Diagnosis and treatment of diabetes mellitus / by O. Leyton.

DIAGNOSIS AND TREATMENT OF DIABETES MELLITUS

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FIFTH EDITION

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BY

O. LEYTON, M.D., D.Sc., F.R.C.P.

PHYSICIAN TO THE LONDON HOSPITAL

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PREFACE.

THE object of this book is to assist diagnosis and treatment of diabetes mellitus, therefore statistics and theories have no place in it. Knowledge is no man's proprietary article, and anyone who makes an addition to knowledge should consider the deed sufficient honour; for this reason references are not made to those who claim priority of observation. There is yet another reason for avoiding references, namely the impossibility of searching the vast literature to determine who really possesses priority. In 1904 I published a paper upon the negative pressure treatment of empyema which was original, and which I believed to be novel, and it was not until years later, after many had re-invented this method, that I discovered that in 1892 a paper had appeared upon the same subject.

When a physician undertakes the treatment of a patient suffering from diabetes mellitus he should put to himself the question: "What is my ideal? Do I hope to cure this case or do I hope to keep the patient alive for many years and preserve him from development of the complications of the disease, or am I going to order him the standard treatment and trust to luck?"

If the physician has the highest ideal and intends to give his patient the best possible chance of recovery, he will have to obtain the closest collaboration, for without it, any attempt is bound to fail.

It is a pity that medical etiquette loads the dice against the qualified practitioner in competition with the quack in the treatment of certain diseases. Take,

for instance, the treatment of obesity. The quack can demand a cash fee for treatment extending over a certain time into the future, whilst the physician can only charge a fee for each consultation. The patient will feel that he has wasted money if he does not avail himself of all the benefit paid for, and therefore will attend his adviser weekly and perhaps confess to having broken rules and be controlled quite efficiently, whilst if the same patient had to make confession and perhaps be reprimanded and pay another fee, he would avoid visiting his adviser. If the physician could demand a fee for the treatment of diabetic patients for six months, it would give him much greater control and allow him to see his patient at comparatively short intervals without laying himself open to the uncomfortable charge of attempting to exploit his patient.

The physician must decide to what extent his patient will assist him. If he refuses to be a total abstainer, all idea of recovery must be abandoned. The best that can be done will be to prevent progress of the disease and to guard the patient against complications.

If the patient will not submit to occasional examination of the blood, all that the physician can hope to do is to retard the progress of the disease. It is not a bad custom to tell the patient who refuses to follow the advice of his physician that it would be wise for him to seek a physician who will give him advice which he can follow.

O. LEYTON.

London, W. 1 ;
December, 1933.

DIABETES MELLITUS.

DEFINITION.

The name "Diabetes Mellitus" conveys different meanings to different individuals; meanings so different that it does not seem possible to reconcile them, and to formulate a definition which will be acceptable to all. This difficulty is inherent in any disease named after the most striking signs and symptoms which develop in the sufferer, and for this reason during recent years there has been a tendency to abandon names of that type and to replace them by terms designed to denote the pathological conditions which cause, or are associated with, the signs and symptoms. The objection to this latter procedure is that it assumes that our knowledge of pathology is accurate and complete and therefore unalterable; an assumption in no way justifiable.

After long consideration I have been driven to the conclusion that, in spite of the numerous and obvious disadvantages of naming a disease after a man who has described it, nevertheless, this course is the wisest, because it does not introduce any assumptions. For instance, the name "Addison's Anæmia" does not assume that the disease is due to sepsis, to achlorhydria, to hæmolysis, the absence of an unknown ferment, or any other cause, but every skilled physician is aware of

all the signs and symptoms of the disease, and how to make a differential diagnosis.

If a disease be called after the symptoms, a contradiction in terms must occur frequently, such as exophthalmic goitre, with neither protrusion of the eyes nor enlargement of the thyroid. We introduce a contradiction in terms when we call a disease "diabetes mellitus", since a large percentage of patients suffering from that disease never at any time during the course of the disease develop polyuria. It might be argued that, although the signs and symptoms are absent near the beginning of the disease, they will develop during its progress, but this is not invariably the case. Just as patients may have passed through all the stages of Graves' disease and died of that disease without developing a large thyroid or protrusion of the eyes, so too, diabetic patients may die in coma without at any time having had polyuria.

That authorities are not agreed upon the meaning of the name "diabetes mellitus" is shown by reference to the definitions in a few of the recognized text-books. At random I have chosen seven :—

Graham, 'Price's Text-book of Medicine' :

"Diabetes mellitus is a disease in which metabolism of carbohydrates together with that of proteins and fats is disturbed. The obvious signs of this are the presence of sugar and acetone bodies in the urine."

Poulton, 'Taylor's Medicine' :

"Diabetes mellitus is a disease characterized by the persistent passage of sugar (glucose or dextrose) in the

urine. Defective action on the part of the islands of Langerhans is the cause of the disease, and the regular administration of insulin is the appropriate remedy for it. The passage of sugar or glycosuria is often accompanied by the passage of large quantities of urine or polyuria to which, as the prominent symptom we owe the name (διαβαινω—I go through). Polyuria without glycosuria arises in many conditions, and a special form known as diabetes insipidus is described later."

Tidy, ' Synopsis of Medicine ' :

" Diabetes mellitus. A condition due to pancreatic deficiency producing chronic abnormality of the carbohydrate metabolism, and characterized pathologically by hyperglycæmia and by long continued glycosuria, and clinically by thirst, polyuria, emaciation and tendency to coma."

Elliot P. Joslin, ' Nelson's Loose-leaf Medicine ' :

" Diabetes mellitus is a disease which is characterized by the presence of glucose in the urine (glycosuria) and an increase of sugar in the blood (hyperglycæmia). It is dependent upon a deficiency of the secretion of insulin caused by functional or organic disease of the islands of Langerhans of the pancreas."

H. Rawle Geyelin, ' Cecil's Medicine ' :

" Diabetes mellitus is a metabolic disease characterized by deficient production of insulin by the pancreas. Since normal oxidation of carbohydrate is impossible without this substance, such loss of pancreatic function causes an increase in the concentration of sugar in the

blood (hyperglycæmia) with consequent secretion of excess of sugar in the urine (glycosuria)."

"With this disorder of carbohydrate metabolism disturbances of protein and fat metabolism are frequently associated."

McCrae, 'Osler Medicine':

"A disease of metabolism, especially of the carbohydrates in which the normal utilization of carbohydrate is impaired with an increase in the sugar content of the blood, and consequent glycosuria. There is a tendency to subsequent disturbance of the fat metabolism with resulting ketosis."

A. A. Steven, 'Practice of Medicine':

"Diabetes mellitus is a chronic disorder of metabolism involving primarily the carbohydrates, and secondly also the proteins and fats and characterized clinically by hyperglycæmia, glycosuria, polydipsia, polyuria, emaciation and a pronounced tendency to an acid intoxication, resulting in coma".

Of these seven, four state that diabetes mellitus is insufficiency of the β cells of the islands of Langerhans, in other words, subinsulism, whilst the other three do not limit the pathological lesion to the pancreas.

The definition for the purpose of this book is, "*Diabetes mellitus is a disease due to a progressive deterioration of metabolism, primarily of that of carbohydrates, and secondarily of that of proteins and of fats. This alteration in the metabolism may progress steadily, sporadically or fulminatingly, and may by medical treatment be arrested or even reversed.*"

DIAGNOSIS.

General Examination of Patient.

When the patient presents himself for examination a detailed history should be taken. It is of interest to note whether any relatives suffer from diabetes mellitus, and to inquire into the evidence that proved that they had that disease and not glycosuria due to a low renal threshold for dextrose. This latter peculiarity is inherited more frequently than diabetes.

The next series of questions should be designed to find out whether the patient has had symptoms, and, if not, to determine when the glycosuria from which he is alleged to suffer was first observed.

Often one is able to learn that glycosuria must have been absent at a definite time when the patient either made application for life insurance, or for some post which necessitated a medical report upon the state of his health.

Many cases of low renal threshold for dextrose are congenital, and although the renal threshold for dextrose is not fixed in an individual for the term of his life, nevertheless the probability of the patient having glycosuria due to a low renal threshold for dextrose is diminished by the fact that at one time he had no glycosuria.

If the diagnosis has been based upon the fact that the urine reduced Fehling's solution the possibility of that reduction being due to some substance other than dextrose must be considered.

He should be asked whether he is abnormally thirsty, or has suffered from thirst at any time, also whether he is passing a greater volume of urine than in the past. The recent acquisition of the habit of passing water during the night suggests polyuria, but the polyuria need not be due to diabetes mellitus.

Loss of weight is very suggestive provided the diet of the patient has not been restricted.

An alteration in the regularity of the bowels is of importance too; the majority of diabetics develop constipation.

Cramp in the legs is a less known symptom; too much importance must not be attached to it, because many individuals who have no glycosuria suffer from cramp.*

The complexion of the patient should be noted; the majority of diabetics, especially those of middle-age, have a characteristic pink colour. The pinkness extends over the areas which are white in the normal healthy individual. Frequently in severe diabetes, and especially in patients who have been ordered large quantities of vegetables, the face is yellow, due to an excess of carotene in the blood. The yellowness is very obvious on the soles of the feet and the palms of the hands. A pallid complexion indicates an insufficient diet in diabetes mellitus, and it is in no way characteristic of the complaint.

The patient should be subjected to a detailed physical

* It is of interest to note here that in some cases of cramp insulin given before the time of going to bed may prevent an attack during the night, even when there is no tendency to diabetes.

examination, special attention being given to the discovery of some source of infection, and therefore the teeth and gums should be examined with care, the throat, tonsils, antrum, and if there be any discharge from the nose the patient should be sent to a rhinologist for him to decide whether there is any evidence of any sinuses being infected.

The patient should be asked whether he has any boils or infections of the skin anywhere. If he suffers from hæmorrhoids they should be examined.

The urine should be centrifugalized and the sediment microscoped to determine whether the kidneys or bladder are infected. The usual physical examination of the chest should be conducted, and if there be any signs of abnormality it is wise to have a skiagram taken. Tuberculosis is not uncommon in diabetes mellitus, and remarkable to relate, apparently the changed metabolism prevents the usual pyrexia, and therefore makes the diagnosis of pulmonary tuberculosis in the early stage quite difficult. It is important to note whether the tubercle bacillus is winning against the patient, because the energy in the diet should be great if the patient has to fight the bacillus of Koch. The abdomen should be examined and special attention paid to the region of the pancreas to see whether any tumour is palpable. The size of the liver should be noted, and if enlarged the possible diagnosis of hæmochromatosis should be considered. The heart should be examined and the pulse-rate noted. If there be any tachycardia without any valvular disease of the heart, the thyroid should be palpated, and if enlarged it may be auscultated. Bruit in the thyroid indicates over activity, and it is always

possible that loss of weight and glycosuria may be due to hyperthyroidism, rather than sub-insulism.

The patient's eyes should be examined to see whether there is any diminution of the fields of vision, and the fundi should be looked at with the object of determining whether there is any evidence of an intracranial tumour. Many changes in the content of the cranium, in addition to growth of the pituitary gland may cause glycosuria. It is only when one fails to find any physical signs of disease that one feels justified in concluding that progressive hyperglycæmic glycosuria is diabetes mellitus. The blood pressure should be recorded and the arteries examined as far as possible in order to determine whether any degenerative process is at work. The nervous temperament of the patient should be investigated because there can be no doubt that anxiety plays a direct part in the metabolism of carbohydrates. It is a well-known saying, that on Wall Street when the stocks go down, sugar goes up. Other observers with any experience must have noted amongst their patients that anxiety increases glycosuria.

During the Great War a patient of mine, who was also a very old friend, used to develop glycosuria, although she kept strictly to her diet, if the intervals between letters from her son in France exceeded three days. The arrival of a letter saying that all was well removed her glycosuria for a period.

The diagnosis of diabetes mellitus is occasionally extremely difficult. In many ways it is comparable with the diagnosis of pulmonary tuberculosis. In most adults the bacillus of Koch has caused changes in the lungs, but the patient is suffering from pulmonary

tuberculosis only when the damage to the lung is progressive, the tubercle bacilli multiplying and destroying tissue. Those physicians who are actuated by an uncontrollable urge to succeed, place expediency before truth, and teach that if pulmonary tuberculosis be suspected it is wise to diagnose its presence, because, should the patient be sent to a sanatorium and lose his symptoms, it will be assumed that he has been cured; whilst if he develops pulmonary tuberculosis at any time in the future the credit will go to the physician who was the first to make the diagnosis.

The conscience is salved by the thought that several months in a sanatorium will do no harm even if unnecessary.

Similar argument has been applied to cases suspected of diabetes mellitus. My view is diametrically opposed to this; no patient should be labelled diseased unless there is definite evidence. In cases suspected of diabetes mellitus it is wiser to wait until the evidence is conclusive and then treat vigorously rather than to diagnose on the offchance, and unnecessarily hamper the life of an individual for an unlimited period.

That the presence of glucose in the urine is not synonymous with diabetes mellitus is gradually being recognized by practitioners of medicine. Less than thirty years ago the following conversation was asserted to have taken place between the husband of a patient and her medical adviser:

HUSBAND: "Are you sure that my wife is suffering from diabetes mellitus, because she seems to enjoy so much better health when her diet is not restricted?"

MEDICAL PRACTITIONER : " Has your wife got sugar in her urine ? "

HUSBAND : " Yes."

MEDICAL PRACTITIONER : " Then she has diabetes mellitus and must stick to her diet."

Dogmatism, the blind offspring of conceit out of ignorance, does not flourish on the present day diet of scientific investigation. Patients presenting glycosuria must be investigated before a conclusion is drawn that they are suffering from any disease. Nearly 2% of glycosurics have the peculiarity of a low renal threshold for glucose ; a peculiarity which, as far as we know, is even less important than having six fingers on one hand.

The condition of glycosuria without excess of sugar in the blood has been termed " diabetes innocens ", " renal glycosuria ", " orthoglycæmic glycosuria ".

ORTHOGLYCÆMIC GLYCOSURIA.

Many years ago Salmonson discovered that individuals may pass glucose in the urine without having an excess of sugar in the blood. The first few cases which came under his observation passed albumen as well as sugar and therefore he came to the conclusion that glycosuria was renal in its origin, and he termed it " renal glycosuria ".

When it was found that the condition was not confined to individuals with damaged kidneys, a new name was given to it, " diabetes innocens ", to indicate that the condition was innocuous. This was a misnomer, because there is no polyuria.

The peculiarity is now termed " orthoglycæmic

glycosuria ", indicating that there is sugar in the urine with a normal amount of sugar in the blood.

There are many thousands of quite healthy people on this earth who pass dextrose in their urine during their whole lives. As far as I know the only harm that this glycosuria does them is to make it difficult for them to insure their lives at the ordinary rates. Ignorance of this form of glycosuria may indirectly lead to harm to true diabetics. We all believe that which we wish to believe. If a patient suffering from diabetes is told by a friend that his doctor told him that he had diabetes and put him on a diet ; that whilst on the restricted diet he became worse and worse and therefore he relinquished it, ate ordinary food and thereby regained his health ; the patient suffering from diabetes will not know that an error in diagnosis had been made in the case of his friend, will relinquish treatment too, with disastrous effects.

For a time I believed that, if the urine of a patient whilst upon ordinary diet contained more than 3·5% of dextrose, that patient was suffering from diabetes mellitus. That view proved wrong.

I have seen a patient who passed over 10% of dextrose in her urine whilst she had no excess of sugar in the blood (Diagram I).

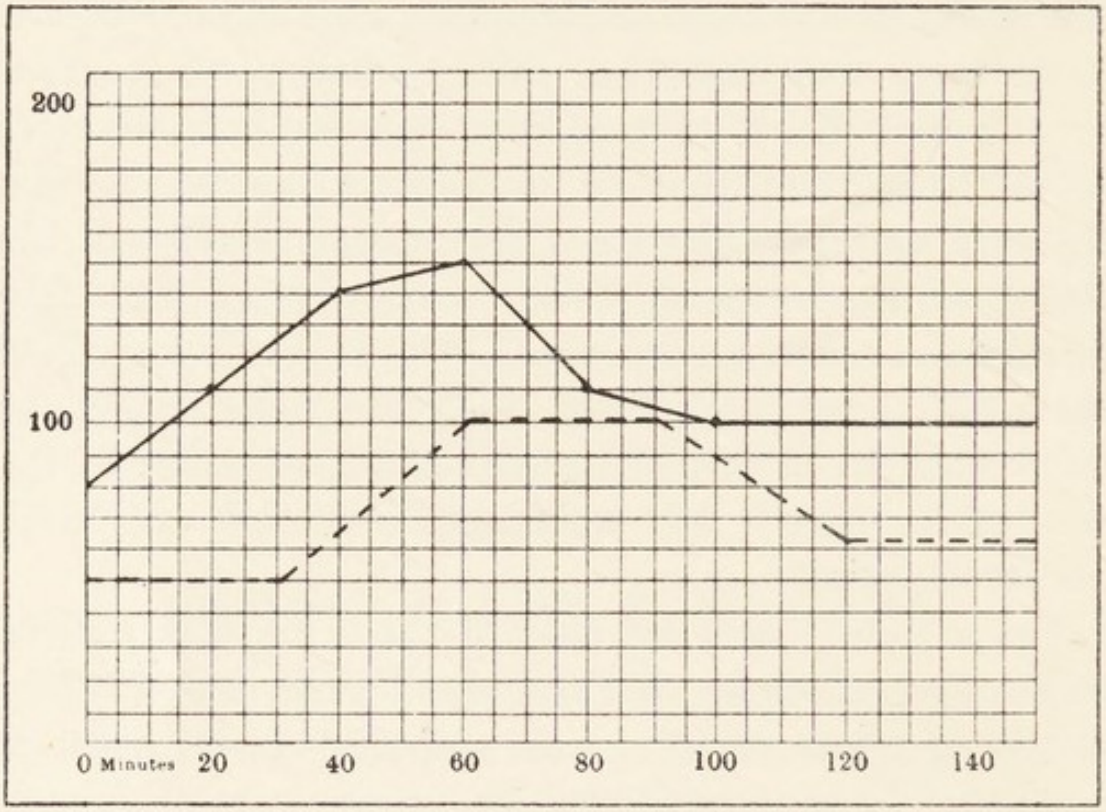
The renal threshold for sugar not only differs in different people, but varies from time to time in the same individual (Diagram II).

I may mention here, because I cannot repeat it too often, that in severe hypoglycæmia the renal threshold for sugar may fall below 0·03%, so that a patient about to die from hypoglycæmia may have sugar in the urine.

The majority do not pass sugar in the urine until the sugar in the blood rises to 0·20%, but there are some whose thresholds are as low as 0·09%, and others with thresholds above 0·25%.

The changes associated with digestion seem to affect

Diagram I.



——— = Sugar in blood in *milli*grammes per 100 c.c.
- - - - = Sugar in urine in *deci*grammes per 100 c.c.

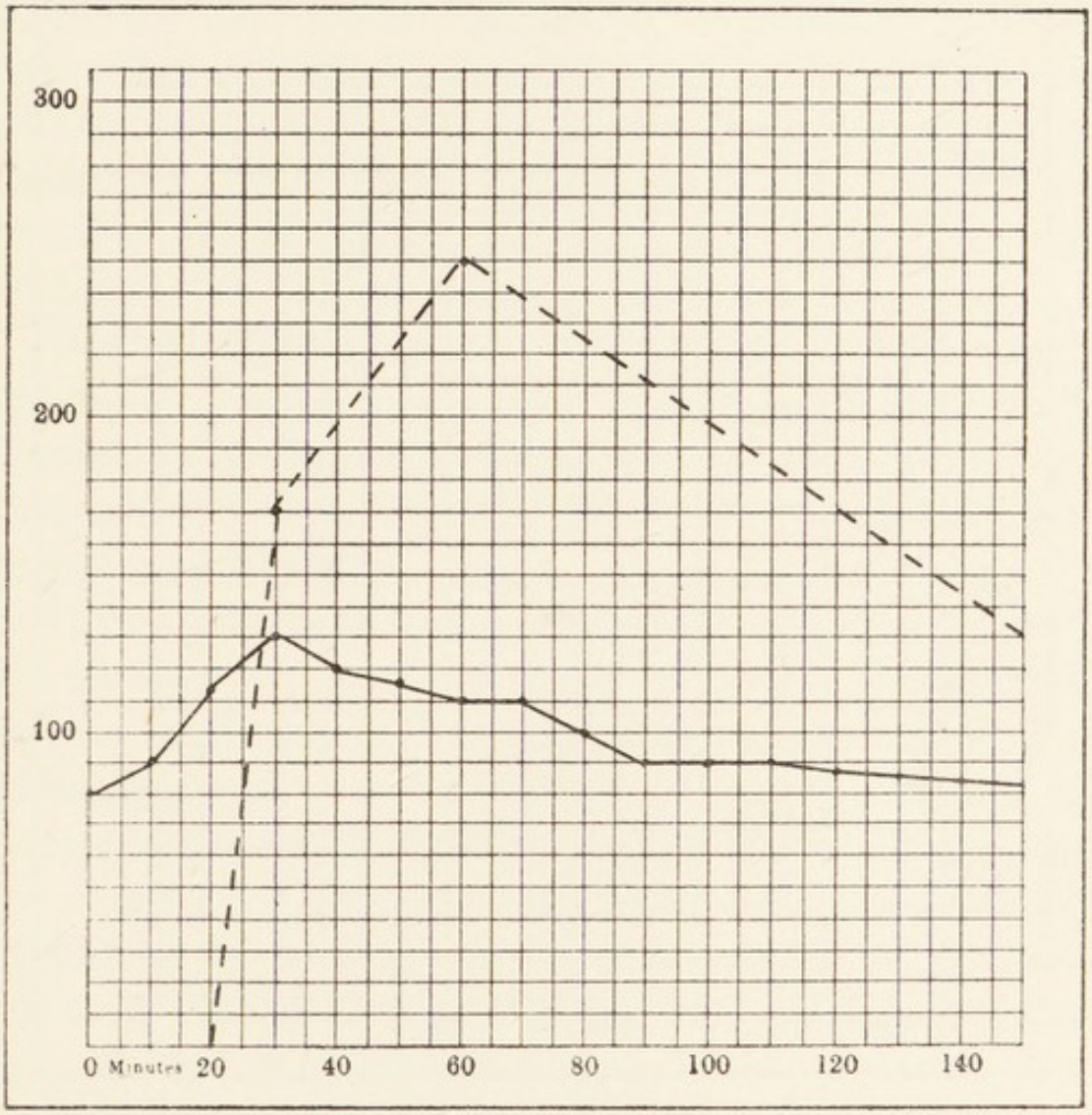
Sugar in blood after the administration of 50 grm. dextrose by mouth did not rise above 0·15 %, whilst the sugar in the urine rose to 10%. This seemed extraordinary. Two samples of blood and two samples of urine were examined in different laboratories and by different observers.

the threshold as shown by the ratio of concentration of sugar in the urine and the blood following a meal in a youth with a low renal threshold (Diagram III).

In diabetes mellitus, not only is there glucose in the

urine, but there is an excess of glucose in the blood (hyperglycæmia). Let it be noted that the statement is that in diabetes mellitus there is hyperglycæmia.

DIAGRAM II.



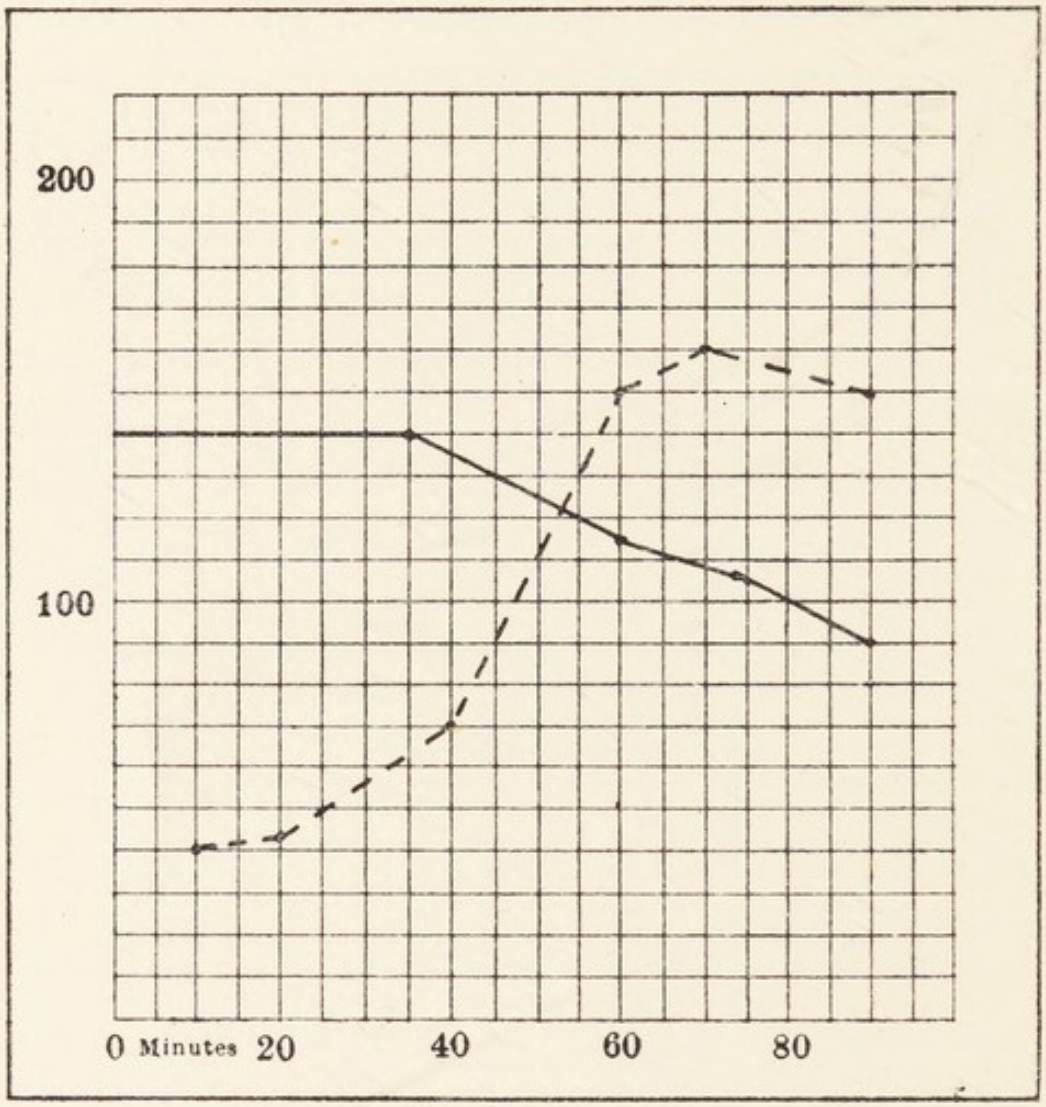
——— = Sugar in blood in *milli*grammes per 100 c.c.
- - - - = Sugar in urine in *centi*grammes per 100 c.c.

