Treatment of diabetes mellitus / by O. Leyton.

TREATMENT
OF
DIABETES MELLITUS

O. LEYTON

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OF
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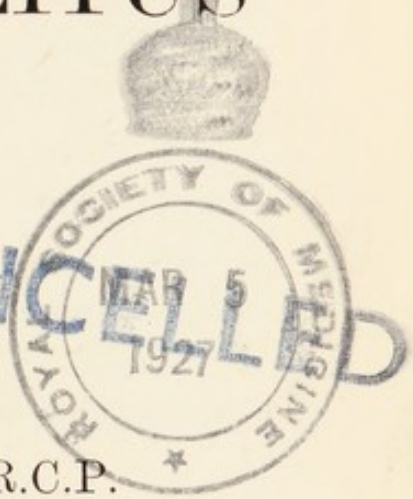

BY

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PREFACE.

THE treatment of diabetes mellitus has been slowly progressive. Rollo, more than 150 years ago, suggested a dietetic treatment; this has been modified from time to time. Pavy took the definite view that it was useless to administer carbohydrate in the diet when dextrose was being excreted in the urine, and advised patients suffering from true diabetes to limit their diet to protein and fats alone. Although this method of treatment prolonged life to some extent, it was rare for the disease to be arrested.

Guelpa believed that diabetes mellitus was of toxic origin and advised fasting accompanied by purging. This drastic procedure led to the temporary disappearance of glycosuria. Other authorities, amongst them Naunyn, advised occasional fasting, but the treatment was empiric and not based upon any sound foundation.

F. Allen was the first to suggest a rational treatment, a treatment based upon a very extensive experimental research upon animals. Allen found that a dog could live with a comparatively small fraction of pancreas provided its food was severely restricted. If the animal were overfed for a period, restriction of food later could not save its live. Allen concluded that the pancreas degenerated if it were overworked.

This forms the basis of all successful treatment of diabetes mellitus, whatever the details.

Before the suggestions of Allen were adopted the

physician contented himself with the attempt to reduce the percentage of sugar in the urine; after the introduction of the Allen treatment a physician was not satisfied unless his patient's urine was free from sugar.

As time passed it was found that although there was, as a rule, but little difficulty in finding a diet for a diabetic patient which rendered him free from glycosuria, nevertheless, in spite of his strict adherence to the diet, glycosuria returned after months or years.

Later the treatment was modified, and the diet of the patient was arranged, not simply to prevent glycosuria, but to maintain the sugar in the blood at a normal level. This was found to arrest the disease in the majority of cases. The disease progressed only if the patient developed an infection or a second attack of diabetes mellitus. The milder cases of disease showed some evidence of amelioration of the condition.

Naturally the more advanced cases could not be treated in this way, because the efficiency of their sugar-burning and storing mechanism was so low that no diet could be devised which would supply them with sufficient energy and keep the sugar in the blood normal. These unfortunate individuals died either from inanition or ketosis.

The introduction of insulin, thanks to the genius of Banting, has revolutionized the details of the treatment of diabetes mellitus, although the underlying idea originated by Allen remains unchanged. Now we have hopes not simply of keeping our patients alive much longer, not simply of arresting the disease, but of a cure.

The only cells in our bodies which have to see us through our lives are the cells of the central nervous

system. They are, as Sherrington puts it, "like a limited committee without the power to add to their numbers"; the cells of the other organs die and are replaced. One has reason to believe that the β-cells of the islets of Langerhans regenerate in time, but the process is a slow one, and recovery may take years to become complete. This chance of recovery makes it advisable for all patients except those in extreme old age to arrange a diet which suffices to nourish their bodies and sufficient insulin to keep the blood-sugar below 0·15%, and thereby avoid over-stimulation of the newly-formed insulin-producing cell, which would lead to its early destruction.

O. LEYTON.

January, 1927.

VOCABULARY.

Amaurosis: Loss of sight.
Alveolaris: Pertaining to part of jaw.
Calories: Units of energy.
Carbohydrate: Sugars and starches.
Cataract: Opacity of lens.
Exophthalmic: With protrusion of eyes.
Glycosuria: Sugar in urine.
Goitre: Enlargement of a gland in the neck.
Hæmorrhage: Bleeding.
Histological: Microscopic examination.
Insulin: Active principle made by certain cells in pancreas.
Katabolize: Break down chemically.
Ketones: Poisons made by abnormally katabolising fats.
Ketosis: Poisoning with ketones.
Lactose: A sugar.
Lævulose: A sugar.
Metabolism: Chemical interchanges occurring in body.
Mitotic: Multiplying.
Osazone: Crystalline compound of sugar.
Pentose: A sugar.
Pituitary: A gland at base of brain.
Protein: A form of food-stuff containing nitrogen.
Renal threshold: The concentration in the blood which just leads to excretion in the urine.
Retinitis: Changes in the retina of the eye.
Staphylococci: Microbes which grow in bunches.
Xanthoma: Yellow raised patches in skin.

DIABETES MELLITUS.

WHAT IS DIABETES MELLITUS?

Our lack of knowledge of the disease which at present is called diabetes mellitus makes it impossible for us to frame a satisfactory definition. Several different conditions are included under the one name; for this reason it is wiser to record some of the more striking characteristics of the disease and the methods which may be adopted to recognize its presence.

