetes.

Sanctioned.	*Forbidden.*
Butchers' meat of all kinds (except liver); potted and preserved meats.	Sugar; saccharine and farinaceous articles of food.
Ham, tongue, bacon.	Pastry and farinaceous puddings.
Poultry, game.	
Fish (fresh, dried, and preserved); sardines, shrimps.	
Broths, animal soups, and jellies (prepared without the addition of saccharine or starchy materials).	Rice, sago, arrowroot, tapioca, macaroni, vermicelli, semolina.
	Potatoes.
Eggs, cheese, cream.	
Butter, suet, oils, and fats.	
Custard (without sugar).	
Reliable bread substitutes (gluten bread, almond and aleuronat cakes).	Wheaten bread and biscuits.
Green vegetables—mustard and cress, watercress, endive, lettuce, spinach, turnip-tops, cabbage, broccoli, Brussels sprouts, spring onions.	Carrots, turnips, parsnips, beetroot, beans, peas, large onions.
	Liver.
Cucumber.	Oysters, cockles, mussels, the "puddings" of crabs and lobsters.
Mushrooms.	
Pickles (cucumber, walnuts, and onions).	Honey.
Nuts (walnuts, almonds, filberts, hazel nuts, Brazil nuts), but not chestnuts.	All sweet fruit and dried fruits.

BEVERAGES.

Sanctioned.	*Forbidden.*
Water, soda-water, and mineral waters	Port, Tokay, champagne, and sweet wines.
Tea, coffee.	Must, fruit juices and syrups.
Dry sherry, claret, Burgundy, hock, Moselle, Ahr wines, most Rhine wines, Austrian and Hungarian table wines (all in moderate quantities, however).	Sweet lemonade.
	Liqueurs.
	Beer, ale, porter, and stout.
Brandy in small quantities.	Rum and sweetened gin.
	Cocoa and chocolate.
	Milk in large quantities.

The diabetic dietaries recommended by most authors agree generally with that just given, but the following are minor points of difference:—

SIR WILLIAM ROBERTS (1) adds "torrified" bread and celery to the articles sanctioned.

PAVY (2) sanctions also turnips, French beans, cauliflower, asparagus, and vegetable marrow, but only in moderate quantity, and when boiled in a large amount of water; also radishes and celery.

SEEGEN (3) allows the following in moderate quantities: – Cauliflower, carrots, turnips, white cabbage, green peas, berries (such as strawberries, raspberries, currants); also oranges and almonds. But he forbids other fruits, such as grapes, cherries, peaches, apricots, plums, and all kinds of dried fruits.

In addition to the articles mentioned, v. NOORDEN (4) sanctions mussels, oysters, lobster, cauliflower, spinach, onions, leeks, asparagus, sorrel, French beans. He also allows the following (amongst other articles), but only in very limited quantities:—Celery, green peas, beans, carrots, mushrooms, radishes, two medium-sized tomatoes, a thin slice of cocoanut, a thin slice of melon, one small acid apple, one or one and a half peach, one tablespoonful of wild raspberries or strawberries, four spoonfuls of currants, six greengages, twelve cherries, half a medium-sized pear.

CANTANI (5) prescribes a very rigid diet of nitrogenous and fatty foods only. He allows—

Bouillon of various kinds.

Beef, tongue, veal, mutton (but liver is forbidden), duck, goose, chicken, pigeon, and game of all kinds.

Fish, crustacea, lobster, crabs.

In the cooking and preparation of the above he forbids the use of flour sugar, wine, butter, vinegar, and lemon juice; but he sanctions the use of olive oil and fats, and recommends dilute acetic acid in place of inegar, and citric acid in place of lemon juice.

CANTANI allows 500 to 600 grms. of nitrogenous food daily. In order to improve the digestion, and to increase the strength of emaciated patients, he recommends 60 to 200 grms. of pancreatic fat. The fresh pancreas of a cow, calf, or lamb is cut into small pieces, and mixed with pig's suet. After three hours it is lightly roasted.

The beverages which he allows are ordinary drinking water, or seltzer water, with the addition of 10 to 30 grms. of rectified alcohol daily, and small quantities of aq. fœnicul., aq. cinnam., aq. menth., etc.

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