Usual curves obtained after 50 grm. dextrose by the mouth in individuals with low renal thresholds. In this case the threshold was well below 0·09% after the dose of sugar.

This does not permit the conclusion that all patients with hyperglycæmia are suffering from diabetes mellitus.

It is necessary to labour this fact, because in the past so many have accepted this error in logic which they would have repudiated in the well-worn instance "all

DIAGRAM III.



——— = Sugar in blood in *milli*grammes per 100 c.c.
- - - - = Sugar in urine in *centi*grammes per 100 c.c.

Illustrates the rise of concentration of sugar in the urine coincident with fall of sugar in the blood.

horses are quadrupeds, and therefore all quadrupeds are horses". There are many causes for excess of sugar in the blood other than diabetes mellitus, even

when the definition of diabetes mellitus is not "sub-insulism".

The diagnosis of an individual case may be very easy, as easy as making a diagnosis of pulmonary tuberculosis with Koch's bacilli in the sputum; or it may be extremely difficult, as difficult as occasionally it is to arrive at a decision whether the host or the parasite is winning the battle in an adult suspected of early pulmonary tuberculosis. In these difficult cases the decision can be arrived at only by observing what changes occur as time passes.

Obviously it will be wise to begin with the simple, and study the complex later. Symptoms usually spell disease, but symptoms develop late, long after the oft-despised "test-tube" methods have permitted the diagnosis to be made.

When the patient complains of thirst, a dry mouth, the passing of large quantities of urine, along with languor and loss in weight, the probability of his suffering from diabetes mellitus is very great, and if glucose be present in his urine the probability approaches a certainty. It is not an absolute certainty, because an individual with a low renal threshold for glucose, suffering from diabetes insipidus may have glycosuria and all the symptoms described above. Again, the symptoms may be associated with disease of the pituitary gland or a neoplasm of the pancreas; conditions which are not included in the definition of diabetes mellitus because medical treatment cannot cause amelioration.

The examination of the blood of the patient who is suffering from the symptoms enumerated above, one

hour after a meal containing at least 60 grm. of carbohydrate, will assist in the diagnosis, because if the sugar in the blood rises above 0·22%, the possibility of the condition being diabetes insipidus with a low renal threshold is excluded. Hyperglycæmic glycosuria *with symptoms* may be diagnosed as diabetes mellitus, provided that neoplasm of the pituitary gland and hypertrophy of the suprarenal glands can be excluded. Diagnosis is difficult when symptoms are absent. Those who believe that hyperglycæmic glycosuria is diabetes mellitus have little difficulty in arriving at a diagnosis; all they have to do is to place their patient upon ordinary diet containing 250 to 300 grm. of carbohydrate daily and estimate the sugar in the blood of their patients an hour or so after the main meals, and also the fasting blood. If the sugar in the fasting blood is above 0·11% and in the blood after meals rises to 0·22% or more, they are satisfied that their patient is suffering from diabetes mellitus and treat him as such.

Until a few years ago, I too held this view, because I had not the courage to break the rule "that when dextrose is found in the urine of a patient, that patient should be treated as one suffering from diabetes mellitus until evidence has been obtained that he is not suffering from that disease".

Does the logician accept a proof of the negative? I doubt it. In the past the patient with glycosuria has been considered not to be suffering from diabetes mellitus if he had a low renal threshold for dextrose, and no hyperglycæmia after a meal or after the administration of glucose by the mouth. All the cases with hyperglycæmia have been considered to be diabetics.

Perhaps it has been due to the inclusion of non-diabetics that dietetic treatment of diabetics has appeared to be so successful.

Patients suffering from hyperglycæmic glycosuria should be divided into two classes :

(1) Stationary hyperglycæmic glycosuria.

(2) Progressive hyperglycæmic glycosuria.

If the ability to store carbohydrate remains the same year after year in spite of an unrestricted diet, the condition should not be considered to be diabetes mellitus. Of course these patients enjoy good health, even when treated as diabetics and placed upon a restricted diet, provided the restriction is not too severe. The patients suffering from progressive hyperglycæmic glycosuria will go down hill if treated by diet alone, and therefore methods to differentiate between these types have been elaborated and are given in detail.

METHODS.

(1) Sugar tolerance test.
(2) Progressive diet test.
(3) Effect of pancreatic rest upon pancreatic efficiency.
(4) Effect of toxins upon pancreatic efficiency.
(5) Intravenous dextrose.
(6) Effect of time upon carbohydrate metabolism.

1. *Sugar Tolerance Test.*

In order that this test shall prove of value, it should be carried out invariably in an identical manner, special care being given to the preparation for the test. The

patient should be placed on a diet containing at least 250 grm. of carbohydrate daily for at least four days before the test is applied. During these four days the total energy in the food should be over 30 Calories per kilogramme of body weight per diem. This is to ensure that the pancreas shall be fully worked during the four days. Then, after fourteen hours' fast, a drink of 50 grm. of glucose dissolved in 250 c.c. of water to which the juice of a lemon has been added is given. It is convenient to carry out the test towards 10 a.m., and for the patient to abstain from breakfast, drinking only a cup of tea without sugar or milk, first thing in the morning. The sugar solution is given at 10 a.m., approximately fourteen hours after the previous meal. A sample of the blood is taken just before the sugar solution is drunk and the patient is told to empty the bladder. It is important that anxiety and fear of pain should be reduced to the minimum during the test, because anxiety increases the activity of the suprarenal glands, and thereby increases the concentration of sugar in the blood. For this reason it is my custom to let my nurse carry out the test, and she does her best to set the patient's mind at rest and to allay fear.

The blood is collected from a finger which is punctured with a sharp lancet, which if used correctly causes very little pain; often the patient is not aware that the finger has been punctured. Samples of blood are collected at intervals of 30 minutes, and after the collection of the blood the patient is told to pass urine. The samples of urine are labelled with the time they are passed and kept separately. The test is continued for

2½ hours. The sugar in the various samples of blood is estimated, and a curve plotted. It is noted how long it takes for the concentration of sugar in the blood to fall again to what it was before the administration of the sugar. The urines passed up to this time are collected, and the sugar and urea of the mixed samples are estimated.

The significance of this test will be considered later.

2. *Progressive Diet Test.*

If the circumstances make it impossible to estimate the sugar in the blood, this test will prove of value, and often assists in the arrival at a diagnosis when the above test is doubtful. The patient is placed on a fixed diet consisting of 50 grm. of carbohydrate, 70 grm. of protein and 90 grm. of fat for a period of three days. Since 58% of protein and 10% of fat are potentially carbohydrate, the total available carbohydrate in the diet (or "G") is 100 grm. The sugar in the urine, if any, is estimated accurately after the volume has been measured, so that the daily total excretion of sugar can be calculated. After the three days 100 grm. of carbohydrate are added to the diet which is maintained for three days, during which the sugar excreted daily is estimated accurately. The third period of three days with a further addition of a 100 grm. of carbohydrate completes the test. If the patient is normal, no sugar will be excreted. If the patient has the peculiarity of a low renal threshold for glucose, then during the second period the sugar excreted will not be more than twice the amount excreted during the first period, and during

the third period not more than three times that excreted during the first period. In other words, the sugar excreted will be in direct ratio to the carbohydrate in the diet. On the other hand, if the patient is suffering from an abnormally low power of utilizing carbohydrate, none may be excreted during the first period; say, x quantity during the second period and $2x$ or more during the third period, although during the third period there is an increase of only 50% in the quantity of carbohydrate in the diet.

The conclusion which may be arrived at from this test will be described later.

3. *Effect of Pancreatic Rest upon Pancreatic Efficiency.*

Attention was drawn to the fact that when carrying out the sugar tolerance test the patient should be placed on a certain diet for several days before the test was applied, because the result of the test will depend upon the condition of the pancreas at the time. After it has been rested for a period its activity may be modified and the test vitiated. It is this fact that may be utilized in attempts to diagnose difficult cases. The patient is placed on a diet of low energy value and containing the minimum quantity of carbohydrate for one week. The sugar tolerance test is then applied. The patient is then told to go on a perfectly ordinary diet containing at least 250 grm. carbohydrate and 30 Calories per kilogramme body weight per diem for one week. The test is then applied again. The comparison of the results may permit a diagnosis being arrived at when other methods have failed.

4. *Effect of Toxins upon Pancreatic Efficiency.*

Some sixteen years ago I recorded the fact that the tolerance for carbohydrate in diabetic subjects was depressed profoundly by infection and drew attention to the fact that in quite a number of cases the tolerance rose greatly by removal of septic teeth or the extirpation of a septic focus.

Every one with experience must have noted how greatly the tolerance for carbohydrate falls when a diabetic patient develops some infection, such as chicken-pox, pneumonia, a boil or even a common cold. This contrasts with carbohydrate metabolism of the normal individual which is not affected so profoundly as to cause glycosuria. It is extremely rare (although well recognized as a rare occurrence) to find, temporarily, sugar in the urine during pneumonia, or in an individual afflicted with boils, but unless the subsequent history of those is known, proof that they were not early diabetics is missing. In the diabetic subject this diminution in power of utilizing carbohydrate due to toxins may follow an injection of comparatively small doses, such as vaccine against the common cold or a few million *coli communis* bacilli.

It is quite true that "supræmic glycosuria" has been described as a condition in which there is an excess of sugar in the urine and in the blood during an infection, most commonly an infection causing cutaneous boils.

When the boils heal the sugar in the blood falls to normal and the sugar disappears from the urine.

In the light of recent observations one hesitates in concluding that this so-called supræmic glycosuria is

not really simply an infection in very mild diabetes and that if the patient be kept under observation for some years diabetes will be found to develop.

5. *Intravenous Injection of Glucose Solution.*

The methods mentioned depend upon the absorption of sugar from the bowel. A more accurate method is by injecting sugar into a vein. Experiments have shown that the normal healthy man may receive intravenously 0.8 grm. of dextrose per kilogramme bodyweight per hour intravenously for several hours without developing glycosuria, provided he fasts for twelve hours before the test is begun.

Some years ago I repeated observations in this direction, examining the sugar in the blood, and found that it rose to 0·18% and remained there. The sugar could be stored sufficiently rapidly to prevent hyperglycæmia. The test should be carried out for three hours and a 20% sterile solution of glucose should be given intravenously at a fairly even rate. Perhaps it is wise to reduce the quantity to 0·6 grm. per kilogramme body weight and if the sugar in the blood does not rise above 0·18% it may be assumed that the power of storing sugar is not much below normal average. The test can be repeated after an interval and is much more accurate than the ordinary sugar tolerance test because, as mentioned above it excludes any variation in the power of absorption. Attention must be drawn to the fact that occasionally following 3-hour intravenous injection of sugar, hypoglycæmia may develop and therefore the patient should be given plenty of carbohydrate by

the mouth when the test has been completed and watched for the following two or three hours.

Consideration of Sugar Tolerance-Test (1).

The value of the sugar tolerance test in a patient who has symptoms of diabetes mellitus is that by repeating it at intervals it permits a comparison of his power of storing sugar after a period of treatment. I have submitted many hundreds of patients to the tolerance test most of which have had the symptoms of diabetes mellitus, of these the test has proved normal in only three cases ; the subsequent history showed that two were not suffering from diabetes mellitus.

When the concentration of sugar in the blood of the fasting patient is well above 0·15% and then rises to 0·30% after the dose of dextrose and remains above 0·25% for two hours or more, it is safe to assume that the patient's power of storing sugar is so greatly below the normal that probably he is suffering from diabetes mellitus. The deviation from the normal may be insufficient to permit one to draw the conclusion that the patient is suffering from diabetes mellitus.

The greater the experience of the observer the greater the deviation he will recognize before concluding his patient is diseased.

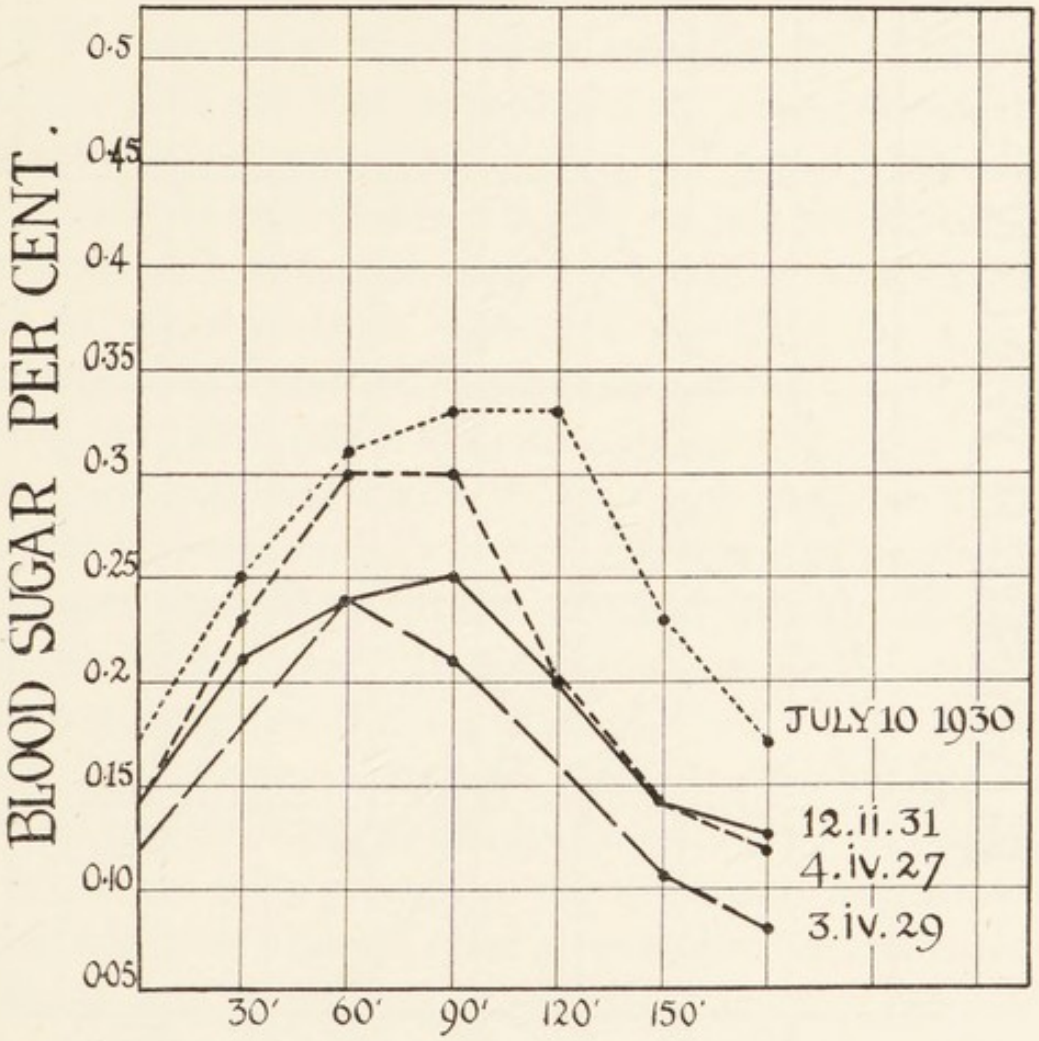
The fact that the power of storing carbohydrate is less than the average normal does not necessarily prove that the patient is diseased. Perhaps a simile will make this clear. Two men, Smith and Robinson, have a weight-lifting competition, and on the first of January Smith can lift 2 cwt. whilst Robinson can lift only 1 cwt.

On the following quarter day they repeat the competition, and Smith can lift 1½ cwt., whilst Robinson can lift 1 cwt. After another period of three months Smith can lift 1¼ cwts., whilst Robinson can still lift 1 cwt. Smith is still able to lift a greater weight than Robinson, but nevertheless there is little doubt that Smith is suffering from some disease because his power of lifting has fallen considerably during six months.

Disease is, as a rule, progressive, whilst congenital peculiarities may be stationary. A single tolerance test will not differentiate between stationary and progressive hyperglycæmic glycosuria. For instance, a man, aged 35, was put through the sugar-tolerance test after having been on an ordinary diet for some days. His fasting blood-sugar was 0·14%, which rose in half an hour after the dose of dextrose to 0·23%, and after another half hour to 0·30%, where it remained for half an hour, and then fell to 0·20% ; after a further half hour to 0·14%, and then to 0·12%. I concluded that this patient was suffering from diabetes mellitus and advised him to go upon a diet and report again later if necessary. Two years later he consulted me because he was spitting blood, and told me that he had kept to the diet for two months only, and during the remaining twenty-two months had eaten whatever he liked. Before I examined him the probable diagnosis flashed through my mind that he was suffering from advanced diabetes mellitus, along with pulmonary tuberculosis ; but upon examination I failed to find any abnormal signs in his chest and persuaded him to subject himself to another sugar-tolerance test ; and on this second occasion it was found that his fasting blood-sugar was 0·12%. The

concentration of sugar in his blood did not rise above 0·24% and fell to 0·08% three hours after the administration of the sugar. This patient has not restricted his diet in any manner and it is seen that four years

Diagram IV.

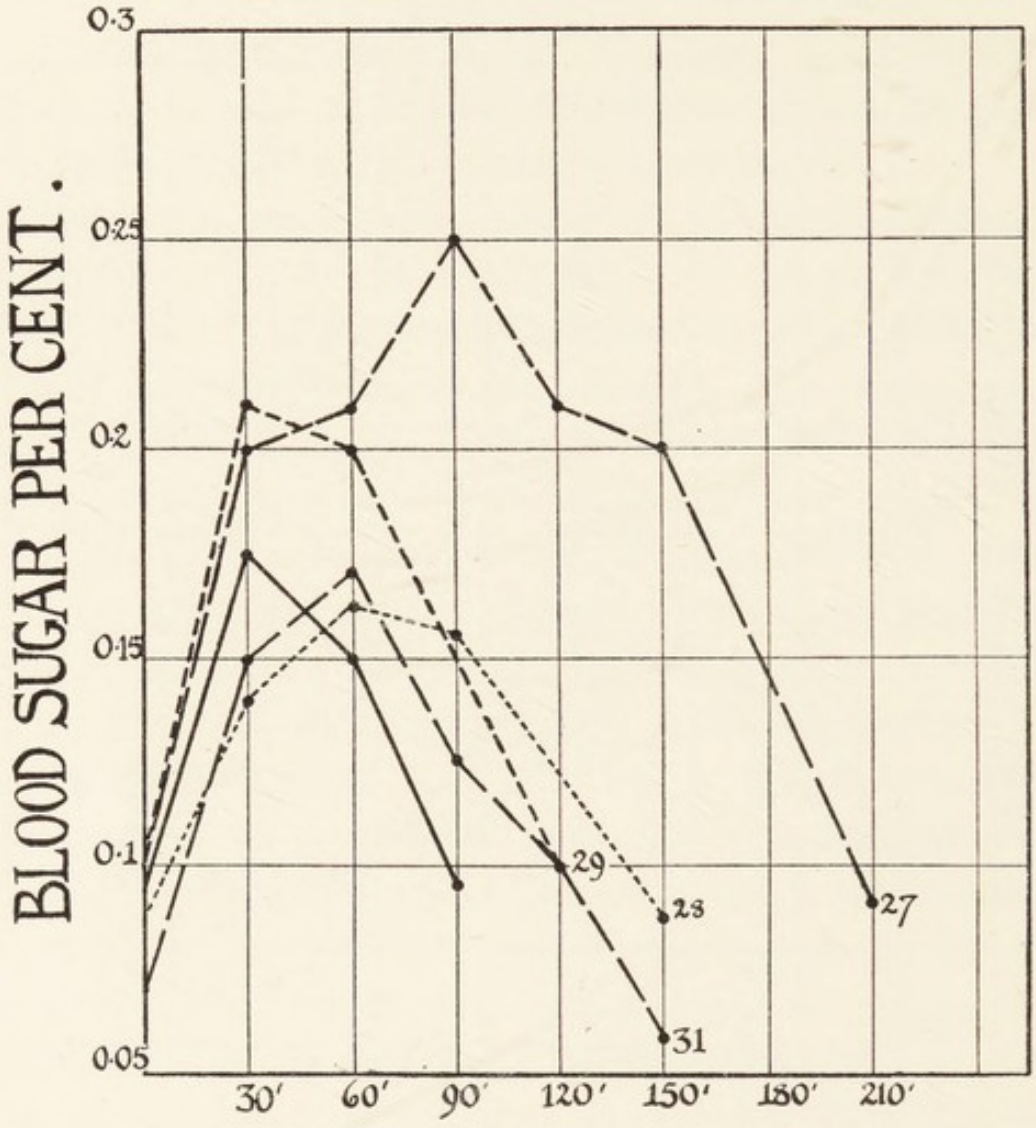


after the first observation his power of storing sugar had not decreased, so that one must assume that this is a case of stationary hyperglycæmic glycosuria. Naturally, if one does not recognize that such a condition can exist one will never be able to find such cases, and until I broke away from the rule that a patient with sugar in the urine must be treated as a diabetic until

there is evidence that he is not suffering from diabetes I was precluded from recognizing this peculiarity.

The same year a woman of 31 came to me with a

DIAGRAM V.



history of sugar in the urine, which she had discovered when she had tested her own urine after examining that of her brother, who was said to be suffering from diabetes mellitus. This patient had sugar in her urine and the concentration of sugar in her blood after an ordinary meal rose to 0·22%. She was submitted to a sugar-tolerance test and the concentration of sugar in

her blood after fasting was 0·10%. Half an hour after a dose of 50 grm. of glucose it rose to 0.20%, then to 0·21%, then to 0·25% and fell at half-hourly intervals to 0·21%, to 0·20%, to 0·14%, to 0·09%. It took close upon three hours to fall to that at which it started.

This test, along with the fact that the sugar content of the blood was so high after a meal, led me to the conclusion that she was suffering from diabetes mellitus, but circumstances, which I need not detail here, made me conclude that it was wiser to let her think that she was not suffering from diabetes mellitus, and to allow her to eat and drink whatever she liked for a year. At the end of a year her sugar-tolerance test was repeated and it was found that the concentration of sugar in her blood did not rise above 0·16%, and it fell to 0·09% within two and a half hours. This patient has been left upon perfectly ordinary diet and subsequent observations have shown that the disease has not made progress (Diagram V).

It is obvious, therefore, that in the absence of symptoms the sugar-tolerance test may be misleading. If sugar has been present in the urine and an excess of sugar has been found in the blood a few sugar-tolerance tests do not permit the conclusion that the patient is not suffering from an early stage of diabetes mellitus. This was well illustrated by a man, aged 40, in whose urine sugar had been found in America, where he had been subjected to a sugar-tolerance test, which had proved that then his power of storing sugar was below the normal. I subjected him to a sugar-tolerance test, which proved that his power of storing sugar was normal at the time of the test. He was advised

to go abroad and "do himself well". On his return five months later it was found that the sugar in his blood did not rise above 0·16% after a meal rich in carbohydrates. I came to the conclusion that he was not suffering from diabetes mellitus, but the subsequent history proves that I was wrong. Two years later, whilst in France, he developed acute nephritis and was advised to go on a diet rich in carbohydrates and containing very little protein. The local doctor in France found sugar in his urine, took him to a diabetic expert in Paris, where he was submitted to a sugar-tolerance test, and the sugar in his blood rose to 0·22%, and in spite of that it was assumed that he was not suffering from diabetes mellitus, but in the following year, when I had an opportunity of examining him, the concentration of sugar in his blood, after giving 50 grm. of dextrose by the mouth, rose to 0·37% and remained high for several hours. This man needed 40 units of insulin twice daily to keep his blood-sugar normal, when he was placed on a fixed diet, containing 180 grm. carbohydrate. The man had taken between five and six years to develop undoubted diabetes, but a series of tests taken at intervals would have shown the slowly progressive nature of the disease. These cases suffice to illustrate that a single sugar-tolerance test may prove of but little value in cases in which symptoms are absent.

Consideration Of Progressive Diet Test (2).

The progressive diet is of value in cases suspected of a low renal threshold for glucose when sugar in the blood cannot be estimated, and therefore, the low threshold cannot be proved. It is not reliable in so far that it

does not assist to differentiate between stationary and progressive hyperglycæmic glycosuria. In both cases the amount of sugar excreted during the second and third periods will be considerably greater than the increase in the amount of carbohydrate in the diet. Of course if the test be repeated at intervals of six months with identical detail, then any deterioration in carbohydrate metabolism may be determined. The sugar-tolerance test takes two to four hours, whilst the progressive test takes nine or ten days.

The fact that the sugar-tolerance test and the progressive diet test do not agree invariably, suggests that some patients are able to store carbohydrate when given as starch at the normal rate, but fail to do so when it is introduced as dextrose. I assume that if a patient can take 300 grm. of carbohydrate daily along with protein and fat to supply him with 40 Calories per kilogramme body-weight per diem without developing a concentration of sugar in the blood above 0·15%, that there is no reason for placing him upon a restricted diet or supplying him with insulin.

A few cases to illustrate this peculiarity :

A man, aged 45, was found to pass dextrose in his urine without presenting any signs or symptoms of diabetes mellitus, but happened to have thrombo-angeitis obliterans in his right leg.

He was placed upon a diet of high energy value and rich in carbohydrate for one week and then submitted to a sugar-tolerance test. At 10.25 a.m. after a fourteen hours' fast the sugar content of his blood was 0·17% ; he was then given 50 grm. of dextrose dissolved in 250 c.c. of water, to which the juice of a lemon had been

added. At intervals of half hours the concentration of sugar in his blood was 0·27%, 0·32%, 0·30%, 0·24% and 0·20%. In other words, two hours after the taking of the sugar solution the sugar in his blood was 0·24% and three hours after 0·20%. He excreted 6 grm. of sugar during the test.

He was admitted for investigation by the progressive diet test. It was found that when he was receiving a diet containing 100 grm. " G " (potential carbohydrate) his urine contained a trace of sugar, but upon increasing the quantity of carbohydrate the quantity of sugar excreted diminished and on 300 " G " the urine was free from any reducing substance as tested by Benedict's solution.*

The sugar-tolerance test was carried out again and found to be similar to the above, but began and remained throughout the test at a level 0·04% lower.

He was advised to eat and drink whatever he liked for six months, and then present himself again for repetition of the test. The third test was practically identical with the second. His health was perfect and no symptoms had developed.

Two examinations a year should be carried out for at least five years.

A second case, a man, aged 35, who felt ill, but had no signs or symptoms of diabetes mellitus, upon routine examination was found to have sugar in his urine.

The sugar-tolerance test carried out as above gave the following : Fasting blood-sugar 0·13% ; at intervals

* This peculiarity of glycosuria becoming less or disappearing upon raising the carbohydrate content of the diet has been observed in several cases.

of half an hour after the swallowing of the sugar solution 0·28%, 0·28%, 0·19%, 0·125%, 0·107%. During the test 5 grm. of sugar were excreted. This patient was admitted to hospital and it was found that he was able to take a diet containing 300 "G" without the sugar content of his blood rising above 0·17%.

He was submitted to further tests—one carried out after pancreatic rest and another after the pancreas had been well exercised.

In the first column are the numbers when the diet had been: Carbohydrate 25 grm., protein 49 grm. and fat 61 grm. The second column after a diet of carbohydrate 240 grm., protein 70 grm. and fat 117 grm.:

0·06%	.	0·10 %
0·114 ,,	.	0·153 ,,
0·166 ,,	.	0·25 ,,
0·18 ,,	.	0·09 ,,
0·125 ,,	.	0·085 ,,
0·133 ,,	.	0·057 ,,

More sugar was excreted during the first test than during the second.

Since the storing of sugar was more rapid when the pancreas had been well exercised the conclusion was drawn that in all probability the patient was not suffering from diabetes mellitus.

Consideration of the Effect of Pancreatic Rest upon the Pancreatic Efficiency (3).

It is impossible to exaggerate the importance of adhering to every detail when carrying out the sugar tolerance test.

If the diets be taken for some time before the two

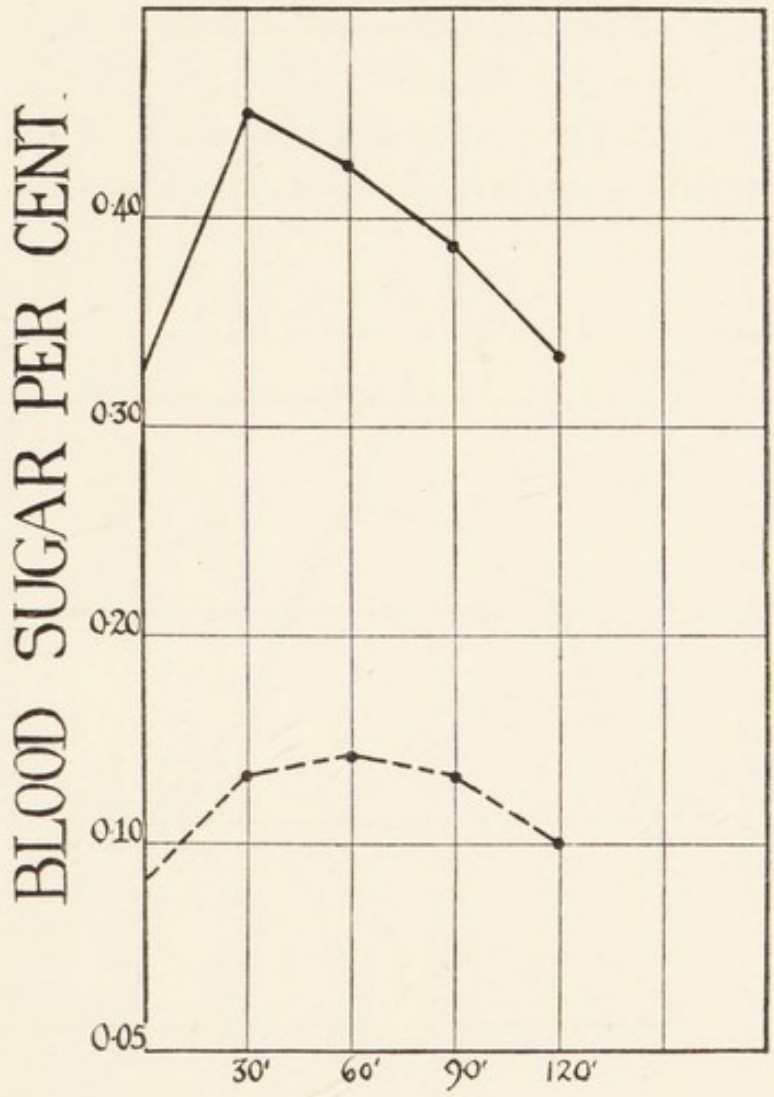
tests do not contain approximately the same quantity of carbohydrate and Calories the results will not be comparable and may be misleading. This is well illustrated in the two tests recorded in the chart.

A man, aged 30, was found to have sugar in his urine. he was placed upon a diet poor in carbohydrate and then, after a 14-hour fast, was submitted to a sugar-tolerance test, with the result that the concentration of sugar in his blood started at 0·08%, and at intervals of half hours after the administration of 50 grm. of glucose was 0·14%, 0·145%, 0·10%. This did not suggest diabetes mellitus. He was told to go upon an ordinary diet for a week and then present himself again for the same test. Then it was found that the sugar in his blood after a 14-hours' fast was 0·32%, rising to 0·45% within half an hour of the administration of the glucose, and it fell to 0·33% after two hours. This comparatively rapid fall was not due to the power of storing sugar being considerable, but to the rapid excretion of sugar through the kidneys (Diagram VI). The conclusion arrived at by studying these two tests is that the rested pancreas of the diabetic patient may perform as well as that of the average normal man. It is interesting to note that if the pancreas of the normal individual be rested for a time it will not get into its normal stride at its usual rate. Diagram VII illustrates this.

Two graphs record tests carried out with all the details the same except that that which rose to 0·175% was taken after the patient had been on an ordinary diet. The second graph, which rose to 0·26% illustrates the test after the individual had been on a diet very poor in carbohydrate for one week.

This peculiarity of the pancreas may be utilized in attempting to arrive at a diagnosis in difficult cases. A man, aged 56, had had sugar in his urine for some number of years. He was in London for a short period

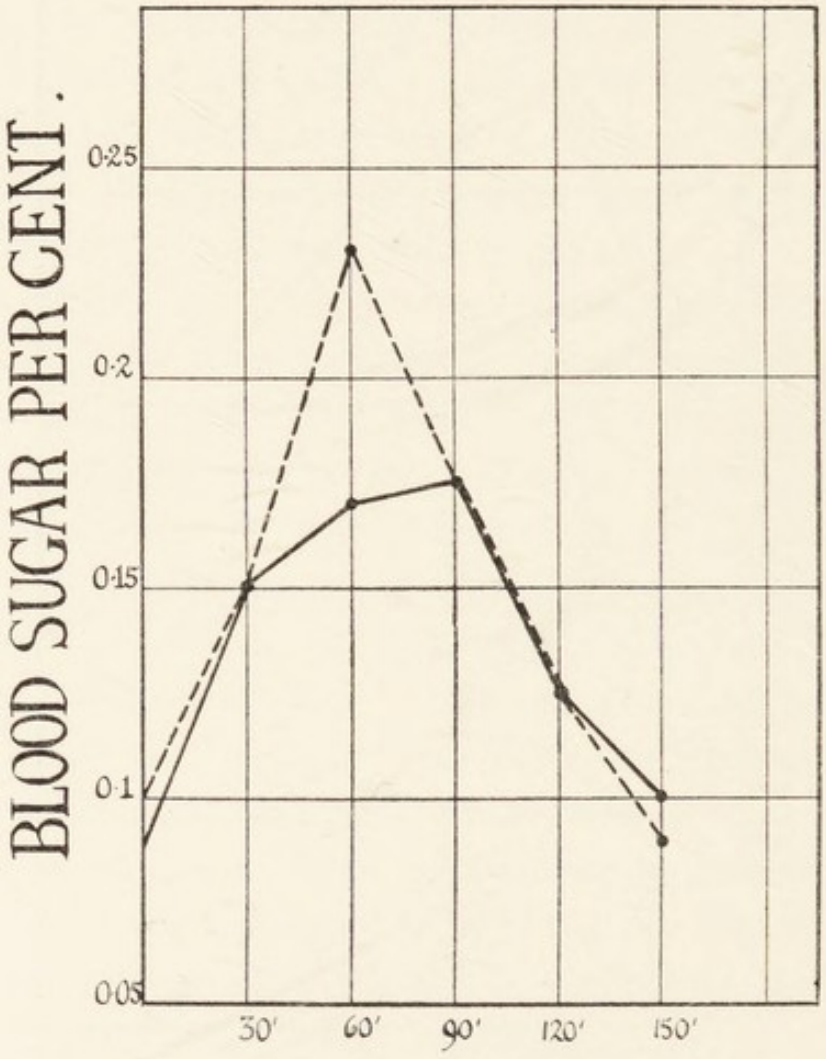
Diagram VI.



before having to return to South America, and was anxious to know definitely whether he had diabetes mellitus and should take care of himself or whether he could treat the sugar in his urine with contempt. The curve resulting from the first sugar-tolerance test rose

to 0·21%, where it remained for half an hour, and it did not fall to 0·10% for close upon two hours after drinking the sugar solution. The concentration of sugar in the blood after 14 hours' fasting was 0·12%, and therefore it was impossible to draw any conclusion

Diagram VII.

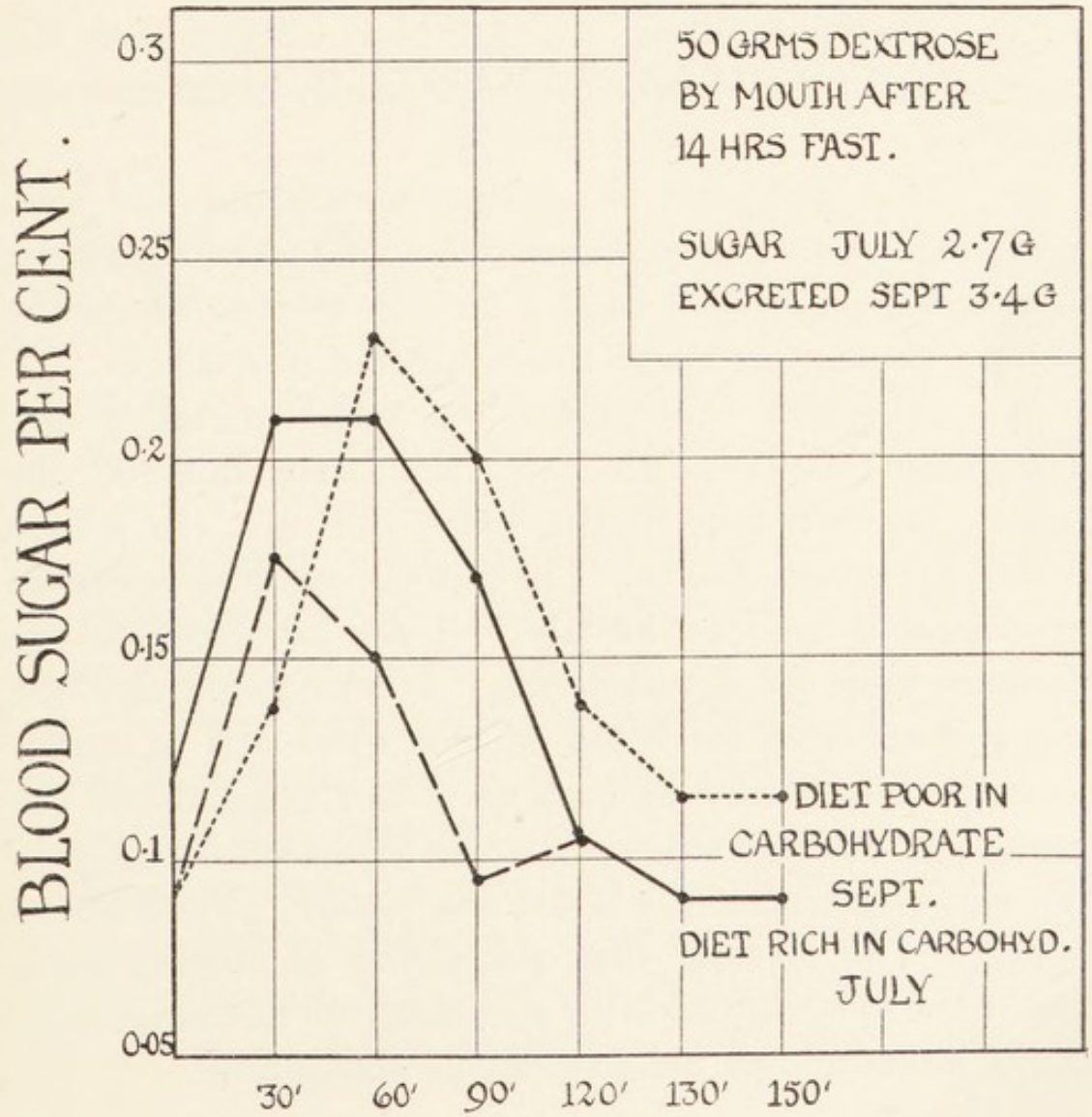


except that if he had diabetes his power of storing sugar had not deteriorated to any very great extent.

I advised him to go upon a diet containing the minimum amount of carbohydrate and to have the test repeated. This he did, and I found that, although the concentration of sugar in his blood after a 14-hours'

fast was lower, namely, 0·09%, but it was 0·14% two hours after the zero time. In addition to this the sugar excreted during the test was 3·4 grm. against 2·7 grm. previously. Therefore his power of storing sugar was poorer after he had been on a restricted diet than when he was upon an ordinary diet (Diagram VIII). The conclusion arrived at was that he might eat and drink what he liked. In order to be on the safe side he was advised to be re-investigated in a year or two's time, but that the probability of his suffering from the disease was very small.

Diagram VIII.



Consideration of Method Based upon Intravenous Injection of Sugar (4).

The capacity of the patient to store dextrose when injected intravenously may assist in determining not only whether the patient is suffering from a diminished power of storing carbohydrate, but also may prove the only way of making a comparison with that power at an earlier date.

For instance, a patient was found to be suffering from glycosuria along with duodenal ulcer. The sugar-tolerance test suggested that the glycosuria was due to mild diabetes mellitus. It had been alleged that the operation for duodenal ulcer occasionally cured diabetes mellitus.

I decided that after the gastro-enterostomy had been performed the sugar-tolerance test would prove fallacious and therefore decided to find out the rate at which the patient could store sugar when injected into a vein.

It was found that when 0·6 grm. of sugar per kilogramme body-weight per hour were injected the sugar concentration in the blood did not rise above 0·18% for several hours. The patient was then operated upon and three months later he was admitted to the diabetic ward for investigation. It was found that the sugar content of his blood after a meal rich in carbohydrate did not rise as high as it had done before the operation, but that when sugar was injected into the vein the sugar content of the blood rose rapidly to well above 0·25%. This proved that the power of storing sugar had fallen quite appreciably and that the rearrangement of the intestine had led to delay of absorption.

One of the great disadvantages of the sugar-tolerance-test is that it depends upon the rate of absorption of sugar and this is a variable factor, not only in different individuals, but also in the same individual on different days.

This has been proved by washing out the stomach at intervals after giving the solution of dextrose and determining the amount of sugar recovered. The percentage of dextrose recovered was from 10% to 40%.

This has been applied in quite a number of cases, and so far it seems to be reliable to assist in diagnosis.

Consideration of the Effect of Toxins upon Pancreatic Efficiency (5).

The test is carried out by placing the patient upon a fixed diet, taking samples of blood at intervals during the day and then causing a mild pyrexia by the injection of either a foreign protein or an anti-catarrhal vaccine, consisting of pneumococci, streptococci and catarrhalis, or a mixed vaccine of typhoid and paratyphoid *A* and *B*. In the majority of healthy individuals the concentration of sugar in the blood during pyrexia induced in this manner falls for a time, whilst in the diabetic the sugar in the blood rises, and, as mentioned above, if the patient has been upon a diet which prevented glycosuria, glycosuria may reappear.

This test has not been carried out on a sufficiently large number of cases over a sufficiently long period for one to say more than that it is of considerable promise. Its use is obviously limited to those times when it is

essential to arrive at a diagnosis in an extremely limited period.

One peculiarity must be borne in mind whilst seeking a diagnosis. Diabetes mellitus, in some cases, appears to progress in waves, and if the position at the time of examination be between two crests, the deviation from the normal may be too small to detect. In some respects the diagnosis of disseminated sclerosis is similar in so far as when signs have been unequivocal, the disappearance of those signs for a time does not permit a change of opinion.

PROGNOSIS.

The prognosis in many diseases depends upon the treatment adopted.

In carcinoma of the breast the results obtained by a timid operator, who does not feel competent to remove all the infected glands, are not comparable with those of a skilled surgeon.

The *Spirochæta pallida* makes a successful stand against the physician who attacks it with a feeble bombardment of mercury.

The future of a patient suffering from diabetes mellitus will depend upon the treatment he receives, just in the same way as does the future of the patient suffering from carcinoma or from syphilis, the only difference being that the immediate results are not so obvious, and therefore blame, if any, cannot be apportioned so easily.

If the diabetic subject comes under treatment sufficiently early to permit the sugar content of the blood being kept below 0·15% continuously, it is extremely

probable that the disease will either be arrested or else there will be a progressive improvement. There are, as far as I know, two conditions which may prevent this :

(1) The patient may develop further attacks of diabetes mellitus.

(2) The patient may receive some infection.

The term "further attacks of diabetes mellitus" needs some explanation. I have seen patients who have been put on a diet and kept to that diet rigidly, and for months been free from hyperglycæmia, and suddenly developed an intense thirst along with polyuria. Examination of the urine has shown a high percentage of sugar, whilst examination of the blood has demonstrated hyperglycæmia. Detailed examination has failed to show any infection, nor has the blood picture suggested an abscess anywhere. Their tolerance has been found to have fallen greatly.

This I call a second attack of diabetes mellitus, the essential feature of which is the sudden onset, not a gradual deterioration of metabolism.

These cases suggest that the disease is due to a toxæmia and not to a congenital defect in the pancreas.

The commonest cause for lack of improvement during treatment is an infection.

To illustrate this I refer to one case. A child of 7 came under treatment and was found to need 40 units of insulin daily to keep the sugar in her blood below 0·15% whilst on a diet of carbohydrate 30 grm., protein 45 grm., fat 60 grm.

During the following two years improvement occurred until 4 units of insulin given twice daily sufficed to prevent hyperglycæmia ; then glycosuria recurred, and

to control it the dose of insulin had to be raised to 40 units daily.

The cause of the sudden lapse was a small abscess at the root of a tooth which showed itself later as a gumboil. When the abscess was drained the dose of insulin required fell, not back to a daily dose of 8 units, but to 16 units, and then an attack of influenza drove it up to 30 units a day for some months.

When discussing treatment I have insisted upon the necessity of not only keeping the urine free from sugar, but of keeping the sugar in the blood below an arbitrary amount, namely, 0·15%. In my experience, when this is accomplished in a patient in whom the disease is of comparatively recent origin, as time passes the patient requires less and less insulin, provided the diet is kept constant.

Whether this is due to the regeneration of the pancreas or some other cause has not been determined definitely, but there seems to be evidence in favour of that hypothesis based upon the microscopic appearance of the pancreases of two children who had been treated upon the lines laid down above and been killed by accidents.

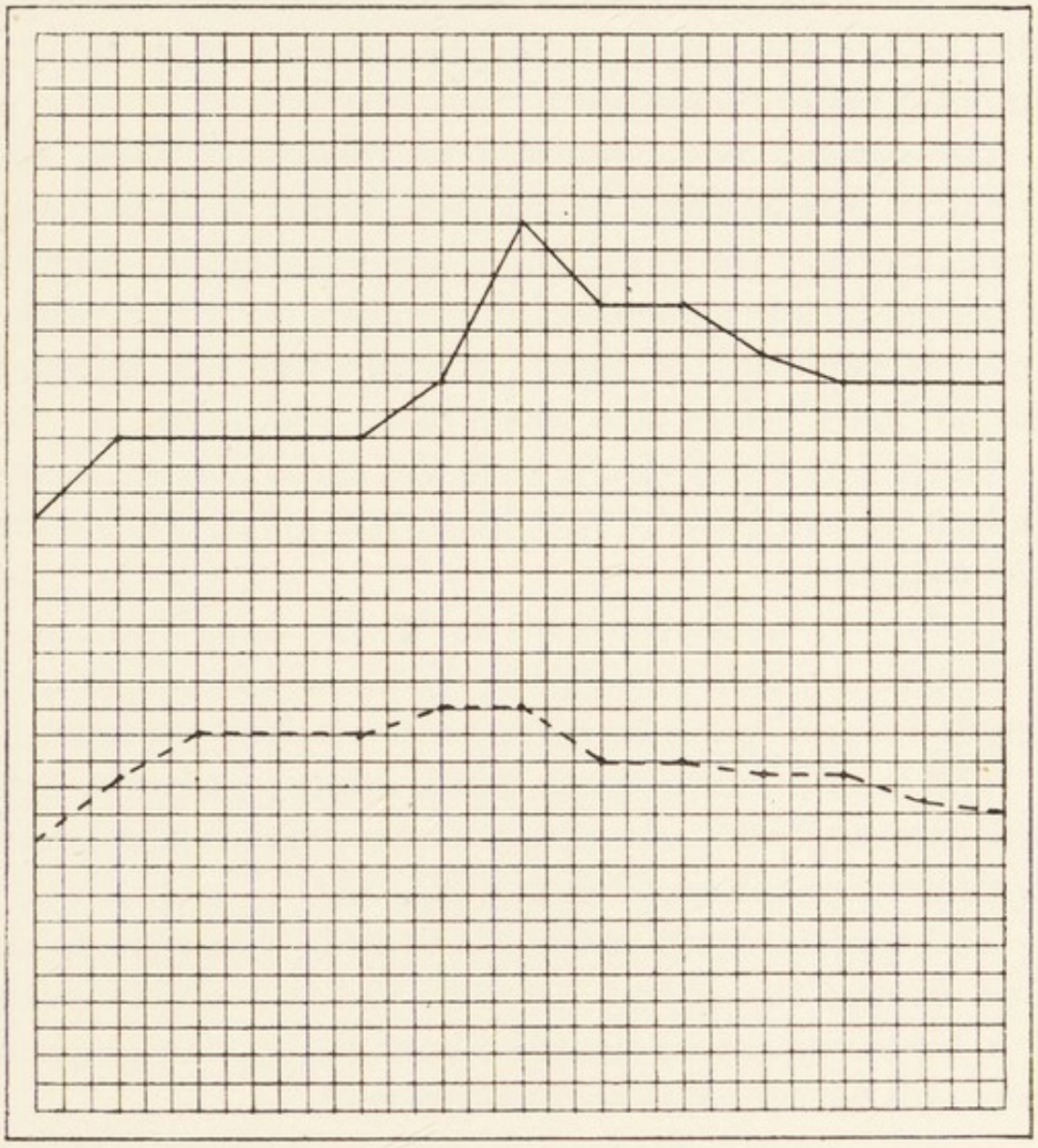
These pancreases have shown an unusual number of mitotic figures in the β-cells of the islands of Langerhans.

When the disease has been present for a long time and the fraction of pancreas left is very small, often it is impossible to keep the sugar in the blood below 0·15% without giving half a dozen injections of insulin in the 24 hours and at least one during the night.

One cannot expect any great regeneration in these cases unless treatment is prolonged over many years. It is only when the evidence of regeneration has passed

beyond doubt that one will be justified in advising a treatment which must interfere with sleep.

Diagram IX.



——— = June 20th, 1923.
- - - - = August 12th, 1923.

The two diagrams illustrate the effect of efficient and inefficient treatment.

Diagram No. IX shows the rise of sugar in the blood

upon the intravenous injection of a 10% dextrose solution at the rate of 1 c.c. per minute, *i.e.* in his case 0·6 grm. per kilogramme body weight per hour for 3 hours.

On June 20th, in spite of excretion of sugar through the kidney the sugar in the blood rises from 0·22% to 0·33% after 90 minutes.

The patient was submitted to treatment which ensured a comparative hypoglycæmia for a little over seven weeks. On repetition of the injection on August 12th the blood-sugar rose from 0·125% to 0·15% without any excretion of sugar. Insulin was not injected for 36 hours before this observation was made.

There can be no doubt that the carbohydrate metabolism of the patient had improved greatly following the treatment.

Inefficient treatment leads to further deterioration.

Details are same as above. Intravenous injection of sugar 0·6 grm. per kilogramme body weight per hour.

The second curve starts 0·04% higher than the first and rises to 0·06%, showing a depreciation in the carbohydrate metabolism (Diagram X).

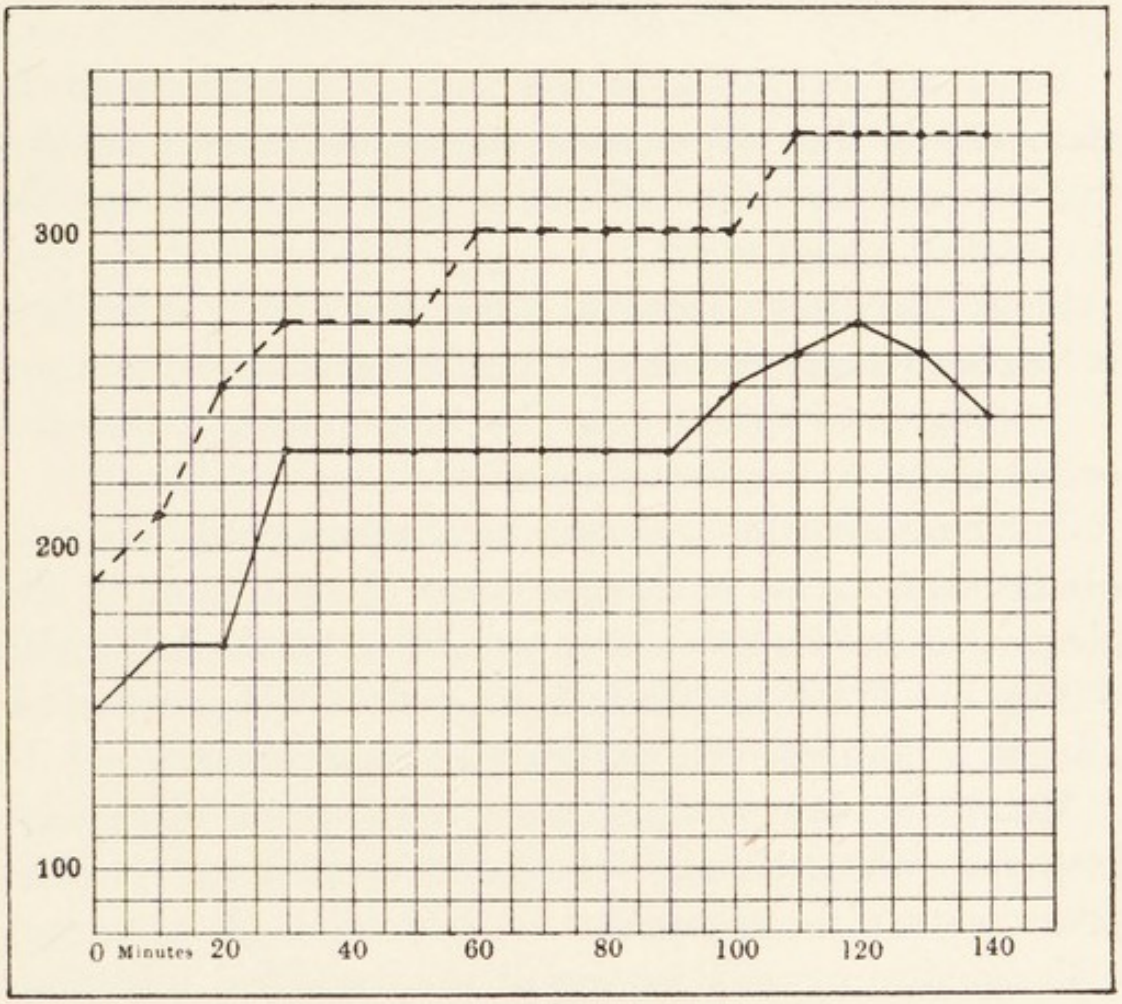
This patient could not be controlled. She stole food, and during the period between the two observations her blood-sugar was usually above 0·15%, although it was rare for her urine to contain sugar.

If the patient be treated simply with the object of keeping the urine free from sugar, then the prognosis is very different. I had excellent opportunity of making observations on the contrast in the prognosis following the two lines of treatment shortly after insulin came upon the market. In early days insulin was very costly,

and some patients could not afford sufficient to reduce their blood-sugar to normal, but only enough to control their glycosuria.

I found that in these, as time passed, glycosuria re-developed although the diet and dose of insulin were

Diagram X.



——— = August 23rd, 1923.
- - - - = September 18th, 1923.

kept constant. In addition to this, some developed the complications of diabetes mellitus, such as neuritis, retinitis and cataract, although they were free from glycosuria they had a more or less continuous hyperglycæmia; their thresholds were 0·20% or above, and therefore sugar did not appear in their urine.

In addition to the causes of deterioration mentioned above there are the administration of anæsthetics, traumatic damage of tissues resulting from accident and from surgical operation.

CAUSES OF DIABETES MELLITUS.

Since one cannot hide the fact, it is well to admit straightway that the cause or causes of diabetes are not known, and therefore all one can do is to criticize the product of imagination.

Since the disease occurs in families and is inherited, it has been suggested that it is of congenital origin.

A congenital defect may be anatomical, metabolic, or infective.

The anatomical defect may be a recognizable absence, diminution, excess or displacement of cells, such as the absence of one kidney ; or a peculiarity in the cell which will make itself evident later. Pseudo-hypertrophic muscular paralysis will serve as an illustration.

Metabolic defects, too, may exist from birth—for instance, alkaptonuria—or make themselves evident later—gout is an example.

Congenital syphilis is one of the very few infections which may occur during gestation.

There are possibly congenital defects similar in some respects to hæmophilia, which peculiarity may be taken as a congenital defect *par excellence*, but it is a defect which comes and goes. An hæmophilic may cut himself one day and lose but little blood, whilst on another day a prick with a pin may continue bleeding indefinitely. It seems generally recognized that the bleeding period

does not exceed 10 days. Those who have studied the condition are satisfied that the disease has a periodicity.

Excessive bleeding will be noticed by a poor observer ; on the other hand, a periodic fall in the resistance to an infection might be missed by the most acute observer ; it is possible that a congenital defect of that type may account for some individuals having frequent attacks of pneumonia.

When an author writes that diabetes mellitus is of congenital origin, what does he wish to convey to the mind of the reader ?

If he is vague purposely he might save ink, because most non-infective diseases appear to be congenital in origin.

If he thinks that the disease is not due to an infection, it is best to make that statement ; if, on the other hand, he takes the view that an infant is predestined to develop diabetes mellitus if it lives long enough because it has come into the world with its β-cells of the islands of Langerhans only short-lived, he should have the courage of his convictions and write to that effect.

The view I favour is that diabetes mellitus is congenital in the same way as tuberculosis is congenital.

Certain families have a low resistance to invasion by the bacillus of Koch.

Some members of some families possess pancreatic cells which are exceptionally susceptible to some poison, probably, but not necessarily produced by bacteria or virus.

The fact that an acute onset may not be accompanied by any pyrexia or malaise has been quoted as evidence against this idea, but acute nephritis leading to

extensive destruction of renal cells may not lead to constitutional symptoms until the failure to excrete causes toxæmia.

The specific nature of toxins is shown by the action of diphtheria toxin upon heart muscle and nerve tissue, of scarlet fever toxin upon the kidneys and epithelium, whilst simple substances, such as tetrahydro-β-naphthylamine hydrochloride, when injected subcutaneously into rabbits, causes the formation of acute gastric ulcer, and phenyl-hydrazine leads to degeneration of liver-cells.

Cases have been recorded in which great improvement has taken place after draining an infected gall-bladder, and some have suggested that this indicates that diabetes mellitus is due to an infection of the pancreas.

This evidence is not conclusive. Removal of septic teeth leads to great improvement too. It is the absorption of toxins that upsets carbohydrate metabolism; it matters not where these are generated; the effect is the same if the focus is in the gall-bladder or in the toes.

I do not wish to infer that this is evidence against the view that the disease is due to direct infection of the pancreas through the ducts, but only that the evidence supplied is insufficient to permit any conclusion being drawn.

INFECTIONS.

The effect of the absorption of toxins made itself evident to me shortly after adopting the Allen treatment of diabetes mellitus in 1916.

I found then that, when a patient suffering from pyorrhœa alveolaris came under treatment for diabetes mellitus, the optimum diet after the removal of the teeth

and healing of the gums might be two or three times as great as that found upon his admission to hospital.

Everyone who has studied diabetic patients has had similar experience; in mild diabetes mellitus the removal of a septic focus may improve the metabolism to so great an extent as to make it doubtful whether the patient is suffering from any metabolic disease.

Apparently, multiple infections may produce bigger effects than single infections, as suggested by the following case: A woman, aged about 60, who had had diabetes mellitus for many years but disregarded advice, met with an accident which led to ketosis. Diet and insulin tided her over the critical stage, but in spite of 75 units of insulin daily the sugar in her blood persisted at 0·25%. She had one septic stump, which she refused to have removed until she could visit her dentist some twenty-five miles away. The patient then developed an abscess round a nail. The sugar in her blood rose to 0·40%, although the diet and dose of insulin remained unchanged. When the abscess discharged, the sugar content of the blood fell again to 0·25%, and later after the removal of the septic stump the concentration became normal and the dose of insulin was reduced.

The factors which determine whether insulin will reduce the sugar content of the blood or not are numerous and as far as I know all have not yet been determined.

In my experience the majority of cases with an infection of the tubercle bacillus react to insulin, whilst cases with infection with the pneumococcus do not.

In staphylococcic infection it depends upon the degree of absorption. I have seen a carbuncle on the neck,

which has separated the skin so that a probe could be passed for three or four inches in every direction, fail to modify the action of insulin.

The injection of a few million bacilli in the form of a vaccine may lead to the sugar in the blood being doubled for many hours.

Occasionally the onset of an infection shows itself first by the development of glycosuria. I remember seeing a little girl of eight who was much distressed, thinking that I might not believe that she had kept her diet strictly because sugar had reappeared in her urine after an absence of six months. Upon inquiry I learnt that her sister would be out of quarantine for chickenpox in three days' time. The prophecy that spots would appear upon the little diabetic patient during the next four days was fulfilled.

If the infection led to only a temporary depreciation of the metabolism, the prognosis of diabetes mellitus in the young would not be so depressing, but unfortunately the mischief, if not permanent, is of long duration. Before we had insulin, children died after two or three infectious diseases, each having lowered their carbohydrate tolerance.

The common cold is a sufficiently intense infection to upset the metabolism and to diminish the tolerance for weeks, months or years.

The treatment of infection is the same as the treatment of severe diabetes ; an attempt must be made to prevent ketosis by cutting down the fat in the diet to the minimum, and to promote the oxidation of carbohydrates by giving heroic doses of insulin along with cane sugar or dextrose.

ANÆSTHETICS.

When operation upon a patient suffering from diabetes mellitus is imperative it should be performed under a local anæsthetic if it be in any way possible. In recent years the technique of local anæsthesia has made great strides, and now even operations such as a complete mastoid may be performed without inflicting pain upon the patient.

In my experience the general anæsthetics, chloroform, ether and badly administered nitrous oxide, have caused comparatively mild diabetes to develop into a serious condition. The serious condition does not make itself evident immediately. For years I have taught that general anæsthetics should be avoided, and from time to time surgeons and practitioners have told me that I am a pessimist on that matter, that they have operated on cases of diabetes mellitus a week or a fortnight previously, and that the patients have done excellently; but they have not told me what the carbohydrate tolerance of the patient was before the operation and what it was three months after the operation.

It is true that not every case is made worse by a general anæsthetic, but most of them are, and at present we have no method of determining beforehand which will be immune to the anæsthetic and which will be adversely affected.

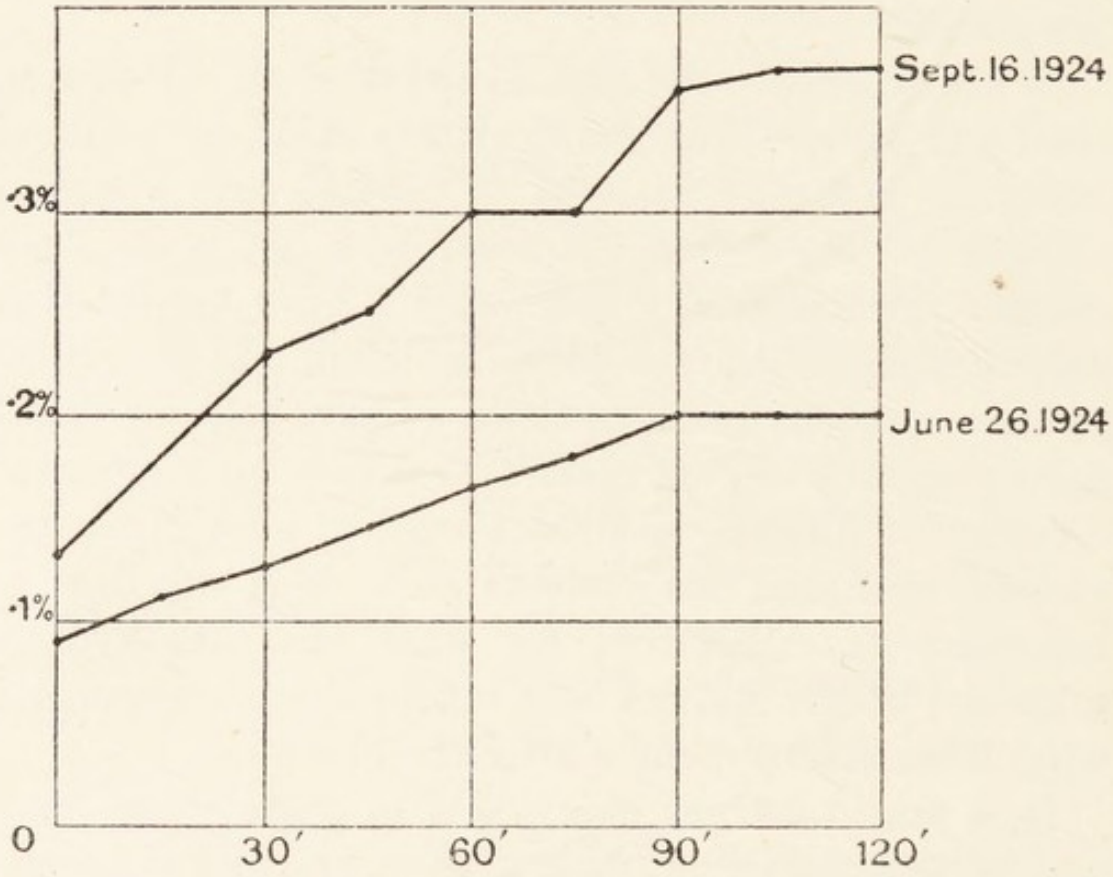
Some time ago opportunity offered to determine the deterioration in the pancreas following an operation for which ether was administered.

The following curves show the rise of the sugar in the blood upon intravenous injection of sugar at the rate

of 0·6 grm. per kilogramme body-weight per hour shortly before the operation and nearly three months after the operation.

I imagine that a patient suffering from diabetes mellitus of pancreatic origin has a certain number of cells destroyed and a certain number damaged. These

DIAGRAM XI.



damaged cells are able to do a certain amount of work so long as they are not submitted to either severe strain or any toxic influence. Toxins such as a general anæsthetic are sufficient to kill these weakened cells and thereby the disease progresses. The evidence confirming this view was supplied by the observations carried out by Allen, who found that after removing the

greater part of the pancreas a condition simulating diabetes mellitus developed in the dog. In reply to a question he let me know that these dogs could be submitted to chloroform anæsthesia several times without making the diabetes worse. This is what one would expect, for in the partially de-pancreatized dog there were only a limited number of cells, but all these cells were healthy and able to withstand the toxic effect of the anæsthetic.

If it is quite impossible to carry out an operation with a local anæsthetic, then, provided the operation be below the waist, an intraspinal injection of stovaine may be given. If the site of the operation be above the waist, gas and oxygen is the least harmful of the general anæsthetics, and when subsidized by nembutal or avertin proves quite satisfactory.

If gas and oxygen cannot be administered, ether must be given : chloroform has proved the most toxic of the general anæsthetics in common use.

TREATMENT.

When a physician undertakes the treatment of a patient suffering from diabetes mellitus he should ask himself whether he possesses the necessary organization to carry out the form of treatment with which he himself would be satisfied. What is his ideal ? Is he satisfied with a standard treatment not adapted especially to the individual who is his patient ?

If he believes that recovery from the disease occurs when the correct treatment is adopted he will prescribe insulin without delay. Just as Crile asserts that

undoubted evidence of over-activity of the thyroid gland calls for immediate removal of a part of it, so, too, undoubted evidence that too great a burden is being thrown upon the non-acinary cells of the pancreas calls for immediate alleviation of the load thrown upon them.

This alleviation can be brought about either by restriction of diet or by subsidizing the pancreas with injections of insulin. There is a prejudice against the use of insulin due to ignorance. If a man were to lose a foot by an accident, and then were to hop around on one foot and refused to wear an artificial limb he would be considered to possess less than the average intelligence. The fact that he would not grow a new foot, and therefore would have to wear the artificial leg all his life would not be accepted as an argument against its use.

A man who has lost a part of his pancreas, if intelligent, will use insulin rather than restrict his activity and hasten the degeneration of his arteries by living upon a diet very restricted in carbohydrates and containing an excess of fat.

Just as it would be the height of folly for a man to buy an artificial leg several inches shorter than the sound one, so too, it is foolish for a man to take insulin in doses too small, so that he is precluded from eating a physiological diet containing sufficient energy to allow him to live a normal life.

The dread of beginning the injection of insulin is due to the popular fallacy that if once begun it must be continued throughout the patient's life. An untruth with a substratum of truth is more difficult to refute than a lie which is wholly a lie.

It is true that, if a patient has reached a stage in which the pancreas has degenerated so far that the supply of insulin is too small to maintain life and is then given insulin, it is probable that he will live only so long as he receives insulin, and therefore he cannot cease taking it, BUT if a patient who makes enough insulin to live is given insulin he may at any time cease taking insulin, and will be in a better position than before he began the injections.

If insulin be given in adequate doses to a patient who is suffering from diabetes mellitus of recent onset, he runs a good chance of being able to cease taking it after a time, but if insulin be begun only when the β cells of the islands of Langerhans have nearly all degenerated completely, then in all probability insulin will have to be continued throughout the life time of the patient.

In other words if insulin be given at the beginning of the disease the patient may be able to discard insulin later, if it be withheld until the disease has made great progress it will have to be continued indefinitely.

Many will not accept this view because they are acquainted with many patients who have lived long and useful lives when treated by restricted diet. I wonder whether there is evidence in these cases that the disease was really progressive hyperglycæmic glycosuria. It is my impression that the dietetic treatment of diabetes mellitus would be abandoned if all observers insisted upon distinguishing between the progressive and stationary forms of hyperglycæmic glycosuria. Then even the very mild cases would be treated early and a good chance of recovery would be offered to them.

Rules cannot be made to apply to all patients, and no doubt some aged patients are better without insulin, and some of these even without restriction in diet.

The treatment of the aged will be considered separately later.

The present-day treatment of diabetes mellitus is still based upon the epoch-making observations of F. M. Allen, who found that the pancreas degenerated if overworked, and might regenerate if rested.

Before insulin was available the work thrown upon the pancreas was determined by the food the patient received, and the length of his life depended upon the skill of the physician, whose duty it was to find out the quantities of carbohydrate, protein and fat which he as an individual patient could utilize without throwing excessive work upon the cells of the damaged pancreas. This was not a very simple task, because some of the patients were able to utilize large quantities of fat and only a little carbohydrate, whilst others needed more carbohydrate than fat.

The metabolisms of normal healthy people probably differ as much as their faces, and in both there is a rough general plan, but the nuances are infinite ; the most successful practitioner recognizes not only these physical differences, but also the differences in the nervous systems.

At the present day the skill of the physician has to be devoted, not so much to the actual quantities of carbohydrate, protein and fat suitable for each individual patient (since this now can be decided to a great extent by the patient himself), as to the correct distribution of the food throughout the twenty-four hours and the

determination of the number, size and times of administration of the doses of insulin.

F. M. Allen's discovery that a rested pancreas may regenerate is the foundation upon which the details of the treatment rest.

Since insulin is now obtainable in any quantity and at a cheap rate the majority of patients may eat what they like, but it is absolutely necessary for them to eat the same allotted quantities of carbohydrate, protein and fat distributed in the same manner day after day.

I take the view that the patient is an individual and not simply one of a class, and believe that it is medical impertinence to try to make all males of a certain height and weight, irrespective of race, etc., consume diets of the same energy value, a medical impertinence almost as gross as dictating to the patient that the proportion of carbohydrate, protein and fat in his diet must be the same as that of some other individual.

Printed lists and fixed tables which can be handed to the patient must be a godsend to the busy practitioner, but so, too, is the hypodermic syringe charged with a dose of morphine.

The conscientious practitioner would no more think of injecting morphine to relieve pain because he was pressed for time and could not investigate the cause of the pain than he would place a diabetic patient upon a diet which might shorten his life because it was difficult for him to find the opportunity to work out one which was suitable.

The time required is not very great, the method is as follows. The patient is asked to write down a list

of the food which he was accustomed to eat before he developed the disease.

Let us assume that he supplies the following :

Breakfast : Two cups of tea with a little milk, two rashers of bacon, two slices of bread, and two slices of toast with butter and marmalade.

Lunch : A chop, steak or cut from a joint, potatoes, vegetable, roll, pat of butter and some cheese.

Tea : Cup of tea and two biscuits.

Dinner : Soup, fish, meat or poultry, potatoes, vegetable, pudding or stewed fruit, biscuits, butter, cheese and fruit. Coffee with cream. He is then asked to return to this diet for a day and to weigh each item in the menu.

He then supplies the following, to which the carbohydrate, protein and fat values are added :

	Carbohydrate.	Protein.	Fat.
Breakfast :			
Two cups of tea with 4 oz. milk	8	6	4
One egg		6	5
2 oz. cooked bacon		20	20
1½ oz. bread	27	3	
1½ oz. toast	30	3	
½ oz. butter			12
1 oz. marmalade	20		
	85	38	41
Lunch :			
3 oz. cold meat		24	9
3 oz. boiled potato	18		
3 oz. cabbage	2		
2 oz. bread	36	4	
½ oz. butter			12
1 oz. Cheddar cheese		10	10
	56	38	31
Tea :			
¾ oz. biscuits	15	3	

Dinner:	Carbohydrate.	Protein.	Fat.
8 oz. clear soup			
3 oz. cooked meat		24	9
3 oz. potato	18		
3 oz. vegetable	2		
4 oz. pudding	30		
1 oz. biscuits	20	3	
½ oz. butter			12
½ oz. cheese		5	5
4 oz. apple	10		
Coffee			
1 oz. cream	1		6
	81	32	32

Total: Carbohydrate 237, Protein 111, Fat 104.
Calories $(237 \times 4) + (115 \times 4) + (104 \times 9) = 2344$

On attaching a table of contents of carbohydrate, protein and fat we see that his diet has been carbohydrate 237 grm., protein 111, and fat 104. Supplying him with 2344 calories.

If the disease is not advanced the total diet may remain unchanged, but the distribution of the carbohydrate at the meals must be arranged so that the greater part is taken at breakfast and dinner, unless the patient be willing to give himself three injections of insulin daily.

If he would like to limit the injections to two, the midday meal must contain less carbohydrate, the potatoes must be removed, and the bread reduced to one ounce. Of this 36 grm. of carbohydrate removed from lunch about 12 should be added to breakfast, and 24 grm. to the evening meal. The carbohydrate at the evening meal should exceed that at breakfast, the reason for this will be given later.

The 12 grm. of carbohydrate added to breakfast may be taken as a 4 oz. apple or a grapefruit, and another half ounce of marmalade. The 24 grm. of carbohydrate added to the evening meal would allow an increase in biscuits by slightly more than one ounce, and an extra two ounces of apple.

The patient would be advised to inject insulin half an hour before breakfast and half an hour before the evening meal, say five units of insulin at each dose. The urine secreted during the fourth hour after the meals following insulin should be collected and examined for sugar.

If breakfast is at 8.30 the patient would empty his bladder at 11.30, that sample would not be tested, but the urine passed at 12.30 would be collected and tested for sugar.

The amount of insulin is increased by two units each dose every second day until glycosuria ceases or hypoglycæmic symptoms develop. When the doses of insulin lead to the urine secreted during the third hour after the meal being nearly sugar-free, arrangements must be made to estimate the sugar content of the blood at various times.

If the patient comes under close observation at the beginning of treatment with insulin much time may be saved because the increase in the dose is then based upon the sugar content of the blood at midday.

The pancreas is stimulated by an excess of sugar in the blood; this stimulation is brought about directly by the action of the substance upon the pancreatic cells, and also through stimulation of a centre in the floor of the fourth ventricle, and, since the essence of successful

treatment is rest for the pancreas, the sugar content of the blood must be kept low, the lower the better. In practice one can arrange food and insulin to prevent the concentration of sugar in the blood rising above 0·15%.

It might be suggested that the treatment therefore is very simple; give large doses of insulin for a time, and recovery will occur. Unfortunately this does not prove to be correct, because if too much insulin be given the sugar content of the blood falls so low as to cause symptoms. Life cannot be prolonged if the sugar in the blood falls below 0·02%.

Before one is satisfied that the treatment is the optimum one must be certain that the concentration of sugar in the blood does not rise at any time above 0·15%, nor fall sufficiently low to lead to uncomfortable symptoms, so-called hypoglycæmic attacks or insulin reactions. Samples of blood should be taken one hour after breakfast, and if these are found to contain less than 0·15% of sugar, samples taken one hour after lunch, after tea and dinner should have the sugar content estimated. If all these are below the arbitrary upper limit 0·15%, then one may conclude that the doses of insulin are of the correct magnitude, and given at the correct times. It would be of interest to learn how low the sugar content of the blood fell at midday, but so long as symptoms do not develop this is of academic rather than practical interest. If the sugar content of the blood rises above 0·15% one hour after breakfast, the dose of insulin should be raised and perhaps the interval increased between the injection of insulin and the meal. To decide which to do first the sugar content of the blood at morning insulin time must be estimated.

If it be 0·15% or in that region, the interval between injection and meal time may be increased, and the effect noted upon the sugar content of the blood one hour after the meal.

If this still remains above 0·15% the dose of insulin must be gradually increased until the desired effect is produced or insulin reactions develop about midday.

When these occur in spite of too high a percentage of sugar in the blood one hour after the meal, it is wise to transfer 10 grm. of carbohydrate from breakfast to two hours after the meal. This has a double effect ; it tends to prevent the sugar in the blood rising too high and to prevent the sugar in the blood falling inconveniently low towards midday. Similar changes may have to be made in the evening.

The teaching that a little sugar should be allowed to be present in the urine of the treated diabetic is founded on fear of hypoglycæmia. The enemy of mankind is the father of fear.

Insulin dissolved in water injected subcutaneously produces an effect for only eight hours and therefore if, in the patient who is receiving two injections, only a small fraction of the pancreas is still producing insulin, the sugar in the blood will rise too high towards four o'clock in the afternoon and four o'clock in the morning.

Since hyperglycæmia stimulates the pancreas, and stimulation of the damaged pancreas leads to further degeneration, steps must be taken to prevent it.

The rise towards four o'clock in the afternoon can be prevented by giving insulin either before or after lunch, depending upon the sugar concentration of the blood about that time. If an injection of insulin be given to

metabolize the carbohydrate it is wise to rearrange the distribution of carbohydrate and divide it almost equally between the three meals, a slight preponderance at the evening meal.

To prevent hyperglycæmia in the early morning either a dose of aqueous insulin must be given between midnight and three o'clock, or insulin suspended in oil must be given in the evening. Fortunately many patients require the midnight dose of insulin for a short time only.

For instance, a girl of 16 who had been treated originally by a restricted diet came to me when her insulin had been gradually increased to thirty units before breakfast. She appeared to be enjoying good health, and since the physician, under whose care she had been, took the view that diabetes mellitus is a progressive disease, however treated, no notice had been taken of the fact that sugar appeared in the urine secreted during the latter part of the day and night. Her mother was a very intelligent woman and had tackled the medical adviser, saying, "What is going to happen to my daughter? She was on five units, you increased it to ten, and now you have increased it to 30, which in no way controls the sugar in her blood". He replied that she could give her more insulin if she liked. This did not satisfy her and she sought other advice. It was found that the patient had to receive four injections during the twenty-four hours in order to keep the sugar in her blood between normal limits, and the total quantity of insulin required daily was 100 units. One injection was given at midnight, but after three months the midnight injection was stopped, and it was found that the

sugar content of her blood in the morning was well under 0·15%, and within a year her dose of insulin was reduced to 45 units, given in two injections, which kept the blood satisfactory throughout the twenty-four hours.

The object in referring to this case is to point out that the multiple doses need not necessarily be given for a long period.

Very severe cases of diabetes mellitus may need several hundred units of insulin daily in order to use a diet which consists of over 200 grm. of carbohydrate. So long as the patients are not very susceptible to "insulin shock" there is no objection; amongst my patients was a Parsee lady who lived on fruit and pulses, and therefore carbohydrate had to supply the main part of the energy in her food; she took over 200 units of insulin daily for several months, and then was able to reduce the dose. She would not have had any inconvenience had she not been susceptible to the drug (perhaps because she did not eat meat), and developed urticaria and therefore had to limit the dose to a minute quantity until tolerance had been established.

The patient must be encouraged to believe that very large doses at the beginning of the treatment do not indicate that the disease is advanced, and have pointed out to him that many who require quite large doses are able to reduce them after a few months. These are facts. Better results are obtained with a generous diet and adequate doses of insulin than with restricted diets and smaller doses of insulin.

The advantages of a diet with moderate quantities of carbohydrate are manifold, the patient is satisfied and will be more likely to obey orders, the danger of

acidosis is reduced to a minimum, and the deleterious effect on the arteries of a high fat diet is avoided.

The patient must have impressed upon him that the amount of carbohydrate, protein and fat is fixed for each meal, and he is not allowed to transfer food from one meal to another.

As soon as the correct doses of insulin and the optimum intervals between injections and meals have been determined, the patient may change the actual foods he takes, working out with the aid of the tables how much of his favourite dishes he may take without altering the constitution of each meal as far as amounts of carbohydrate, protein and fat are concerned.

Unfortunately, some of the substances primarily carbohydrate contain a certain amount of protein and fat in addition. In the majority of food stuffs this is so small that it may be neglected, but in a few, such as nuts, the fat exceeds the carbohydrate, and must be taken into consideration when arranging a meal. Perhaps an illustration will explain matters. For instance let the fixed breakfast be of 80 grm. carbohydrate, 25 grm. protein, and 40 grm. fat. Most patients like bread, and therefore 2 oz. must be allowed for, which contains 36 grm. of carbohydrate and 6 of protein. Milk to put in tea or coffee, say $2\frac{1}{2}$ oz. will contain 5 grm. of carbohydrate, 4 grm. of protein, and 3 grm. of fat, reducing the carbohydrate still available to 39 grm., the protein to 19 grm., and the fat to 37 grm. The 39 grm. may be taken as marmalade, which would allow 1 oz. of marmalade, chiefly consisting of peel, leaving 20 grm. for fruit, such as 6 oz. of orange. The 20 grm. of protein might be taken as 4 oz. of fish,

perhaps herring or mackerel which would contain 10 grm. fat, reducing the fat available to 27 grm., which would allow 1 oz. of butter to be added, so that the breakfast will consist of tea, with $2\frac{1}{2}$ oz. of milk, 4 oz. of fish, 2 oz. of bread, and 1 oz. of butter and 1 oz. of marmalade, and 6 oz. of orange. This would satisfy a very large percentage of people, but perhaps the patient hails from north of the Tweed and is accustomed to porridge for breakfast. On having recourse to the table he sees that $\frac{1}{4}$ oz. of raw oatmeal contains 5 grm. of carbohydrate and 1 grm. of protein ; $\frac{1}{4}$ oz. would make a very poor plateful. He would need 1 oz. of oatmeal, which would make rather more than 4 oz. of porridge. For this 20 grm. of carbohydrate and 4 grm. protein he must exchange either the orange or the marmalade, and a fraction of an ounce of fish. Probably he would like cream with the porridge. The tables state that 3 oz. of thin cream contain 5 grm. of carbohydrate, so that he would exchange the $2\frac{1}{2}$ oz. of milk for the 3 oz. of thin cream, some of which he would put on his porridge and some in his tea. This thin cream contains 20 grm. of fat and therefore the quantity of butter would have to be reduced to $\frac{3}{4}$ oz., and the patient would have to choose a fish containing less fat than herring or mackerel, such as whiting, plaice or sole. Some patients prefer fruit at breakfast. Most of the fruits contain carbohydrate chiefly, and therefore if the patient likes to take 1 oz. of bread and $2\frac{1}{2}$ oz. of milk, which will be 23 grm. of carbohydrate, he can have 27 grm. of carbohydrate in the form of fruit. The tables show him how much of each kind of fruit he may take.

A very great variety can be arranged without altering

the total quantities of carbohydrates, protein and fat at each meal.

The arrangement of diets with fixed quantities of carbohydrate, protein and fat presents no difficulty to those patients whose minds grasp the most elementary mathematics, nevertheless some with artistic temperaments are quite unable to master the underlying principle ; for these a series of menus are given, menus of meals of definite quantities of carbohydrate, protein and fat. Notes are added to show how these can be modified.

Breakfast containing 60 grm. carbohydrate, 25 grm. protein and 40 grm. of fat.

	Carbo-hydrate.	Pro-tein.	Fat.
Breakfast I :			
Tea, as much as desired			
Milk, four tablespoonsful	4	3	2
Bacon, 2 oz. lean back ; the liquid fat to be eaten with bread		20	20
Bread, 2 oz..	36	4	
Marmalade, ½ oz.	10		
Butter, ¾ oz.			18
1 Grapefruit	10		
	60	27	40
Breakfast II :			
Tea, as much as desired			
Milk, 2 oz.	4	3	2
Oats, 1 oz. to make porridge	20	5	
Thin cream, 2 oz.	2		12
Bread, 2 oz..	36	4	
Eggs 2		12	10
Butter, ¾ oz.			18
	62	24	42

	Carbo-hydrate.	Pro-tein.	Fat.
Breakfast III:			
Tea, as much as desired			
Milk, 2 oz.	4	3	2
Oats, 2 oz. to make porridge	40	10	
Cream, 2 oz.	2		12
Bread, 1 oz..	18	2	
Bacon, 1 oz. weighed raw		10	10
Egg 1		6	5
Butter, ½ oz.			12
	64	31	41
Breakfast IV:			
Tea			
Milk, 1 oz.	2	1	1
Bacon, 2 oz. lean weighed raw		20	20
Egg 1		6	5
Bread, 3 oz..	54	6	
Butter, ½ oz.			12
Grapefruit, ½, or apple, 2 oz.	5		
	61	33	38
Breakfast V:			
Coffee unlimited			
Milk, 5 oz.	10	8	6
Thin cream, 2 oz.	2		12
Fish, 4 oz., kipper, etc. weighed raw		20	8
Bread, 2 oz..	36	4	
Butter, ½ oz.			12
Grapefruit, 1, or 4 oz. apple	10		
	58	32	38
Breakfast VI:			
Coffee unlimited			
Milk, 6 oz.	12	9	7
Oatmeal, 2 oz.	40	10	
Cream, 2 oz.	2		12
"Vita Weat," 1 piece, or 1 Huntley & Palmer's breakfast biscuit	6		
Butter, ½ oz.			12
Bacon, 1 oz.		10	10
	60	29	41

	Carbo-hydrate.	Pro-tein.	Fat.
Breakfast VII:			
Tea unlimited			
Milk, 2 oz.	4	3	2
Eggs, 2		12	10
Butter, 1 oz.			24
Bread, 1 oz..	18	2	
Dutch cheese, ½ oz.		12	8
Orange, 6 oz.	20		
Apple, 4 oz.	20		
	62	29	44

(Bread may be toasted after weighing.)

The carbohydrate in the meal may be modified by adding or subtracting bread, each half ounce counting as 9 grm. of carbohydrate. Pieces of "Vita Weat" or Huntley & Palmer's breakfast biscuits count as 6 grm. of carbohydrate, and therefore it is easy to arrange the meal to contain the prescribed quantity.

Since the ounce of butter counts as 24 grm. of fat it is easy to modify the fat content.

The protein content can be altered too, but the majority require between 1½ and 2 grm. of protein per kgrm. bodyweight per diem, and therefore the variations are not so great as for the other forms of food.

	Carbo-hydrate.	Pro-tein.	Fat.
Luncheon I:			
A loin chop weighing raw 5 oz.		24	15
Vegetable unlimited	2		
Vita Weat, two pieces	12		
Butter, 1 oz.			24
Cheese, 1 oz.		10	10
	14	34	49

	Carbo-hydrate.	Pro-tein.	Fat.
Luncheon II:			
Fish, 6 oz. weighed raw		24	12
Vegetable unlimited	2		
Vita Weat, one piece	6		
Cheese, 1 oz.		10	10
Butter, 1 oz.			24
Grapefruit, ½, or apple, 2 oz., or 4 oz. strawberries	5		
	13	34	46
Luncheon III:			
Omelette, 2 eggs		12	10
Butter, ½ oz.			12
Tomato or asparagus heads or truffles	2		
"Vita Weat," 1	6		
Butter, ½ oz.			12
Cheese, 1 oz.		10	10
Apple, 2 oz.	5		
	13	22	44
Luncheon IV:			
Omelette, 2 eggs		12	10
½ oz. butter			12
1 oz. kidney or ham or lobster, or ¾ oz. cheese		10	
"Vita Weat," 2 pieces	12		
Lettuce or watercress	2		
Butter, ½ oz.			12
Cheese, ½ oz.		5	5
	14	27	39
Luncheon V:			
Cold salmon, 4 oz.		24	10
Lettuce, cucumber	2		
Mayonaise, 2 oz.			30
Potato, cold boiled, 2 oz.	12		
	14	24	40

	Carbo-hydrate.	Pro-tein.	Fat.
Luncheon VI:			
Brains, weighed raw, 6 oz.		24	8
Butter, ½ oz.			12
Bread crumbs, ¼ oz.	6		
Green vegetable	2		
Vita Weat, one piece	6		
Butter, ½ oz.			12
Cheese, ½ oz.		5	5
	14	29	37
Luncheon VII:			
Cold roast chicken, 3 oz.		24	6
Lettuce, etc.	2		
Mayonaise, 2 oz.			30
Potato, cold boiled and sliced, 2 oz.	12		
	14	24	36
Dinner I:			
Clear soup unlimited			
Lean meat, 3 oz.		24	9
Fat of meat, ½ oz.			12
Potatoes, 4 oz., weighed raw or boiled	24		
Vegetables, such as cabbage, cauliflower, cucumber, lettuce, kale, asparagus, celery, string beans, vegetable marrow, chicory, endive, and spinach unlimited.	2		
Butter, 1 oz.			24
Cereal, 1 oz. } milk pudding	20		
Milk, 10 oz. } milk pudding		16	12
	66	40	57
Dinner II:			
Clear soup unlimited			
Fish, 8 oz., weighed raw, may be grilled, boiled or fried		32	12
Potato, 4 oz.	24		
Vegetable	2		
Bread, 1 oz.	18	1	
Cheese, 1 oz.		10	10
Butter, 1½ oz.			36
Fruit apple, 8 oz., or pear, 6 oz., or strawberries, 16 oz., or raspberries, 12 oz.	20		
	64	43	58

Dinner III:	Carbo-hydrate.	Pro-tein.	Fat.
Clear soup			
Sweet bread or brains, 6 oz.		24	9
Vegetable unlimited	2		
Pudding, composed of flour, 2 oz., 1 egg, sugar, ¼ oz., suet, 1 oz., dried fruit, ½ oz.	57	14	29
Cream 2 oz.	2		12
Apple, 2 oz.	5		
	66	38	50
Dinner IV:			
Thick soup, ½ pint	20		
Roast chicken, 3 oz.		24	9
Vegetable unlimited	2		
Bread, 2 oz..	38	4	
Cheese, 1 oz.		10	10
Butter, 1 oz.			24
Apple, 2 oz., or strawberries, 4 oz.	5		
	65	38	43
Dinner V:			
Clear soup unlimited			
Game or poultry roast, 4 oz.		32	12
Potato, 2 oz., weighed raw or boiled	12		
Vegetable unlimited	2		
Apple tart, 4 oz., stewed apples with a little sugar and 2 oz. crust	10 36		5
Thick cream, 4 oz.	4		48
	64	32	65
Dinner VI:			
Clear soup			
Fish, 3 oz.		12	
Chicken, 2 oz.		16	6
Salad	2		
Mayonaise salad dressing, 2 oz.			30
Potato, 2 oz.	12		
Fruit tart, 2 oz. crust	36		5
Fruit, 4 oz. apples, raspberries or currants	10		
Thin cream	2		12
	62	28	53

The following tables permit the diets being varied:

Five Grammes of Carbohydrates are Contained in the Following Quantities of—

Grm.	Oz.		Protein.	Fat.
70	2¼	Almonds, edible part	6	15
60	2	Apples, raw		
100	3½	Apples, stewed		
100	3½	Apricots, ripe, raw		
200	7	Apricots, stewed		
50	1¾	Apricots, dried, stewed		
300	10	Artichokes, globe		
200	7	Artichokes, Jerusalem		
300	10	Asparagus, boiled		
	6	Asparagus, tinned		
6	¼	Arrowroot		
30	1	Bananas		
30	1	Beans, Haricot		
350	12	Beans, scarlet runners		
60	2	Beetroot, boiled		
140	3	Bilberries, raw		
200	7	Bilberries, stewed		
7	¼	Biscuits		
100	3½	Blackberries, raw		
140	5	Blackberries, stewed		
9	⅓	Bread, white, fresh		
8	¼	Bread, white, stale		
9	⅓	Bread, brown, fresh		
180	6	Brussel sprouts, boiled		
120	4	Brussels sprouts, steamed		
400	14	Cabbage, spring, boiled		
500	17	Cabbage, winter, boiled		
80	2½	Carrots, boiled		
400	14	Cauliflower, boiled		
500	16	Celery, raw		
1000	32	Celery, stewed		
90	3	Cherries, weighed with stones		
100	3½	Cherries, stewed		
800	28	Chicory, raw or cooked		
100	3½	Cocoanut	3	25

Grm.	Oz.		Protein.	Fat.
200	7	Cocoanut milk		
500	16	Cranberries, stewed		
100	3½	Cream, thin		
150	16	Cream, thick, fresh		
300	10	Cucumber, raw without skin		
180	6	Currants, black, raw		
300	10	Currants, black, stewed		
130	4½	Currants, red, raw		
180	6	Currants, red, stewed		
110	3⅔	Damsons, raw		
180	6	Damsons, stewed		
210	7⅓	Egg-plant, raw		
200	7	Endive		
180	6	Fennel, raw		
240	8	Fennel, cooked		
70	2⅓	Figs, green, imported, raw		
30	1	Figs, green, homegrown, raw		
25	1	Figs, dried, stewed		
90	3	Gooseberries, raw, ripe		
330	11½	Gooseberries, stewed, unripe		
80	3	Grapefruit, fresh, without skin		
50	1⅓	Grapes		
80	3	Greengages, raw		
160	5½	Greengages, stewed		
60	2	Horseradish, raw		
7	¼	Jam		
1000	32	Kale		
160	6	Leeks, stewed		
700	23	Lettuce, raw		
150	5	Loganberries, raw		
290	10	Loganberries, stewed		
7	¼	Macaroni, raw		
10	⅓	Marmalade		
200	7	Marrow, vegetable		
200	7	Melons, water		
70	2½	Milk, fresh		
90	3	Mulberries, raw		
900	30	Mustard and cress, raw		
75	2¾	Nectarines, ripe (including stone)		
100	3½	Brazil, without shells	18	60

Nuts.

Grm.	Oz.		Protein.	Fat.
100	3½	Barcelona	10	30
17	⅝	Chestnuts		
70	2¼	Hazel	10	40
45	1½	Peanuts	10	14
45	1½	Pistachio	8	20
100	3½	Walnuts	10	24
		Olives (contain no usable carbohydrate)		18%
90	3	Onions, boiled		
100	3½	Onions, spring, raw		
80	2¾	Orange, without skin		
80	2¾	Orange juice		
50	1¾	Parsnips, boiled		
75	2½	Peaches, fresh, weighed with stone		
40	1⅓	Peaches, dried stewed		
70	2¼	Pears, with skin		
100	3½	Pears, stewed		
40	1⅓	Peas, fresh	1	
28	1	Peas, dried	1	
28	1	Peas, tinned	1	
56	2	Persimmon, raw		
200	7	Pickles, without sugar		
50	1¾	Pineapple, edible part, fresh		
56	2	Plums, Victoria, raw, ripe, weighed with stone		
200	7	Plums, stewing varieties, stewed weighed with stones		
40	1½	Potatoes, new, boiled		
28	1	Potatoes, old, boiled		
40	1⅓	Prunes, stewed		
200	7	Pumpkin, raw, weighed with skin		
300	10	Radishes, raw		
180	6	Raspberries, raw		
200	7	Raspberries, stewed		
500	17	Rhubarb, stewed		
6	⅕	Rice, raw,		
	⅕	Sago		
270	9	Salsify, boiled		
360	12	Seakale, boiled		
15	½	Soya bean meal	12	3

Grm.	Oz.		Protein.	Fat.
270	9	Spinach, boiled	5	
120	4	Strawberries, ripe	1	
6	$\frac{1}{5}$	Tapioca		
7	$\frac{1}{4}$	Toast Melba		
200	7	Tomatoes, raw		
90	3	Truffles, cooked	4	
150	5	Turnips, boiled	5	
500	17	Watercress, raw		

In this table the ounce has been calculated as equal to 30 grm.

*Twenty Grammes of Protein may be Taken in the Following Forms—

Grm.	Oz.		Fat in grm.	Carbo-hydrate grm.
100	$3\frac{1}{2}$	Bass, steamed	5	0
100	$3\frac{1}{2}$	Bream, red, steamed	4	0
100	$3\frac{1}{2}$	Brill, steamed	3	0
112	4	Cod, steamed	1	0
84	3	Cod, fried in batter with crumbs	5	3
84	3	Cod's roe, parboiled and fried	12	3
100	$3\frac{1}{2}$	Dabs, fried in batter with crumbs	14	10
180	$6\frac{1}{2}$	Eels, stewed	36	0
100	$3\frac{1}{2}$	Flounder, steamed	2	0
100	$3\frac{1}{2}$	Gurnet, red, steamed	3	0
84	3	Haddock, steamed	1	0
106	$3\frac{3}{4}$	Hake, steamed	3	0
100	$3\frac{1}{2}$	Hake, fried in batter and crumbs	11	5
84	3	Halibut, steamed	4	0
100	$3\frac{1}{2}$	Herring, fried	19	0
77	$2\frac{3}{4}$	Herring roe, soft, floured and fried	16	5
100	$3\frac{1}{2}$	John Dory, steamed	1	0
100	$3\frac{1}{2}$	Lemon sole, steamed	1	0
130	$4\frac{3}{4}$	Lemon sole, fried in batter with crumbs	16	10
100	$3\frac{1}{2}$	Mackerel, fried	11	0
100	$3\frac{1}{2}$	Mullet, red, steamed	4	0
112	4	Plaice, steamed	2	0
112	4	Plaice, fried in batter with crumbs	16	7
100	$3\frac{1}{2}$	Salmon, steamed	13	0

* The twenty grammes' unit permits greater accuracy than the five grammes' unit, when weighing ounces and fractions of ounces.

Grm.	Oz.		Fat in grm.	Carbo-hydrate grm.
133	4¾	Skate, fried in batter with crumbs	20	9
84	3	Smelts, floured and fried	24	4
112	4	Soles, steamed	2	0
100	3½	Soles, fried in batter with crumbs	18	5
92	3¼	Sprats, fried in fat only	36	0
92	3¼	Trout, steamed	3	0
100	3½	Turbot, steamed	2	0
112	4	Whitebait, floured and fried	50	5
100	3½	Whiting, steamed	1	0
112	4	Whiting, fried in batter with crumbs	11	7
		SMOKED FISH.		
84	3	Bloaters, grilled	16	0
100	3½	Haddock, smoked, steamed	1	0
84	3	Kipper, baked	11	0
100	3½	Sardines in oil	23	0
84	3	Sprats, smoked	20	0
106	3¾	Crab, boiled	5	0
100	3½	Lobster, boiled	3	0
100	3½	Prawns, boiled	2	0
180	6½	Cockles, boiled	1	0
118	4¼	Mussels, boiled	3	0
200	7	Oysters, raw	2	0
84	3	Scallops, steamed	1	0
112	4	Whelks, steamed	2	0
112	4	Winkles, boiled	3	0
		MEATS.		
70	2½	Sirloin of beef, roasted	8	0
63	2¼	Steak, stewed	6	0
100	3½	Steak, fried	20	0
63	2¼	Mutton chop, lean, grilled	18	0
70	2½	Leg of mutton, boiled	16	0
84	3	Pork, leg, roasted	16	0
70	2½	Pork, loin, roasted	23	0
70	2½	Pork, loin chop, grilled	20	0
63	2¼	Veal cutlet, fried in batter with crumbs	5	3
84	3	Venison, haunch, roasted	6	0
63	2¼	Hare, stewed	6	0
63	2¼	Hare, roasted	5	0
77	2¾	Rabbit, stewed	6	0

Grm.	Oz.		Fat in grm.	Carbo-hydrate grm.
84	3	Bacon, back, rashers, fried	43	0
84	3	Bacon, streaky	41	0
84	3	Ham, lean	11	0
84	3	Beef, corned	13	0
		POULTRY.		
77	2¾	Chicken, boiled	8	0
70	2½	Chicken, roasted	5	0
92	3¼	Duck, roasted	21	0
70	2½	Goose, roasted	18	0
63	2¼	Grouse, roasted	3	0
56	2	Guinea-fowl, roasted	6	0
56	2	Partridge	5	0
63	2¼	Pheasant, roasted	7	0
70	2½	Pigeon, roasted	10	0
56	2	Turkey, roasted	5	0
		MISCELLANEOUS.		
170	6	Brain, calf, boiled	12	0
170	6	Brain, sheep, boiled	13	0
84	3	Heart, sheep, roasted	18	0
70	2½	Kidney, sheep, fried	6	0
63	2¼	Liver, calf, fried in batter with crumbs	10	2
63	2¼	Liver, ox, fried in batter with crumbs	10	3
92	3¼	Sweet-bread, stewed	8	0
112	4	Tongue, ox, boiled	26	0
112	4	Tripe, stewed	12	0
56	2	Caviar	—	—
112	4	Cheese, Blue	28	0
56	2	Cheese, Cheddar	24	0
84	3	Cheese, Camembert	20	0
56	2	Cheese, Cheshire	24	0
84	3	Cheese, Cream	30	0
56	2	Cheese, Dutch	8	0
84	3	Cheese, Roquefort	28	0
140	5	Paté de Foie Gras	48	5

In this table the ounce has been calculated equal to 28 grm.

FAT.

One ounce of butter = 24 grm.
,, ,, fat of meat = 24 ,,
,, ,, olive oil = 28 ,,

Method of Administrating Insulin.

Insulin must be administered either subcutaneously, intramuscularly or intravenously. The last method is used when there is urgency for insulin to produce an effect or when there is severe infection and a chance of rapid destruction. Insulin and compounds of insulin, when given by the mouth, either act not at all, or are so variable that they are impracticable at the present time.

A hypodermic syringe is taken to pieces, placed in cold water, and boiled for 3 minutes; after the water has boiled for a minute and all the air expelled, the needle is dropped in, apparently this leads to less blunting of the point than if it is placed in cold water and boiled with the syringe. The syringe is allowed to cool and then assembled, the rubber cap of the vial containing insulin is wiped with spirit and then the syringe is filled with the volume of air equal to the volume of insulin which is to be abstracted from the vial. The needle of the syringe is made to pierce the rubber cap and the piston of the syringe is pushed home, the vial and syringe are then reversed and the piston pulled out until the syringe contains the prescribed dose. If bubbles appear they rise to the top and may be returned to the container by pushing in the piston and fresh fluid is extracted by drawing the piston down again. By manipulating in this manner the requisite dose of insulin without bubbles can be obtained even if the syringe leaks a little. The needle is then withdrawn from the container.

The object of introducing air before withdrawing insulin is to prevent a negative pressure developing in

the vial which would lead to considerable difficulty in filling the syringe.

The insulin is then injected into the patient; the skin over the selected area should be wiped with spirit or acetone, the skin lifted and the needle of the syringe made to pierce the skin at right angles. Care should be taken that the needle pierces the skin, intra-cutaneous injection is painful.

The needle should be inserted for not more than three-quarters of its length. If a needle breaks it is most likely to break at its junction with the nozzle; if inserted up to the nozzle when it breaks, it cannot be retrieved; if a few millimetres project from the skin, it can be pulled out with a pair of depilatory forceps. Depilatory forceps should be included in the tackle for subcutaneous injection. Should a needle be broken off in a patient it is wise to leave it, the chance of it causing trouble is infinitesimally small.

After use, the syringe and needle are rinsed in spirit and kept in this fluid. Repeated boiling of a syringe damages it because the coefficients of expansion of glass and metal are not identical and therefore the junction does not remain airtight.

The site of injection must depend upon circumstances; those who have to inject themselves find the thighs the most convenient site. If the same site be used repeatedly the tissues become hard and there is difficulty in introducing the needle, and in addition to this, upon withdrawal of the needle some of the insulin escapes. It is questionable too, whether absorption of insulin is not delayed when the injection is made into this hardened tissue.

In order to prevent this happening the following method may be adopted. Three imaginary parallel lines are drawn down the thighs, one in the middle and one an inch exterior, and the third one inch interior.

The first injection is made at the top of the right-sided exterior line, the second at the top of the left-sided exterior line, the third injection one inch down the right line and so on; each line will allow about ten injections, so that the six lines will afford 60 sites, and therefore if only two injections are made daily the same site need not be used for one month, during which time the tissues will have had opportunity of making a complete recovery.

If the patient can have the injections performed for him he may have a series into the muscle of the upper part of the gluteal region; this part is very insensitive and usually gives rise to no discomfort.

Some individuals are sensitive to some makes of insulin; personally I favour an insulin free from preservative, but the local reaction does not necessarily depend upon trikresol. If one make of insulin causes local redness and swelling followed by irritation, another make should be tried.

It is rare for the patient to have discomfort following injections of all makes.

If the injection causes stinging due to the slight acidity of the solution, this can be avoided by mixing the insulin in the syringe with an equal part of sterile 2% solution of sodium bicarbonate. This will cause the insulin to be thrown out of solution, but the suspended insulin will be absorbed and the effect upon the metabolism in man cannot be distinguished from the injection

of the acid solution. The actual piercing of the skin may cause pain in some especially sensitive individuals ; some of these find relief by the application of a drop of phenalaine oil through which the needle is passed into the skin.

Occasionally, but fortunately very rarely, the injection of insulin is followed by a severe attack of urticaria. The treatment of these cases must be postponed until they have developed tolerance, and in order to produce tolerance the dose must be reduced to a few cubic millimetres and then gradually increased ; it is unusual for it to take more than a week for tolerance to be established.

THE SYRINGE.

For the really intelligent patient a "Tuberculin" syringe marked in hundredths of a cubic centimetre and fitted into a spirit proof case is the ideal. He is able to work out the volume of his dose for the different concentrations of insulin and error cannot arise in the same way as when a syringe is marked in units for one concentration of insulin and another concentration is used.

Insulin is supplied in aqueous solution in three concentrations, 20 units per c.c., 40 units and 80 units.

I think that if the patient is unaccustomed to measure or to do arithmetic it is wise for him to use a syringe marked in units for the concentration of insulin he is to use.

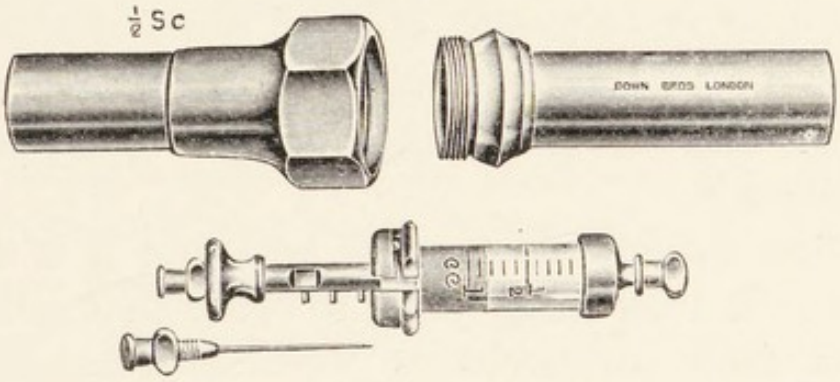
The concentration used naturally depends upon the dose required ; it is wise when possible to keep the volume of the injection below $\frac{1}{2}$ c.c., therefore, if the

dose is up to 10 units of insulin of 20 units per c.c. is used between 10 units and 20 units insulin of 40 units per c.c., and above 20 units, of 80 units per c.c.

A portable syringe in a spirit-proof case may be obtained which can carry the dose of insulin in it for an almost indefinite time.

The piston of the syringe can be locked in certain positions, whilst the end of the syringe is sealed with a cap. The needle is housed in the piston.

Diagram XII.



For use, the cap is removed and the needle fixed to the nozzle. One drop of fluid is then allowed to fall from the end of the needle before inserting it under the skin. The object is to remove any spirit which may be in the needle.

If the patient is going upon a journey, he can pack in his bag a few ready loaded syringes and thus save himself much trouble.

INSULIN.

Insulin is made by many manufacturers, and at the present day all brands in England are excellent.

The standard of purity is high, crystalline insulin

has a potency of 25 units per mgrm. ; several insulins upon the market have a potency of more than 20 units for each milligramme of solid in the solution.

The dearest brands are not necessarily the purest.

The advisability of adding antiseptic to the aqueous solution is far from established. It is true that the British Pharmacopœia, 1933, insists upon antiseptics being added if the solution of insulin is packed in rubber capped vials containing more than one dose.

One can only advise the addition of antiseptics to the solution of insulin by making two assumptions, namely, that the injection of small doses of antiseptics over very long periods is harmless and that the antiseptic does not lead to local inflammation upon injection under the skin.

The first assumption may be true, but it is difficult to prove. It took many years to prove that salicylates used as food preservatives were detrimental to a susceptible minority and a very long time to discover that phenolphthaleine is not completely innocuous, so that it is still early days to assert that trikresol is harmless.

It is beyond doubt that some individuals and especially quite young individuals are susceptible to trikesol and develop small areas of inflammation around every injection ot insulin containing that antiseptic, whilst an insulin free from antiseptic fails to cause any discomfort.

If pathogenic micro-organisms were able to grow in a solution of insulin in the absence of antiseptic, the risk of local irritation and perhaps some change in the kidneys could not be avoided, but it has been proved

repeatedly by several observers that the acidity of the solution of insulin is sufficient to prevent bacteria multiplying and to kill certain varieties.

It is true that before it had become the habit of patients to keep their syringes in spirit there was the possibility of their introducing carelessly sufficient alkaline water into the vial of insulin to reduce the acidity, but this showed itself invariably by the solution turning turbid.

Only water-clear insulin should be used, although turbidity may result from minute quantities of surgical spirit being injected into the insulin solution. The castor oil (contained in the surgical spirit) is thrown out of solution and makes the insulin turbid. Although the injection of this would be harmless, it is not wise to depart from the rule that any vial of insulin which contains a solution which is not water-clear should be returned to the manufacturer.

The syringe should not be kept in surgical spirit, since if traces of surgical spirit are injected they cause much more irritation than traces of methylated spirit or rectified spirit.

INSULIN IN SUSPENSION IN CASTOR OIL.

One of the disadvantages of the use of insulin in aqueous solution is that its time of action is limited to 8 hours; this may necessitate several injections during the 24 hours if the patient is suffering from severe diabetes mellitus. In order to keep the concentration of sugar in the blood below 0·15% throughout the 24 hours, injections of insulin may be needed, not only before

the three main meals, but also towards and shortly after midnight when the pancreas is unable to elaborate sufficient insulin to store the carbohydrate liberated from protein metabolism during sleep.

Some number of years ago I carried out observations with the object of devising some method of delaying the absorption of insulin. The first to be tried was the addition of albumen to the insulin solution; this proved unavailing. I then tried dry powdered insulin in suspension in various oils.

If the suspension be in olive oil, the absorption is practically as rapid as when dissolved in water, but when suspended in castor oil the insulin is absorbed slowly.

The charts illustrate the effect.

There are undoubtedly several disadvantages in using insulin suspended in castor oil :

(1) A larger dose is required than when aqueous insulin is used.

(2) In some patients the injections cause pain.

(3) The suspension is viscid and therefore the technique of the injection is less easy.

(4) The absorption of the oil may be very slow indeed.

(5) The cost is still greater than that of aqueous insulin.

Some observers assert that however carefully the oily suspension of insulin is administered there is a risk of the development of abscesses. I cannot help thinking that this must depend upon the care with which the suspension is prepared.

There should be no difficulty in sterilizing the suspension. If the insulin and the oil are completely

DIAGRAM XIII.

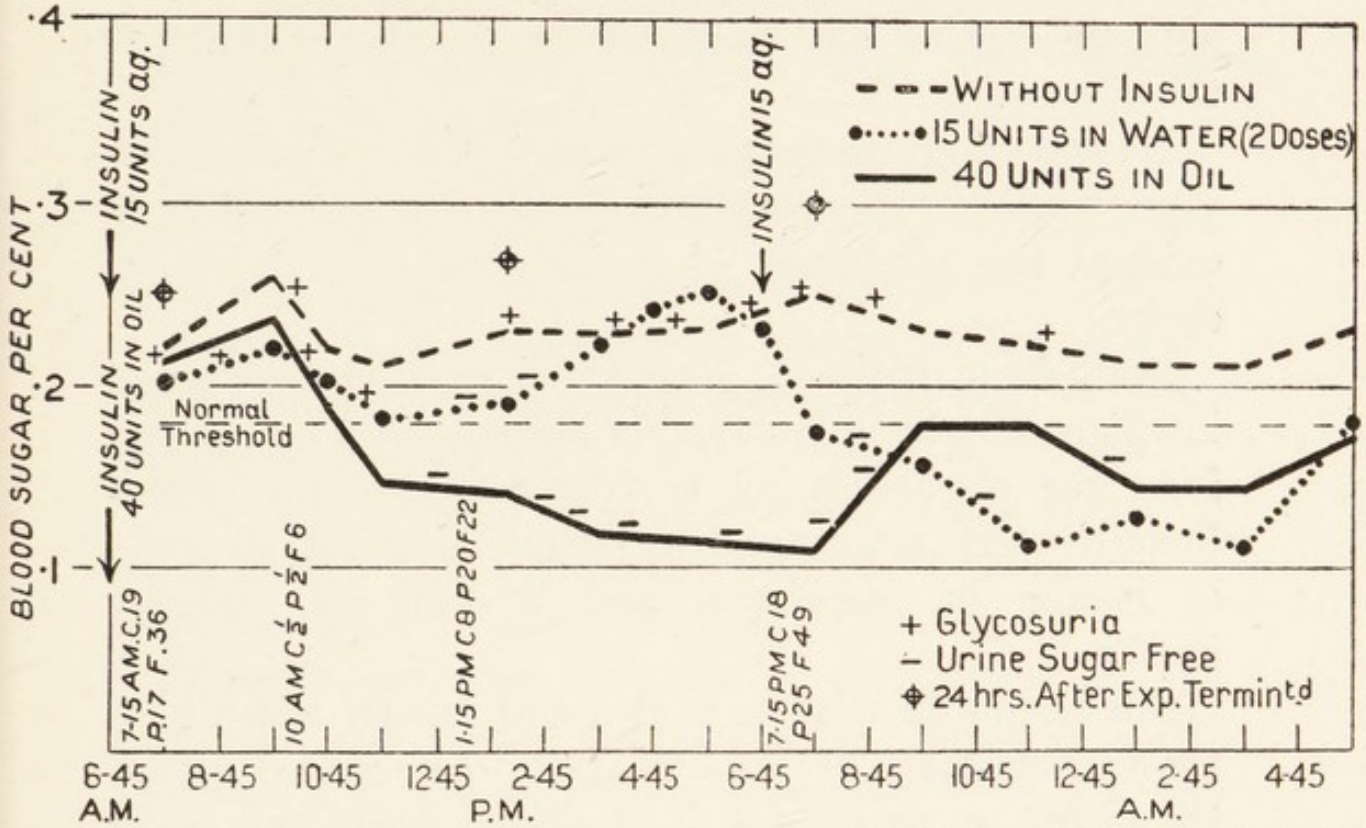


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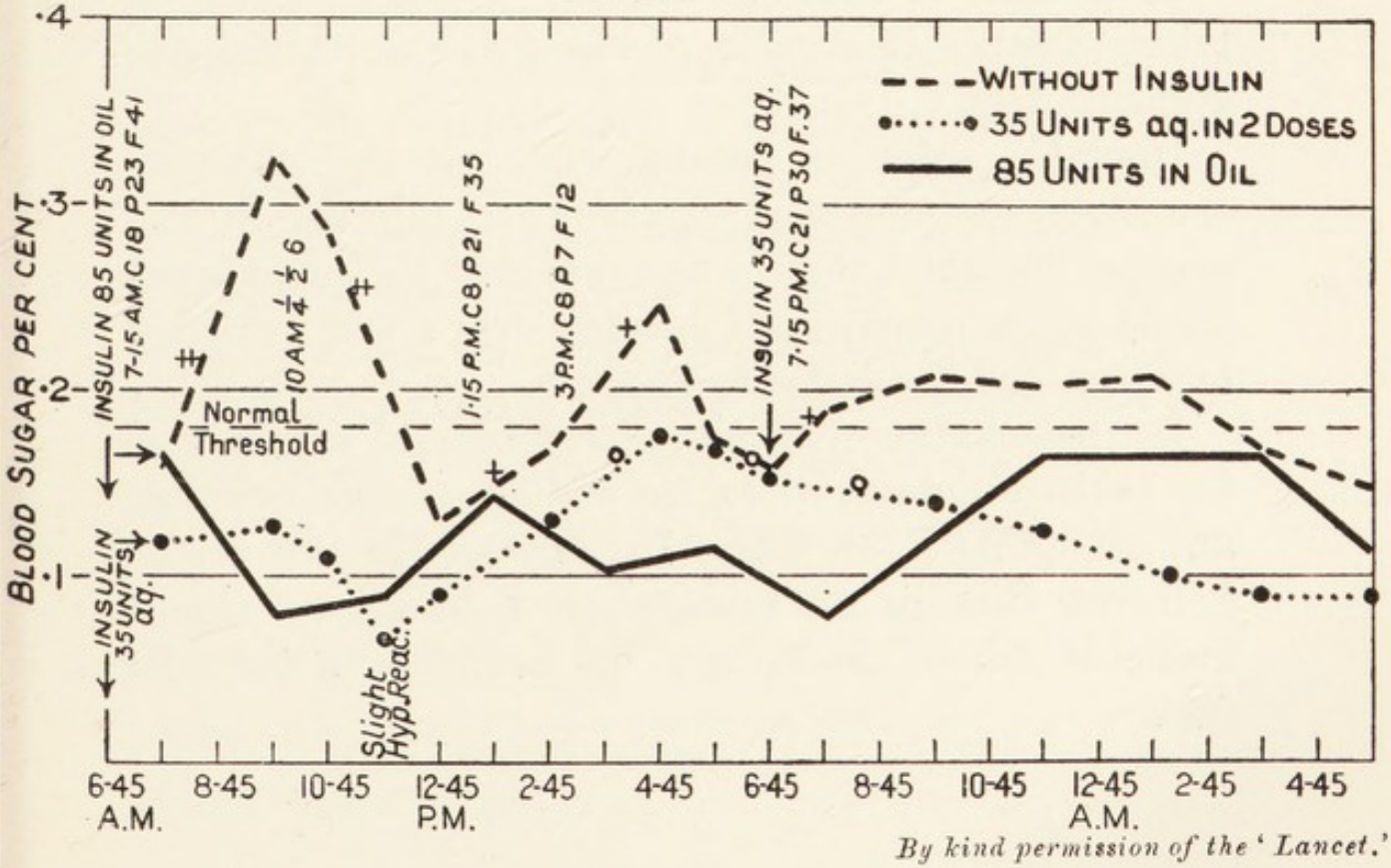
DIAGRAM XIV.



By kind permission of the 'Lancet.'

free from moisture, the suspension may be autoclaved without causing any material loss in the activity of the suspension.

Several of my patients have used this suspension for years without experiencing any inconvenience and have enjoyed the advantage of needing only one injection daily.

One of my patients, a youth of more than average intelligence, who unfortunately has not made a recovery from the disease owing to frequent infections, gives himself every morning an injection of about 40 units of insulin in suspension and 8 units of aqueous insulin.

The insulin in solution is absorbed rapidly and allows the carbohydrate of his breakfast to be stored whilst the insulin in suspension is absorbed slowly and takes care of the carbohydrate of lunch and dinner.

From time to time the efficacy of this is tested by taking a series of samples of blood and estimating the sugar content.

Insoluble salts of insulin, such as the phospho-tungstate, are absorbed slowly when injected in suspension, but since there is no proof that the preparation would prove innocuous if injected over a long period, I have not had the audacity to use it.

In conversation with one of my friends, a man who has perhaps done more for the welfare of diabetics than any excepting F. M. Allen, Banting and his associates, I learnt that in all probability a harmless, almost insoluble salt of insulin may be available in the near future.

DIABETES OF GREAT SEVERITY.

Diabetes of unusual severity may need unusual methods in its treatment.

It is far from uncommon for a diabetic patient to need a gradual increase in the dose of insulin when upon a fixed diet because there is some hidden focus of infection. It is not possible to emphasize too strongly the necessity of detailed examination of all diabetics with the object of discovering a source of bacterial toxins.

When, in spite of the most careful examination, no focus can be found it is advisable to see the effect of changing the flora in the intestine.

It seems probable that the benefit derived by the purgation and fasting introduced by Guelpa and also the fasting at the beginning of treatment on the lines laid down by F. M. Allen depends to some extent upon the diminution in absorption of products of putrefaction from the alimentary tract.

This can be accomplished by either placing the patient upon water only, a procedure which is not without risk in the severest types of diabetes mellitus, or by giving sugar and water and nothing besides.

A similar effect can be obtained by limiting the diet of the patient to foods rich in carbohydrate; the following régime has succeeded in a number of cases:

8 a.m. A cup of tea, 2 oz. of bread toasted, and half an ounce of marmalade.
11 a.m. 10 oz. of orange juice, 2 Huntley & Palmer's breakfast biscuits.
2 p,m. Four pieces of Vita Weat and 1 oz. of currant jelly.
5 p.m. A cup of tea, and 8 oz. of apple stewed with 1 oz. of sugar.
8 p.m. The juice of two lemons with water, and 1 oz. of sugar along with two biscuits.
11 p.m. 8 oz. of grapes.

This diet, along with six injections of insulin, each about half an hour before food and in sufficient quantity to keep the sugar content of the blood below 0·15%, leads frequently to a change in the metabolism which permits the doses of insulin to be reduced after two or three days. So long as reduction in insulin continues to be necessary, the diet should be continued; when a condition of equilibrium has been attained a return to the earlier diet should be made and then it will be found that in a very large percentage of cases smaller doses will suffice to prevent hyperglycæmia than were required before the purely carbohydrate diet.

Unfortunately, the improvement is not necessarily permanent, and a repetition of the almost pure carbohydrate diet may be necessary from time to time.

A still more efficacious method seems to be the administration of lactose to which the lactic acid-forming bacillus has been added.

Occasionally, but rarely, the addition of a guanidine compound given by the mouth may permit a slight reduction in the dose of insulin.

All patients who receive insulin should become acquainted with the symptoms of hypoglycæmia before they leave hospital or nursing home.

This usually can be arranged by their having carbohydrate omitted from their breakfast on one occasion.

Symptoms may develop 3 hours after the injection of insulin and may be dispelled by taking two lumps of sugar. If the patient has not experienced the symptoms he may become alarmed and fail to recognize the condition.

All patients on insulin should carry sugar with them at all times. Hypoglycæmia will be discussed later.

TREATMENT OF CHILDREN.

Diabetic children make wonderful patients.

The treatment in no wise differs from that of the adult; the adult is given a suitable diet and the child is given a suitable diet, but these are not identical, nor proportional.

The child needs a diet of relatively high energy value and relatively more protein.

The adult requires not less than 0·75 grm. of tissue-repairing protein per kilogramme body-weight per diem, whilst the growing child needs not less than 3 grm. of tissue-repairing protein per kilogramme body-weight per diem.

If the child is starved of protein he cannot grow; unfortunately, he is not like retarded plants, which make up for retardation quite rapidly when environment is favourable, but remains short for all time.

The growing child must have plenty of protein in his diet, much of which may have to be given as milk. The energy of his diet must be high too, depending upon age, up to 80 Calories per kilogramme body-weight.

The young child may dread the sting following the injection of insulin and cry before each injection.

The discomfort can be reduced by using an insulin free from preservative and adding to the insulin in the syringe a quarter the volume of an 8% solution of bicarbonate of soda.

The content of the syringe will become cloudy due

to precipitation of the insulin, but the action will be unimpaired and the neutral liquid will not sting in the same way as the slightly acid solution of insulin.

THE TREATMENT OF DIABETES DEVELOPING AFTER THE AGE OF SIXTY.

Throughout this book emphasis has been laid upon the fact that no two people are exactly alike, and that treatment must be adapted to the individual.

As a rule when diabetes mellitus develops after the age of 60 it is insidious in onset and does not give rise to symptoms. Glycosuria is discovered upon routine examination or perhaps because balanitis or vulvitis makes the patient seek medical advice.

When there are symptoms or complications the disease should be treated in the same way as if the patient were young, but in the absence of symptoms the patient should be examined to determine whether the excess of sugar in the blood is causing any deterioration of the tissues.

The blood-pressure is measured and the size of the pulse at the ankle determined with an oscillometer.

The retinæ are examined for retinitis, hæmorrhages and changes in the blood vessels. The lens is examined to see whether cataract is present. The reflexes are examined to find out whether there are changes in the nervous system.

If there is no evidence that the tissues are degenerating and the patient has no polyuria or other symptoms there is no object in imposing restrictions. The patient is advised to continue living as in the past, *but to present*

himself to his usual medical adviser every 3 months in order that there shall not be any delay in beginning treatment should there be evidence that hyperglycæmia is proving detrimental. I have known patients enjoy many years free from symptoms and free from restrictions and die from complaints totally unconnected with diabetes mellitus.

If the onset be acute, then of course the ordinary treatment is adopted ; the aged have as good a chance of making a recovery as the young.

SUBSEQUENT TREATMENT.

Having prescribed for the patient a diet which is approximately that which he has been accustomed to eat before he became ill along with sufficient insulin which, when given at the times ordered, keeps the sugar in the blood below 0·15% throughout the 24 hours, no change should be made for several months.

Often, after a time, the patient begins to complain of fatigue towards mid-day and great hunger shortly before mid-day meal. If the sample of blood is taken and the sugar in it estimated it will be found to be very low ; if below 0·07%, samples of blood should be taken one hour after the four meals. If at these times the concentration of sugar does not rise to 0·14%, a slight reduction in the dose of insulin should be made, perhaps a decrease of 2 units.

When the symptoms of hypoglycæmia recur the above observations are repeated, and perhaps a further reduction may be indicated.

Experience has taught me that a rapid decrease in insulin and its cessation under a year rarely proves satisfactory ; in early days I used to advise it and saw a number of relapses. It is better to give too much insulin than not enough. Occasionally the dose of insulin has to be increased from time to time, but this in the great majority of cases is due to some infection.

Hope should be kept alive in the breast of every patient ; from time to time I have seen patients who have had to add to their doses of insulin month after month, and then, without any apparent reason, become stationary and later been able to reduce the doses and finally discard insulin.

I think that it is wise to forbid the patient to test his urine for sugar, because it is so hard for the uninitiated to realize that the disease may progress whilst the urine is sugar-free. When I allowed my patients to test the urine, from time to time I saw patients whom had had diet and doses of insulin adjusted to keep the sugar content of the blood below 0·15% throughout the 24 hours, return because glycosuria had re-occurred. Upon questioning the patient I learnt that they had added a little more bread to the diet and found that the urine remained sugar-free and therefore had made further additions until the test became positive and then reduced the quantity again until the urine was sugar-free. The addition of carbohydrate without any addition of insulin had led to the sugar content of the blood often rising above 0·15% with the usual result, namely, progress of the disease.

The patient should not be allowed to reduce his dose of insulin without permission. The physician should

make his patients promise not to reduce their doses in any circumstances without obtaining his permission. One of the reasons for doing this is to guard them against damage should they have the misfortune to come under the treatment of a practititioner of medicine who "does not believe in insulin" or one who says that when another disease such as pneumonia attacks the patient the new disease must be combatted and the diabetes must take care of itself. The patient tells the doctor that he has promised not to reduce his dose of insulin, and would he therefore kindly ring up the physician and obtain his permission. This gives him the opportunity of explaining that any intercurrent infection calls for more insulin and not less.

The argument advanced will be that the patient is unable to eat the prescribed diet and therefore should not have insulin lest hypoglycæmia develop.

The infected patient should continue to receive at least as much carbohydrate as when well, but should reduce the protein and fat. The infection will reduce the activity of the insulin and therefore, in spite of the total energy of the diet being less, the patient will require at least as much insulin. Naturally, the form in which the carbohydrate is given is changed to suit the requirements of the patient.

DO PATIENTS RECOVER FROM DIABETES MELLITUS?

In order to reply to this question it is essential for the word "recover" to be defined.

I purpose using it in its popular sense rather than its academic, because if we use the latter, recovery does not occur after any disease.

The academic definition is, "a return to the condition which existed before the disease or injury." Robust health may follow an attack of typhoid fever, but there may be some Eberth's bacilli lurking in the gall-bladder, the periosteum or other tissues, and even if the bacilli have been exterminated, nevertheless, agglutinins persist in the blood for a variable time after the patient has made a recovery (using the word in its usual meaning). Again, however well a patient may appear to be after pneumonia, the fact that there may be some alteration in the fibrous tissue of the lung precludes the statement that he has recovered (giving the word its academic definition). I shall assume that, if the patient has returned to robust health and a year after ceasing treatment does not present any signs of disease, then one may say that he has recovered.

The fact that he may suffer from the disease again in the future does not prevent our saying that he has recovered. We are accustomed to talk about a patient's recovery from pneumonia in spite of the fact that some number have further attacks after intervals of a year or even less.

It would not be correct to say that a patient had recovered from myxœdema so long as he was taking thyroid gland by the mouth; so too, we could not record a case of recovery from diabetes mellitus so long as the patient was receiving insulin, however robust he might be. If, on the other hand, a patient who has suffered from undoubted diabetes mellitus has ceased to take insulin for a year and is able to katabolize a normal diet without developing hyperglycæmia, that patient may be said to have recovered from diabetes mellitus, in spite

of the fact that he may develop another attack at some future date.

The cause of the disease is not known, and therefore it is not possible to distinguish between relapse and second attack.

The term "relapse" is used when recovery is not complete. Applying the same rule to pneumonia, we might assert that a second attack was a relapse, but most use the term "relapse" to indicate an exacerbation of the condition before complete return to health has occurred.

Terminology does not alter facts.

There is no doubt that patients who have had all the signs and symptoms of diabetes mellitus have, after a period of treatment with insulin, been able to cease taking insulin and return to an unrestricted diet, and have persisted in this normal condition for more than 5 years.

If it were argued that these patients had never suffered from diabetes mellitus, the reply would be that they had had a complaint indistinguishable from that disease, and that the definition of the disease does not assert that recovery does not occur. I am the first to admit that recovery is not common and that a large percentage of alleged recoveries are not true recoveries but simply cases of mild diabetes mellitus which has been aggravated temporarily by some infection; when the infection passed, the condition ameliorated immensely.

It is granted that recovery is rare; the question arises: What conditions are inimical?

In my experience there are four factors which are responsible for the rarity of recovery.

(1) The administration of adequate doses of insulin to rest the pancreas often leads to mild hypoglycæmic attacks which frighten the patient and his medical adviser, and therefore, in the vast majority of cases, inadequate doses of insulin are prescribed.

(2) The fact that alcohol stimulates the pancreas, and is therefore inimical to recovery, is recognized by very few.

(3) Infections tend to cause further destruction of the pancreas, but few are fortunate enough to escape all infection for long periods. It is true that the damage caused by an infection frequently may be curtailed by raising the dose of insulin during the infection, but this procedure is not the general custom.

(4) Subsequent attacks of diabetes mellitus before recovery from the first has occurred. Since the cause is not known, prophylactic methods, too, are unknown.

It is not an easy matter to make the unintelligent patient persist in a sustained effort over years, especially when he learns quite early that he feels better when his blood contains too much sugar than when it contains too little, and the majority of patients judge their condition by their sensations.

I give very brief data of some cases of true recovery.

The following table includes only those patients who have been able to dispense with insulin and continued to report progress.

Three of the patients have relapsed owing to severe infection or return to alcohol. Only four of the cases have been free from insulin for periods in the region of 7 years. The number of cases that have been able to halve the doses of insulin is very large.

Sex. and age	Interval.*	Beginning of treatment.		End of treatment.†	Sex and age.	Interval.*	Beginning of treatment.		End of treatment.†
		Diet.	Units of insulin.	Diet.			Diet.	Units of insulin.	Diet.
		(g.)		(g.)			(g.)		(g.)
M 60	1/12	250	105	250	M 49	1/12	116	30	250
M 47	14	145	70	185	M 54	2/12	110	25	200
M 65	4	195	70	195	M 46	2/12	168	25	168
F 52	1	215	70	215	M 43	1	180	20	180
M 34	3/12	150	50	150	M 47	2	115	20	300
M 54	3/12	110	40	194	F 65	3/12	100	20	150
M 63	1/12	111	40	204	M 56	4	230	20	250
M 53	20	240	36	240	F 57	2/12	114	20	130
M 61	3/12	99	30	170	M 65	8	174	20	174
M 66	1/12	135	30	300	M 40	10/12	180	10	180

(g.) = total potential carbohydrate expressed in grammes.
* Interval in years between onset and treatment with insulin.
† Units of insulin required at end of treatment = *nil*.

Those observers who base their treatment upon the sugar content of the blood of their patients four hours after meals obtain results which are not comparable with those obtained by the treatment detailed above.

HYPOGLYCÆMIA.

"Hypoglycæmia" means less than the normal quantity of sugar in the blood. Like most terms used in medicine, it is ill-defined and conveys different meanings to different people. In order that the reader shall have no doubt about the meaning of the term when used in this book, it shall be defined arbitrarily as less than 0·07% of dextrose in the blood taken from a finger-tip.

One might perhaps define pyrexia as a condition in

which the temperature in the rectum is above 101° F.; a circumstance which occurs after five minutes in a Russian bath or upon prolonged immersion in a really hot bath. Symptoms may be absent in pyrexia, just as they may be absent in hypoglycæmia, depending upon the peculiarities of the patient. In both conditions, when excessive, symptoms develop, usually some time before life is threatened. Some may be free from discomfort with the sugar in the blood as low as 0·04%, whilst others will present symptoms of hypoglycæmia with a concentration of sugar in the blood as high as 0·125%; the reason is unknown. In a few cases it appears as if those accustomed to hyperglycæmia develop symptoms when there is a rapid reduction in the sugar content of the blood.

It has been assumed that the symptoms following too large a dose of insulin (termed by some, "insulin shock"*) are due to too low a concentration of dextrose in the blood. Insulin, when given in therapeutic doses to diabetic subjects, raises the respiratory quotient and thereby supplies evidence that it leads to the burning of sugar, but all experiments published up to the time of writing have failed to show what happens to the dextrose when insulin is given in a sufficient dose to produce hypoglycæmia. It is well within the limits of possibility that it is changed into a toxic substance possessing some of the toxic properties of alcohol and that the symptoms arise from this acting upon the central nervous system.

It has been alleged that the injection into rabbits of

* This is not a good name because an identical condition was recorded as occurring in a few diabetic patients given inadequate quantities of carbohydrate before insulin was discovered.

some of the products of decomposition of dextrose leads to convulsions similar to those which develop in hypoglycæmia.

It is true that the introduction of dextrose abolishes the symptoms rapidly, but the rate does not preclude the possibility that the dextrose decomposes the noxious substance.

It is essential for all patients receiving insulin to be acquainted with the symptoms associated with too little sugar in the blood. Every patient should be submitted, whilst under close supervision, to conditions which are likely to cause hypoglycæmia, in order that he may learn the early symptoms and realize how rapidly these symptoms disappear on taking the appropriate remedy, namely, sugar.

The relatives or those associating with the patient should be informed too, because often the patient's mentality may be changed temporarily and he may refuse to take sugar.

The commoner symptoms are—

(1) Apprehension.
(2) Cold sweat.
(3) Shakiness, occasionally tremulous sensation.
(4) Intense muscular weakness.
(5) Difficulty in speaking.
(6) Confused thought.
(7) Convulsions.
(8) Coma.

1. Apprehension appears in many forms. One of my patients imagined that there was an assassin at his back, and was continually looking over his shoulder to see him. Often there is an ill-defined sense of coming disaster.

2. Cold sweats are common, occasionally extremely profuse; a bath towel may be saturated in a few minutes. Occasionally this symptom appears late.

3. Shakiness is perhaps the most constant of all signs. If the patient stretches out his hands they are seen to have a coarse tremor, the excursion being of the order of a centimetre when compared with the fine tremor of Graves' disease, which is of the order of a millimetre.

If the patient writes and puts in full stops and dots the "i's", the erratic position of these leave little doubt in the mind of the observer.

4. Intense muscular weakness is subjective. The patient is able to walk and to move.

5 and 6. Difficulty in speaking shows itself in two ways: actual articulation is affected, due, I expect, to poor control over the muscles, and in addition to this, confusion of thought makes the patient use the wrong words. In many respects the speech of the hypoglycæmic simulates that of a man under the influence of alcohol.

7. Convulsions: I have never seen a patient in hypoglycæmic convulsions, but from the description given to me by nurses they must be very similar to epileptic convulsions.

8. Coma may be profound. The differential diagnosis between hypoglycæmic coma and diabetic coma is discussed elsewhere.

The symptoms are innumerable; amongst the more bizarre symptoms related to me are—sensations of wetness behind the eyes, deadness of the throat, emptiness of the throat, itching of the skin as if a new

woollen vest were being worn, alterations in vision, double vision, whilst perhaps the most alarming of all signs is hemiplegia; either side may be affected, although the first three cases to come under my observation were affected on the left side.

The mental changes are the most distressing, but fortunately not very common. These vary in intensity from slight inebriation to homocidal mania.

The individual may talk nonsense in a loud voice, may carry out contortions accompanied by grinning, laughter or weeping, or may attack his dearest friend.

A letter from the wife of a well-educated man who had given himself an overdose of insulin, due to his syringe leaking and his estimating the loss incorrectly, describes an attack most vividly:

"After lunch he looked ghastly, and for about an hour and a half he was very restless, excitable, making mysterious signs, laughing at nothing (he never laughs), making occasional spasmodic movements. Then he began to stretch his hands behind his head and giggle and laugh, and then for ten minutes to a quarter of an hour he appeared to be quite insane.

"He sprang into the air and twisted like a professional contortionist; he stood on his head in an armchair and made gurgling noises; he turned on his back and shot his legs out in front of him. I could do nothing with him, so sent for a doctor who lives nearby, but he was out.

"Suddenly he pitched against an armchair and went down on the floor with the armchair knocked over also. This seemed to bring him to himself, and he was subdued and spoke sanely, though he still looked frightfully ill.

" I implored him to take some sugar, but he would not until he had taken a blood test. This he found very low, about 0·06%, so he took sugar and cake."

Symptoms simulating hypoglycæmia may develop in highly-strung individuals who are under treatment with insulin even when the concentration of sugar in the blood is above 0·12%. This is of so frequent an occurrence that pseudo-hypoglycæmia has become a recognized term.

On one occasion, on telling a witty old lady the possibility of her developing apprehension, shakiness, muscular weakness and difficulty in speaking, I was interrupted with the statement, " I suffer from all of those without taking insulin ".

It is wise to take samples of blood during the hypoglycæmic attack just before giving sugar. The determination of the sugar in the blood will allow one to decide whether it is true hypoglycæmia or pseudo-hypoglycæmia.

It must, however, be born in mind that patients who have had very high concentrations of sugar in their blood for a long time are more likely to suffer symptoms when the blood falls to normal than those who have not had habitual hyperglycæmia.

CAUSES OF HYPOGLYCÆMIA.

The commonest causes are either an overdose of insulin, or the absorption of insufficient carbohydrate for the insulin administered.

An overdose of insulin need not necessarily be due to carelessness in the measurement of the volume in the syringe, nor to carelessness leading to failure to note the concentration of the solution; it may be due to a

sudden cessation of a toxæmia due to the bursting of an abscess or recovery from some microbic disease. Attention has been drawn to the fact that some bacterial toxins appear to neutralize the effect of insulin.

The failure to absorb a meal is a frequent cause of hypoglycæmia ; emotion may paralyse the alimentary canal. Of this I had a good demonstration shortly after insulin had been placed upon the market. A practitioner phoned to me that a man who was under treatment with insulin had had an epileptic fit. I knew that the patient was over 40, and had not had fits previously.

Since he was having injections of insulin it seemed probable that he was hypoglycæmic and I advised the practitioner to administer sugar. The practitioner replied that he did not like awakening a patient who was sleeping after an epileptic attack. I insisted that if he was not willing to promise to awaken the patient and make him swallow a solution of sugar I should come without delay.

The following day the patient came to see me and explained what had happened ; he had given himself his usual dose of insulin before breakfast and taken the prescribed quantities of porridge and bread. Shortly after breakfast he had entered upon a discussion which had become heated and annoyed him greatly. Towards midday symptoms had developed which, unfortunately, he had not recognized ; by the time he had felt really ill and wished to ask me to come to see him, he was unable to express his desire in words.

Another cause of poor absorption is the hurrying of food through the bowel too rapidly ; this may be caused by emotional disturbance or the unwise administration

of aperients. Delay in absorption may be caused, too, by excitement, such as a game of chess or a deal upon the Stock Exchange, a bet at a race course, or even increased responsibility, such as the piloting of a ship through a fog, or even the entertainment of guests after dinner.

It is essential that all those practising medicine shall be acquainted with the symptoms of hypoglycæmia. Some years ago, a man well over 60, living more than 200 miles from London, wrote to me that he could not pay me his bi-annual visit when it was due, because he had been sent to bed for six weeks following a " heart attack ". When I had the opportunity of questioning him, I learnt that he had given himself insulin one evening, then eaten his usual meal, and gone to a political meeting which had interested him enormously. After the meeting he had seen some friends home, and then started for his own home. Whilst walking by some railings he felt giddy, took hold of them, and slipped down onto the pavement. He then got up, walked home, and was greeted by his daughter, " What has happened to you, Daddy ? It is now twelve o'clock and we expected you home at ten ". He must have been unconscious for close upon two hours. When I remonstrated with him for not having taken sugar when he felt giddy, he told me that he had had insulin for more than two years, that he had carried sugar for eighteen months, and then ceased to do so. His heart was quite sound. A knowledge of the symptoms of hypoglycæmia might have saved him six tedious weeks.

Hypoglycæmia may develop due to some cause which has evaded us up to date.

That the mechanism of its production is through the nervous system seems probable. I give a short record of a case.

A man, æt. 29, with a history of diabetes of four year's duration was admitted to the London Hospital and placed upon a diet of 50 grm. of carbohydrate, 90 grm. of protein and 130 grm. of fat. This occurred quite a number of years ago. It was found that 10 units of insulin twice daily were required to keep the sugar content of his blood below 0·15%.

After 10 days of constant diet and dose of insulin he developed hypoglycæmia, and in spite of being given 142 grm. of dextrose, he died 52 hours after the last dose of insulin.

During the interval the concentration of sugar in his blood rose to 0·125% and slight glycosuria was noted. In other words a patient who was unable to burn 50 grm. daily without subsidizing his pancreas to the extent of 20 units of insulin suddenly burnt more than 140 grm. together with that liberated from protein without any insulin and continued to do so until the sugar in the blood was reduced to 0·02% when he died.

The symptoms in this case simulated encephalitis lethargica and had my house physician not doubted the diagnosis of hypoglycæmia and continued to give dextrose the result might have been different.

TREATMENT OF HYPOGLYCÆMIA.

The manifestations of hypoglycæmia are so varied that it is wise to give sugar by the mouth to any patient receiving insulin who develops unusual symptoms. Even if the patient is hyperglycæmic at the time, little harm

will be done by the administration of a single dose of sugar. Hyperglycæmia does not lead to the immediate development of symptoms. I have seen a man with 0·9% of sugar in his blood in robust health seemingly; the high concentration of sugar followed the administration of 50 grm. dextrose given to determine the sugar tolerance of an individual who had glycosuria, and whose medical adviser felt certain he must have had orthoglycæmic glycosuria because he was free from signs and symptoms.

It is true that in some cases of coma the sugar in the blood rises to 1·0%, but coma is not due to the hyperglycæmia, but to the ketones which have been formed because the patient has been unable to burn carbohydrate.

At the present day, diabetic coma is treated by producing hyperglycæmia because there seems to be evidence that, provided other factors are not changed, the greater the concentration of sugar in the blood, the greater the amount of carbohydrate katabolized.

If the hypoglycæmic patient can swallow, recovery will follow the administration of half an ounce of cane sugar dissolved in a little water. If the patient is comatose, one cubic centimetre of 0·1% adrenaline hydrochloride solution should be injected, or 10 units of pitressin should be injected intramuscularly, and sugar given by the mouth as soon as consciousness returns. These substances liberate stored carbohydrate; if none happens to be stored they will prove ineffectual and an ounce of sugar dissolved in 5 oz. of water should be injected slowly into the rectum. If a sterile solution of dextrose is available, 150 c.c. of a 20% solution should

be injected intravenously, or a 5% solution subcutaneously ; in this latter treatment not more than 30 c.c. should be injected in one place.

In the majority of cases the result is definite and rapid.

I have seen these doses fail to produce an effect. If consciousness does not return, further doses of dextrose should be injected and the diagnosis persisted in until response to treatment has been negligible in spite of the sugar in the blood having risen and remained at 0·20%.

Unless the patient be under close observation, insulin should be withheld for 24 hours after an hypoglycæmic attack. It must be borne in mind that a patient may have a series of hypoglycæmic attacks without having received any further dose of insulin. It is true that it is rare ; further attacks must be treated with further doses of sugar.

Several lives have been lost through this not having been recognized.

OBESITY COMPLICATING DIABETES MELLITUS.

More than 40% of patients who develop diabetes mellitus have at some time weighed considerably more than the normal average. Often weight is lost rapidly during the interval between the beginning of the disease and the adoption of treatment. In many, this tendency to obesity returns when the disease is controlled.

How the weight of an individual is governed remains an unsolved problem ; we realize that weight depends upon the energy of the food absorbed and the rate at which it is burnt.

No explanation has been offered of the fact that some

individuals are able to raise their rate of metabolism when they eat much food and do not gain weight, whilst others have a very low metabolic rate and gain weight rapidly if the energy in their food rises above a comparatively low limit. I have seen a number of patients who have steadily gained weight when on a diet supplying only 23 Calories per kilogramme body weight per diem.

Since thyroid tends to raise the sugar concentration in the blood I am averse to its use, and I have not had sufficient experience of di-nitrophenol to assert that it is harmless in diabetes mellitus and therefore treat cases of obesity with diabetes mellitus by reducing the diet to an energy value which makes it impossible for the patient to put on weight. In order to do this the diet must contain a very small quantity of fat, just sufficient to supply the necessary vitamines. The deprivation of fat is a great hardship to some. In order to meet this, a butter substitute of low energy value may be prepared by making a mayonnaise with liquid paraffin and adding to it a little cream to give it a flavour.

The yolk of one egg and two ounces of cream will make half a pound of butter substitute. The energy of half a pound of butter is well over 4000 Calories, whilst that of the substitute about 200 Calories.

Liquid paraffin is not absorbed, and therefore has no energy value.

It may be used as substitute for olive oil, not only as a salad dressing, but also for frying.

I advise those who have not tried it, not to condemn its use without making a test. During the war much of the salad oil used in England was liquid paraffin

coloured yellow, and those who did not know believed it to be olive oil.

If substances to raise the metabolic rate are used the basal metabolism should be measured from time to time to be certain that no damage is being done, and di-nitrophenol should not be given in doses exceeding 5 mgrm. per kilogramme body weight per diem.

FAT ABSORPTION.

Occasionally, but rarely, absorption of fat occurs at and around the areas over which the injections of insulin are made. This absorption causes greater deformity in fat subjects than in lean. The absorption is not uniform. I have seen cases in which the subcutaneous fat of the upper part of the thighs has disappeared, whilst the fat of the lower halves has been unaffected, and all attempts to diminish the deformity by reducing the fat by limiting the injections to the lower half area have failed. Fortunately in some cases the fat reforms if the injections are stopped.* Most patients are willing to lose the fat of the upper part of the gluteal region, and therefore injections should be limited to that site in these rare cases.

The cause of the fat absorption has not been determined. Some assert that it is due to the introduction of the needle, and does not depend upon the injection. Others take the view that it is due to the antiseptic in the insulin solution, whilst the theory that there are minute quantities of a fat-splitting ferment in the insulin solution although extremely unlikely, cannot be absolutely excluded.

* *Vide* arms in illustrations, pp. 110 and 111.

It is alleged that in Denmark, where an insulin free from preservative is used by the majority, fat absorption is not seen. It is difficult to believe that the absorption

H. M—, æt. 55 (15 . 5 . 28).

is due to the mechanical effect of the repeated punctures because the absorption may occur at some distance from the actual injection.

Since I have seen fat absorption occur in a susceptible

H. M—, æt. 61 (15 . 8 . 33).

patient when an insulin free from preservative has been used, I favour the view that it is something intrinsic in the preparation of insulin. The manufacturers who claim to make the purest insulin in the world have not solved the problem because I have seen more cases of fat absorption when their product has been used than from any other ; this observation does not suggest that that special brand is more likely to cause fat absorption, because I have not kept records of relative numbers of patients using different brands, and perhaps I have seen more patients using that brand than using any other.

ALCOHOL.

The history of the use of alcohol in the treatment of diabetes mellitus is not without interest.

For many years physiologists have taught that ethyl alcohol can replace a certain percentage of carbohydrate and of fat in the diet of man. It is true that the metabolism of the total abstainer takes a short time to adapt itself to the use of alcohol.

Diabetic subjects have been allowed to take colourless whisky and brandy without obscuration, and also gin, because these spirits are free from sugar.

When F. M. Allen introduced the restricted diet as the treatment for diabetes mellitus, some patients suffering from advanced disease had to reduce their diets to such small quantities that they contained insufficient energy to maintain life. It was thought that in these cases the addition of alcohol would supply energy without leading to hyperglycæmia. I can call to mind a girl of 17 who unfortunately could metabolize

a diet of only 15 Calories per kilogramme body-weight per diem. She had a conscientious objection to taking brandy or whisky, but was persuaded to take diluted rectified spirit, and with this addition she maintained her weight. After some months, upon her telling me that she would like to cease taking alcohol for a time, and if it was found that she lost weight during that time she would never raise any objection to taking it in the future, I consented to her ceasing it. Her weight was maintained. It was shortly after this that the U.S.A. " went dry ", and in that country observers soon came to the conclusion that alcohol was not of material benefit to the diabetic patient.

A period then followed during which the patients were not ordered to take alcohol, but were not prohibited from doing so. Every one with considerable experience observed that those patients who took alcohol did not do so well as the total abstainers.

The explanation of this was not simple.

Alcohol depresses the highest centres, and therefore a glass or two of alcohol may lead a man to break the rules and eat that which has been forbidden. This explanation could not apply in all cases, because some patients who took alcohol were under such close supervision that any departure from the rules was impossible.

The explanation may lie in the fact that alcohol seems to stimulate the pancreas ; it has been shown that a medicinal dose of alcohol will lead to a fall in the concentration of sugar in the blood, and probably this is brought about by the activity of the pancreas.

Since insulin has been available I have observed that my patients who are total abstainers have been able to

decrease their dose of insulin in much greater proportion than those who have been accustomed, and continued, to take even small quantities of alcohol. In some of these latter cases, after the individual has ceased to take alcohol he has been able to diminish, and in a few cases cease to take insulin.

A case illustrating this was a man of about 108 kilogrammes weight, aged 45, who came with a history of diabetes mellitus of five years' duration and told me that he was accustomed to take about three quarters of a bottle of whisky daily. Since he asserted that he had been stout for years, and felt better when his weight was about 18 stone, no attempt was made to reduce him. He was placed upon a fixed diet, and thirty units of insulin twice daily kept the sugar content of his blood below 0·15%. From time to time he reported progress, samples of blood were taken and invariably found to be below the arbitrary limit of 0·15%, but in spite of this he failed to develop hypoglycæmic symptoms or show any signs that his pancreas was functioning more vigorously. After this had continued for three years I told him that I was beginning to think that alcohol prevented recovery. Immediately he offered to be a total abstainer for a time, and if improvement occurred he would continue to abstain. During the first six months the dose was reduced to 22 units twice daily, and after four years he was able to cease taking insulin.

Based upon my own experience I hold out hopes of ceasing to take insulin to those only who are willing to abstain from alcohol, but never press a patient to become an abstainer by telling him that if he were to he would be able to recover. As a rule patients will

offer to cease taking alcohol for a period to see what benefit will accrue.

In all probability very small quantities of alcohol well diluted have negligible effects, but the method of determining this is not easy.

DIABETIC COMA.

The chemical compound which is the cause of diabetic coma has not yet been isolated. Until comparatively recently it was believed that ketones, such as acetone, diacetic acid and oxybutyric acid were the main factors, and might lead to loss of consciousness and death, but doubt has been thrown upon this by the demonstration of a greater concentration of these substances in some diabetic subjects who were conscious, than in some who were comatose. In all probability the most virulent poison is associated with the formation of ketones, but does not bear a constant quantitative ratio to the ketones mentioned above.

Ketosis arises from a perverted katabolism of fat. It has been expressed graphically that fat burns with a clear flame only along with carbohydrate, and smokily when it burns alone ; the smoke is the ketone.

This is not absolutely accurate, and it must be admitted that all the factors governing the metabolism of fat have not been discovered. There is no doubt that protein plays an important *rôle*, and that the ratio of fat to carbohydrate may much exceed 4 to 1 without causing ketosis, provided only minute quantities of protein are administered.

Ketosis arises when the action of insulin is inhibited or the quantity reduced below a certain minimum.

It matters not if the insulin is made by the pancreas of the patient or isolated from that of an animal and injected into the patient. It matters not if the inhibiting agent is a toxin of bacterial origin or due to damaged tissues following contusion, laceration or burning.

Ketosis may also be due to the deprivation of carbohydrate or to any condition which materially reduces the katabolism of carbohydrate.

The onset of diabetic coma is, as a rule, insidious and thereby differs from that of hypoglycæmic coma, which is either sudden or preceded by symptoms which have been referred to under the heading of " Hypoglycæmia ".

In diabetic coma the patient first becomes apathetic, then drowsy, and for some time before he loses consciousness his breathing becomes laboured and he is said to suffer from air hunger. The coma deepens gradually. In the early stages the patient can be roused ; as time passes this becomes more and more difficult and he passes into a condition very similar to that induced by a general anæsthetic.

The treatment may be divided under four headings :

(1) The removal of any infection, which is inhabiting the action of insulin.

(2) The supply of sufficient carbohydrate and insulin to prevent any further formation of poisonous substances.

(3) The removal of the poisons.

(4) The support of the cardiovascular system.

(1) If the infection can be localized, it should be removed if possible or steps taken to prevent further

absorption. Unfortunately, this can be accomplished in only a small percentage of cases.

(2) Insulin should be administered intravenously without delay. The initial dose should be at least 100 units.

Courage and foolhardiness are close neighbours separated by the narrow fence of knowledge. Heroic doses of insulin may be necessary to save the life of the patient; the knowledge of the concentration of the sugar in the blood prevents foolhardiness. Sugar must be supplied in sufficient dose to prevent the further production of ketones. Since a short temporary hyperglycæmia will do no appreciable harm, too much sugar should be given rather than too little, which might lead to the patient passing from diabetic coma into hypoglycæmic coma and dying without regaining consciousness.

Experience has shown that 1 grm. of carbohydrate per unit of insulin will guard against hypoglycæmia when diabetic coma is being treated.

After the initial dose of 100 units of insulin intravenously, 20 units of unsulin should be injected intravenously every hour along with 20 grm. of dextrose until consciousness is regained.

A word of warning may be necessary against continuous subcutaneous injection if insulin. Although 10 units of pitressin injected subcutaneously continuously during twenty-four hours will replace two doses of 20 units each given at twelve hours' interval, nevertheless insulin injected continuously at one site ceases to produce any effect after two or three hours.

From time to time the sugar content of the blood

should be estimated and, should the percentage rise, greater doses of insulin may be given or *vice versa*.

Although examination of the urine for sugar may prove reliable in the majority of cases, nevertheless, there is a risk; from time to time the renal threshold for dextrose is found to fall quite low and then the patient may receive insulin when he should receive sugar only, and a fatal termination from an unsuspected cause will have to be recorded.

Years ago several authorities did not favour the administration of carbohydrate in diabetic coma, arguing that there was sufficient sugar in the blood and that an excess of sugar in the blood diminished the activity of insulin. It is obvious that even if the percentage of sugar in the blood has risen to 1·0, and it rarely rises as high, the quantity of sugar to be burnt will be only 50 grm., which is quite insufficient. The view that a high concentration of sugar in the blood hampered the action of insulin has been shown to be incorrect; in fact, the reverse is true, the greater the concentration of sugar in the blood the greater the quantity of carbohydrate stored and/or burnt by a unit of insulin.

(3) The removal of poisons can be conducted through the kidneys, the bowel or by phlebotomy.

Often the patient in diabetic coma is somewhat dessicated, the tongue is shrivelled, the eyes sunken and the skin loose.

Too small a volume of blood is circulating, intravenous injection of saline or its introduction under the skin appears to be essential not only to support the heart, but to lead to greater activity of the kidneys. Care

must be taken not to inject too great a volume of saline intravenously lest pulmonary œdema be induced. If the patient is able to swallow, beef tea, well seasoned, may be given with the object of stimulating rather than assuaging thirst.

In the majority of cases of profound diabetic coma, the urea content of the blood rises owing to the inactivity of the kidneys, and therefore the administration of diuretics cannot be expected to prove of much value since the most powerful diuretic (urea) is already present in excess; nevertheless, the purely physical effect of potassium acetate may be a help.

An enema should be given without delay, followed by an aperient if the coma is not so deep as to preclude swallowing.

If, in spite of treatment, improvement does not occur, a pint or two of blood may be replaced by blood from a donor of the same blood group.

(4) The heart muscle may be stimulated with digitalis, strophanthus and coramine, but one must not expect any great response from the myocardium so long as it remains under the influence of toxins.

As a rule the temperature of the patient falls below normal and therefore a liberal supply of hot water bottles is essential, special care being taken to prevent burning the unconscious diabetic patient, because the burn may not only cause much suffering and heal very slowly, but may even prove fatal.

If a diabetic patient receiving insulin is found in coma, sugar should be administered without delay, and then an attempt should be made to decide whether the coma is due to hypoglycæmia or to ketosis.

In either condition carbohydrate should be given, but if the coma is due to ketosis, heroic doses of insulin must follow the sugar; if the condition is due to hypoglycæmia, the insulin would kill the patient.

It is necessary, therefore, to be acquainted with the signs and symptoms of the two conditions.

	Diabetic coma.	Hypoglycæmic coma.
Colour	Flushed	Pale.
Respiration	Laboured	Shallow.
Pulse	Rapid	Rapid, occasionally slow.
Temperature	Subnormal	Normal.
Tissues	Dessicated	Normal.
Urine	Sugar present	Sugar often absent.
Urine	Ketones usually present	Ketones absent.
Plantar reflex	Flexion	Extension.
Sugar content of blood	Raised	Subnormal.

Every individual case must be considered and treatment modified to suit it.

TREATMENT OF EXCESSIVE BLOOD-PRESSURE.

Endarteritis is a complication of diabetes mellitus, and this is sometimes accompanied by a high blood-pressure, which in turn leads to hæmorrhage into retina or brain.

An attempt should be made to keep the blood-pressure low in these cases.

The treatment which has proved successful in my hands has been a drastic reduction in the amount of common salt in the diet.

Sodium Chloride Content of Foods.

(From Friedenwald and Ruhrah.)

	NaCl %.
Meats.	
Rabbit	0·085
Lamb	0·09
Pork, lean	0·10
Beef, lean	0·11
Veal	0·13
Calves' liver	0·14
Mutton	0·17
Fowl.	
Chicken	0·14
Duck	0·14
Turkey	0·17
Fish.	
Eels	0·021
Salmon	0·061
Pike	0·092
Perch	0·100
Salmon trout	0·120
Cod fish	0·166
Mackerel	0·210
Halibut	0·310
Haddock	0·390
Eggs.	
Duck eggs	0·13
Goose eggs	0·14
Hen eggs	0·21
Hen eggs (yolk)	0·039
Fruits.	
Plums	0·0045
Damsons	0·0046
Apricots	0·0047
Oranges	0·0057
Strawberries	0·0100
Watermelon	0·0110
Cherries	0·0130
Grapes	0·0240
Pineapple	0·0710
Currants	0·0930

	NaCl %
Milk and Cream, Butter.	
40% cream	0·45
20% cream	0·55
16% cream	0·60
Whole milk	0·75
Salt-free butter	0·02–0·21
Bread, Cereals, etc.	
Salt-free wheat bread	0·18
Oatmeal	0·014
Quaker oats	0·082
Rolled oats	0·350
Macaroni	0·067
Rice	0·039
Hominy grits	0·29
Sugar and Chocolate.	
Raw sugar	0·11
Lump sugar	0·049
Chocolate	0·073
Vegetables.	
Carrots	0·016
Onions	0·09–0·016
Artichokes	0·036
Asparagus	0·040
Cauliflower	0·050
Rhubarb	0·059
Cucumber	0·060
Radish	0·075
Young beans	0·089
Tomato	0·110
Lettuce	0·120
Potato	0·160
Celery	0·250

If this be reduced sufficiently the amount excreted exceeds that taken in, and in time the body is drained of sodium chloride, and in order to maintain the normal tonicity of the circulating fluid the volume of fluid is reduced. The fall in blood-pressure is due to the same cause as that following phlebotomy, but is not so evanescent.

A salt-free diet entails much care. Not only must the foods be chosen from those which contain but little salt, but ordinary bread must be replaced by salt-free bread or biscuits free from salt. A table (p. 121) showing the salt content of some foods is given to allow the choice to be made of those which contain very little. Either the sodium chloride content of the daily diet must be reduced to 0·5 grm. or the patient may be allowed as much as he desires. Slight restriction is absolutely useless. After six weeks of salt-free diet the patient will lose his appetite and small amounts of salt must be added, but only a few grains.

If a diet containing very little salt cannot be arranged and the kidneys, when tested, prove to excrete efficiently, then potassium thiocyanate in doses up to twelve grains daily may be prescribed. In some cases this drug reduces blood-pressure by 30%.

TREATMENT BY DRUGS.

Treatment by drugs administered by the mouth has proved disappointing.

It is true that the guanidine compounds synthalin and synthalin B both assist in storing and probably in burning carbohydrate, but their use is very limited.

The extra amount of carbohydrate which can be used by the patient is only about 50 grm. daily, and this not in all cases.

Synthalin causes nausea in a certain percentage of patients ; this nausea may be modified by the administration of dehydrocholic acid and in mild cases, when the patient has become very tired of the subcutaneous injection of insulin, a course of synthalin may prove very acceptable. One must remember, however, that it is an artificial method of assisting carbohydrate metabolism and rarely leads to the sensation of well-being which results from a normal diet normally katabolized by insulin.

Preparations of pancreas, either fresh or dried, when given by the mouth prove of little practical use. It is true that in some cases complex salts of insulin assist carbohydrate storage, but the ultimate effects of the acids combined with the insulin may prove far from innocuous.

Drugs which delay absorption or destroy appetite may diminish glycosuria ; the quantity of sugar excreted is not invariably a gauge of the severity of the disease, and a reduction in the amount need not necessarily prove that there is improvement.

DIABETIC GANGRENE.

Although the cause of diabetic gangrene remains an unsolved mystery, nevertheless, it is often induced by some infection of the skin of the toes or feet. Obviously, therefore, very careful attention to the feet should be a part of the treatment of a diabetic. Not only is

scrupulous cleanliness essential, but the nails should be kept short and any tendency to in-growing toe-nails corrected by appropriate wedges. Corns should not be cut, but the feet should be soaked in hot water to which a little washing soda has been added and the corn rubbed away with a piece of shark's skin.

Care must be taken not to draw blood. If any accident occur which breaks the skin, the lesion should be wiped with tincture of iodine and allowed to dry; on no account should a moist dressing of iodine be applied.

Endarteritis obliterans is a common complication of diabetes mellitus of long standing, especially when treated by restricted diet, but there does not seem to be any direct relation between the extent of the changes in the blood-vessels and the severity in the depression of the carbohydrate metabolism.

Although observations with the oscillometer show that at least half the cases of gangrene of the foot have pulses at the ankle, nevertheless this does not preclude the possibility of all cases having obliterative changes in the smaller vessels prior to the development of gangrene.

The treatment of dry gangrene consists in warmth and a dry atmosphere. The affected part should be covered with one layer of lint and placed under a cradle, the air in which is heated by a few electric lamps. Ventilation should be free. If electricity be not available hot bricks should be used, or some source of heat other than that of hot air from a spirit lamp, which is not satisfactory, because it is too moist.

If the gangrene is moist, the affected part should be

soaked in hypertonic salt solution as hot as can be borne for periods of a quarter of an hour, several times a day. The strength of the salt solution should be about 2%, and the temperature up to 110° F. After soaking, the limb should be dried with a warm towel and then washed with methylated spirit and dried again. Success depends upon the dryness of the tissues and therefore this part of the treatment is essential. The limb is then placed in dry, warm air.

So long as no bone becomes affected there is hope of saving the foot; infected bone rarely separates, and time is usually saved by removal.

Occasionally, the alteration in the blood supply is due to thrombo-angeitis obliterans and not to endarteritis obliterans; in the former condition the blood supply to the affected area may be improved by producing pyrexia with a foreign protein or sulphosin. In order to decide whether repeated pyrexia is likely to do good the skin temperature should be recorded when the temperature of the patient is normal and during a pyrexial attack; if the difference between the skin temperature and the blood temperature be only three or four degrees during pyrexia and ten or more degrees at normal temperature, there is evidence of increased blood supply and the effect of repeated pyrexia should be tried.

DRUGS.

It has been alleged that the injection of extract of muscle benefits patients suffering from endarteritis obliterans. Critical experiments have failed to show that there is any increase in the volume of the pulse,

but since some patients assert that the pain is diminished it is advisable to try the effect ; adenosine in increasing doses, beginning with 0·01 grm., probably supplies the active principle in the extract of muscle.

When adenosine proves useless, acetyl choline may be tried. If these two drugs fail to relieve the pain, an analgesic such as aspirin, veramon, amidopyrine may be given and, should these also fail to relieve pain, the morphine derivative, dilaudid, must be given in doses of 0·002 grm. subcutaneously. This morphinon compound rarely causes sickness, it does not cause constipation, nor does it spoil the appetite.

Should the case be hopeless due to extension of gangrene to the flaps of the stumps when amputation has been performed at the highest level, then diamorphine or some narcotic analgesic should alleviate dissolution.

OPERATION IN DIABETIC GANGRENE.

Until a few years ago it was generally accepted that any operation at a site where there was no pulse would be doomed to failure.

This has proved wrong, and there is roughly a 50% chance of success when amputation is carried out at a pulseless area.

A good number of years ago a patient of mine pleaded for a Syme's amputation, asserting that he was quite willing to have a further operation should it prove necessary.

At the operation a tourniquet was not used ; no vessels were ligatured, because none bled.

The wound healed by first intention, and two years

later a second Syme's amputation was carried out on the same patient with an equally good result.

Since then I have often persuaded the surgeon to remove the minimum amount of tissue regardless of the absence of a pulse, and about half the operations have proved successful. The percentage of successes in endarteritis obliterans is slightly less than in thrombo-angeitis obliterans, due, I think, to the smaller blood vessels not being involved in the latter condition.

COMPLICATIONS AFFECTING THE EYES.

Five conditions may arise in patients suffering from diabetes mellitus which may be due to that disease :

(1) Sudden alteration in refraction.
(2) Two types of cataract.
(3) Retinitis.
(4) Amaurosis.
(5) Iritis.

REFRACTION.

At the onset of acute diabetes mellitus when the concentration of sugar in the blood rises suddenly, the refractive indices of the various media of the eyes may change and a short-sighted individual may become long-sighted for a period. Since the change may be of short duration, it is obviously unwise to have the lenses of the spectacles changed until treatment has had a chance of rectifying the excessive quantity of sugar in the tissues.

A similar change in refraction may be due to early

cataract, and when it occurs in an individual who has a low renal threshold for dextrose and therefore glycosuria, may need very full investigation to arrive at the differential diagnosis.

CATARACT.

Cataract must be divided into true diabetic cataract and senile cataract occurring in a diabetic subject.

It is beyond doubt that there is a form of cataract confined to young diabetics characterized by being bilateral. It begins by the appearance of white flakes evenly distributed close to the capsules of the lenses. These increase rapidly and spread throughout the lens, leading to complete opacity within a month or two.

Vigorous treatment, that is a reduction of the sugar content of the blood to normal, will prevent progress of this morbid condition; indeed, occasionally, but rarely, there may be an absorption and the sight will then improve.

Senile cataract in the elderly diabetic subject is of importance because the following question is raised: Does it indicate that the patient should adopt vigorous treatment?

I have advocated that, when an aged individual develops hyperglycæmic glycosuria without symptoms and without evidence that the alteration in metabolism is damaging the tissues, perhaps it is wisest to advise the patient to eat only sufficient to satisfy hunger and make no other change in his life. If senile cataract is due to hyperglycæmia, obviously more drastic treatment should be adopted.

It has been suggested that senile cataract is similar to true diabetic cataract, and that the great difference in the rate of development is due to the comparative hardness of the lens in the aged. This suggestion cannot be accepted by those who have had an opportunity of examining true diabetic cataract with suitable optical instruments and seen the difference in its commencement.

However, the majority agree that even the most elaborate methods fail to show any difference between senile cataract in the aged with and without diabetes mellitus.

For this reason some assume that when cataract occurs in patients of advanced age suffering from diabetes mellitus it is purely senile and is in no way influenced by the metabolic error.

In my opinion this assumption is unsound. I am amongst the many observers who have seen senile cataract in diabetic subjects arrested when vigorous treatment has been adopted, and some have recorded definite amelioration in the sight.

Therefore, I am in favour of advising the diabetic patient with cataract to adopt treatment which will reduce the sugar content of the blood to normal and telling him that there is a chance of arresting the disease of the eye and perhaps ameliorating his vision a little. If, however, the opacity increases in spite of treatment, he will, nevertheless, have the satisfaction of knowing that it was unavoidable, and also that when operation becomes advisable his condition will have improved and that the treatment will have increased the probability of a successful issue.

RETINITIS.

The differentiation between diabetic and albuminuric retinitis may be impossible; in cases in which there is hyperglycæmia no harm will result by assuming that it is diabetic in origin, even if there is renal inefficiency in addition.

The adoption of treatment often leads to the absorption of exudations, but of course has no effect upon the tissues which have been damaged by hæmorrhage.

In the majority of cases the hæmorrhages occur in diabetics whose arteries have undergone degeneration and in whom the blood-pressure has become high.

The special treatment of this condition has been given.

AMAUROSIS.

Before diabetes mellitus was treated by an attempt to reduce the sugar in the blood to the normal, patients did not recover their sight after diabetic amaurosis had developed.

This has been completely altered by the modern treatment, and frequently sight is restored within a few weeks.

IRITIS.

Iritis of diabetic origin does not materially differ from the condition produced by other causes and can be diagnosed only by the rapidity with which it is reduced by appropriate treatment of hyperglycæmia.

COMPLICATIONS INVOLVING THE SKIN.

There are three types of complexion peculiar to diabetics : pink, yellow and bronzed.

No satisfactory explanation of the pink hue of the diabetic has been offered ; it is, however, so characteristic that it may permit diagnosis at sight. The yellow complexion is much rarer since the diets prescribed have become richer in carbohydrate. When very little carbohydrate was eaten, large quantities of vegetables were comsumed to supply bulk, and these contained carotene which was poorly excreted and led to the skin being stained yellow. The colour was seen best on the palms and the soles of the feet.

The bronzed complexion is associated with enlargement of the liver in the condition called hæmochromatosis.

The pink and bronzed complexions do not alter however excellent the treatment ; the yellow complexion depends partially upon the diet.

Eczema is a common complication usually in the region of the orifice of the urethra. The cause appears to be an irritant formed by a fungus which grows on skin which is occasionally moistened with dilute solutions of dextrose.

There seems reason to believe that the change in metabolism, too, is a potent factor, because, although I have seen many dozens of cases of orthoglycæmic glycosuria, many with high percentage of sugar in the urine, I have seen only two with eczema of the vulva.

The treatment is true cleanliness along with constitutional treatment of diabetes. Recovery, as a rule, is very rapid.

I have met with a large variety of skin lesions in diabetics, but have not been able to satisfy myself, with the exception of xanthoma, that they are due to the altered metabolism, except in so far that the resistance to microbe infection is depressed.

REPRODUCTIVE SYSTEM.

Diabetes mellitus, like most debilitating diseases, causes impotence in the male and cessation of menstruation in the female. The treatment described in this book leads to a return of virility or katamenia in the majority of young subjects.

PREGNANCY.

Before insulin was available it was the duty of the physician to advise his female diabetic patients to avoid pregnancy. Now, provided the disease is not very severe, he is justified in advising his patients to risk pregnancy provided they can be under close medical observation during the period of gestation.

It seems to be a myth that the pancreas of the fœtus can supply the mother with insulin. In the majority of cases a slight increase in the dose of insulin proves necessary during pregnancy, whilst after parturition this increase may prove no longer necessary.

Pregnancy alters the metabolism of some diabetics very materially, and a watch must be kept upon the patient to see whether she is developing glycosuria or ketonuria, needs an increase in the dose of insulin or is developing a ketosis. The former is met by increasing

the dose of insulin and the latter by increasing the carbohydrate relatively to fat in her diet.

Moderate increases in the doses of insulin do not necessarily indicate danger, but should the increases become geometric, then the pregnancy should be terminated.

The method to be adopted must be decided by the physician and gynæcologist in consultation and the following data must be remembered: That chloroform and ether are contra-indicated because frequently they render the disease more severe. As far as diabetes mellitus is concerned, nembutal, avertin and nitrous oxide may be used; local anæsthetics and spinal anæsthesia do no harm in the vast majority.

There may be an advantage in sterilizing the patient, since the probability of one pregnancy making the disease worse, it is probable that a further pregnancy would have a similar effect.

The operation of removal of the uterus performed by a skilful surgeon has a lower mortality risk than that of emptying the uterus after the fourth month.

In the majority of cases the decision arrived at will be to remove the uterus under regional or spinal anæsthesia, depending upon the custom and experience of the surgeon. The procedure sounds drastic, but is the method which is least likely to cause anxiety.

The absorption of toxins made by damaged tissue is very much less in hysterectomy than after emptying the uterus. If there be no gynæcologist available and the pregnancy is of less than three months' duration, the uterus may be emptied and curetted under spinal anæsthesia.

Should the pregnancy not lead to any deleterious effects upon the metabolism and goes to full term, the judgment of the obstetrician must be exercised in deciding how parturition shall be conducted. Pain and exhaustion must be avoided; morphine and hyoscine are permissible.

If the labour becomes lengthy, and not infrequently the uterine muscle of the diabetic appears to become fatigued quite rapidly, the advisability of Cæsarian section must be considered, remembering that it gives opportunity of sterilizing.

The mother may be allowed to suckle her child provided the disease is comparatively mild.

DIABETES COMPLICATED BY OTHER DISEASES.

Graves' disease is not an uncommon complication of diabetes mellitus.

Often the disease is sufficiently pronounced for the diagnosis to be made at sight, whilst occasionally it is only when the patient fails to gain weight or perhaps loses weight whilst on insulin and a diet which supplies more than 40 Calories per kilogramme body-weight that evidence of too rapid metabolism suggests that there must be hyperthyroidism.

During recent years I have treated these cases with radon in doses of about 2000 mc., repeated twice at intervals of three months. Naturally, when the hyperthyroidism is diminished, the dose of insulin required falls.

ADDENDUM.

CARBUNCLE.

Occasionally an acute infection of the skin or subcutaneous tissue occurs which may lead to extensive destruction. The condition is not confined to patients suffering from diabetes mellitus, but is commoner amongst them than those free from hyperglycæmia.

Carbuncle may begin as a small pimple, then form pus and discharge, whilst a circle of similar pimples appear around the primary one and the tissue between may become intensely inflamed and then necrose.

Fresh pimples develop in the periphery and the process may extend until several square inches have been destroyed. Sometimes the process appears to commence in the subcutaneous tissue and a lump appears which gradually softens and then breaks down like a rotten apple.

The prevention of carbuncle, that is, a method of maintaining the normal resistance to infection has not been discovered. Vaccine treatment rarely succeeds in diabetic subjects. Just as carbuncles may develop in individuals without any diabetic tendency, so too diabetics with a sugar content of their blood never rising above 0·15% may become infected and large areas necrose.

If the patient already has had carbuncles of the superficial type, then on the appearance of a pimple which grows rapidly the advisability of its removal by the surgeon must be considered provided it is at a suitable site. Unless the operation can be carried out early and all the infected tissue removed, surgical treatment may do more harm than good.

If it cannot be removed, let it be fomented with hypertonic solutions.

An attempt to prevent the spread of the infection by the application of an ointment containing antiseptic rarely succeeds, and when it appears to do so, there is no proof that it was the ointment that controlled the infection, but nevertheless,

since ointment cannot do harm provided it is applied gently and not rubbed in there is no argument against its use. A favourite dressing is a mixture of magnesium sulphate and glycerine, this should be changed every six hours and kept warm by the application of an electric pad, or hot-water bottle.

Any manipulation of the carbuncle is fraught with the greatest danger. An attempt to squeeze out pus may be manslaughter. It may lead to absorption of toxins or perhaps to the formation of a septic embolus, either of which may prove fatal.

It is obvious that a large carbuncle cannot be drained efficiently by two, three or four incisions, and it is no good draining one or two per cent. of the tissue.

Incisions cannot fail to open vessels and increase the chance of the formation of septic emboli.

When the tissue has broken down and there are a number of sinuses, gently syringing with hydrogen peroxide may perhaps hasten recovery.

When patients demand a view of their carbuncles it may be wise to spray them first with a 2% solution of brilliant green, a harmless antiseptic which will efficiently camouflage the horrid sight.

It is alleged that 10% of diabetics who develop carbuncles die from the infection.

Those cases which have proved fatal in my practice have been operated upon before they have come under my care. The absorption from a carbuncle differs in different cases; when considerable the quantity of insulin required to control hyperglycæmia, that is to say to keep the sugar content of the blood between 0·08% and 0·15%, may become very great indeed.

This does not mean that the pancreas has been destroyed beyond redemption.

Care must be taken to give adequate quantities of sugar when hypoglycæmic attacks develop; as the absorption of toxin diminishes these will occur and may be very acute.

Amongst my patients is a man who had a huge carbuncle upon his neck and had two septic emboli and needed at one time over 140 units daily, and now, after two and a half years, is on a good diet and needs no insulin.

APPENDIX I.

Test for Sugar in Urine.

BENEDICT'S qualitative test for dextrose in the urine is carried out as follows : A solution is made containing copper sulphate 18 grm., sodium citrate 180 grm., sodium carbonate crystals 200 grm., distilled water to 1000 c.c. 10 c.c. of this solution along with 15 drops of urine are poured into a test-tube, which is placed in a water-bath and boiled for 6 minutes. If the solution remains clear it is safe to assume that there is no excess of sugar in the urine.

APPENDIX II.

Estimation of Sugar in the Blood.

The estimation depends upon the property of the glucose present to reduce an alkaline copper solution to cuprous oxide, and the production of a deep blue-coloured compound by chemical interaction between the cuprous oxide and a solution of phosphomolybdic acid. The latter reagent not only combines with the cuprous oxide, but also destroys all the blue colour of the un-reduced alkaline copper solution. We can thus estimate the amount of glucose present by comparing the colour produced with that developed by a known standard glucose solution.

Apparatus.—A colorimeter.

Boiling tubes of resistance glass graduated to hold

12·5 c.c. and 25 c.c., the lower end of the tube being provided with a bulb of 4 c.c.

The estimation of sugar in the blood may be carried out in the following way :

0·2 c.c. of blood are collected from a needle-prick in the finger in a tubular pipette and mixed with 2 c.c. of water. To this is added four drops of 10 % solution of sodium tungstate and four drops of three-quarter normal sulphuric acid. The mixture is shaken and then made up to 4 c.c. with water. This is filtered through a small filter-paper of 4·25 cm. diameter. 2 c.c. of filtrate are mixed with 2 c.c. of alkaline copper solution, and boiled in a water-bath for six minutes, the mixture being in a tube with a bulbous end so that only a small surface is exposed to the air. Then 2 c.c. of phosphomolybdic acid solution are added and the total volume made up to 12·5 c.c. with water, and is well shaken. This solution is placed in a colorimeter and estimated against the standard solution, made by boiling 0·1 mg. of sugar dissolved in 2 c.c. of water and 2 c.c. alkaline copper solution and then adding 2 c.c. of phosphomolybdic acid solution. If the depth of colour is the same, it means that the blood contains 0·1% sugar. The relative depth of colour indicates the percentage of sugar in the blood. The alkaline copper solution is made by dissolving 40 grm. anhydrous sodium carbonate, 7·5 grm. tartaric acid and 4·5 grm. crystalline copper sulphate in water and making up to one litre.

The phosphomolybdic acid solution is prepared by boiling 35 grm. of pure molybdic acid in 200 c.c. of a 10% solution of sodium hydrate and adding 200 c.c. of water. After boiling for half an hour the solution is

cooled and diluted with about 250 c.c. of water. 125 c.c. of 85% phosphoric acid is added and the total volume made up to 500 c.c.

APPENDIX III.

Test for Acetone in Urine.

Three drops of saturated solution of sodium nitroprusside are added to 10 c.c. of urine which have been saturated with ammonium chloride. Two c.c. of strong solution of ammonia are floated on the mixture and left to stand for ten minutes. The development of a reddish-blue (so-called petunia) colour indicates the presence of acetone.

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