The name "diabetes mellitus" means an excessive flow of sweet urine. In advanced cases of the disease polyuria with glycosuria are the most obvious signs, but polyuria with glycosuria may occur without the patient suffering from diabetes mellitus, as for instance in a case of pituitary disease in an individual with a low renal threshold for sugar.

When a disease is named after its signs, anomalies may occur, because frequently it is possible to make the diagnosis before the cardinal signs have developed. We can recognize "exophthalmic goitre" before enlargement of the thyroid or protrusion of the eyes has developed, and therefore the term "hyperthyroidism" has been used to denote the condition.

Since, too, we are able to recognize diabetes mellitus before there is polyuria or persistent glycosuria, it is

time for the name to be changed. For want of a better term I suggest "hypoglycopyresis," to denote a depression in the power of burning sugar.

This name leaves much to be desired, because not only is it cacophonous, but it may be inaccurate in so far as some cases of diabetes mellitus are not only unable to burn sugar normally, but unable to store it at the average rate.

For quite a long time I have exercised my mind and those of some of my scientific friends in an endeavour to design experiments to prove that some cases of diabetes are unable to store carbohydrate and others unable to burn it.

If there were clear-cut cases it is probable that a rise in the respiratory quotient after a meal rich in carbohydrate along with an abnormal rise in the sugar in the blood would indicate inability to store, whilst no change in respiratory quotient but nevertheless some retention of sugar would indicate inability to burn.

The amount of sugar retained would indicate the storing power.

The probability of finding a case in which only one mechanism is affected seems to me very remote.

The absence of ketones in the urine may be taken as proof of a mild diabetes, and not as evidence that the sugar-burning capacity is unimpaired.

In my opinion a diminished power of storing sugar does not necessarily indicate a fault in the liver.

If dextrose be placed in the small intestine of an animal the blood leaving the liver contains glycogen, but if the animal be rendered diabetic by removing its pancreas the carbohydrate leaves the liver as dextrose.

Now, upon the injection of insulin into the diabetic animal the carbohydrate leaving the liver is found to be glycogen.

For this, amongst many other reasons, it appears to be probable that the secretion of the pancreas is essential to the storing of sugar.

The histological observations of Allen and others show that the majority of patients suffering from diabetes mellitus have pathological changes in the pancreas, the β-cells of the islands of Langerhans being diminished in number or the appearance of the cells suggesting that their function is impaired. This class of hypoglycopyresis might be termed " subinsulism."

The fact that insulin, the active principle of the internal secreting part of the pancreas, reduces the sugar in the blood of most patients suffering from diabetes mellitus confirms the view that the disease is usually of pancreatic origin, and this in spite of the fact that Dickens and Dodds found that the pancreas taken from the cadaver of an individual who had died in diabetic coma contained, weight for weight, more than half the quantity found in the normal human pancreas of a substance which, when injected into rabbits, lowered the sugar in the blood.

That faults in the metabolism resembling very closely those found in diabetes mellitus, but due to some change other than that of the pancreas, occur occasionally, is beyond doubt. I have seen cases of diabetes mellitus which have reacted to insulin in the usual way for months or even years pass into a stage in which insulin has been completely inactive, the injection of 100 units failing to diminish the sugar in the blood.

This change was not due to any toxin, as far as could be determined by detailed examination at the autopsies.

Perhaps it would be wise to reserve the term "diabetes mellitus" (so long as it is used) for a condition of hyperglycæmia (excess of sugar in the blood) due to pancreatic insufficiency.

Whether the insufficient internal secretion of the pancreas gives rise to primary alteration in the metabolism of fat and protein as well as carbohydrate is not easily decided.

There is evidence for and against.

If the normal individual be deprived of carbohydrates he will burn fat abnormally and form ketones. This suggests that the abnormal metabolism of fat in diabetes mellitus is of secondary origin, but occasionally we find that a diabetic patient can utilize a greater quantity of carbohydrate than fat, and that in the majority the withdrawal of fat from the diet allows them to oxidize a larger quantity of carbohydrate.

DIAGNOSIS.

The difficulty in determining what departure from the average activity of the pancreas shall be deemed disease is as great as in the case of thyroid. In both the argument applies which made the horse's tail bare. It is true that the great majority of cases are diagnosed with ease because the signs are definite, namely, intense thirst, polyuria, sugar in the urine, wasting and loss of energy.

Probably every careful physician tests the urine of every patient for sugar.

Every patient whose urine reduces an alkaline copper solution* upon boiling should be considered to be suffering from diabetes mellitus until data have been collected which prove that the diagnosis must be corrected.

The first investigation should be to decide whether the substance which reduces the copper solution is dextrose or some other body, such as lævulose, pentose, lactose or glycuronic acid.

The most convenient method is by determining whether the substance can be fermented by yeast.

If it can be, either the osazone should be prepared or the sugar in the blood should be estimated.

If the characteristic glucosazone crystals appear the presence of dextrose (glucose) is proved and the patient is diagnosed as a case of glycosuria.

Glycosuria is not identical with diabetes mellitus.

There are 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 this glycosuria does them is to make it difficult for them to insure their lives at the ordinary rates, and the only harm they do other people is that when, by an error of their medical advisers, they have been diagnosed as suffering from diabetes mellitus and find that their health is better when they break away from the diet prescribed, they tell their diabetic friends. These friends, suffering from true diabetes mellitus, may do likewise and come to grief.

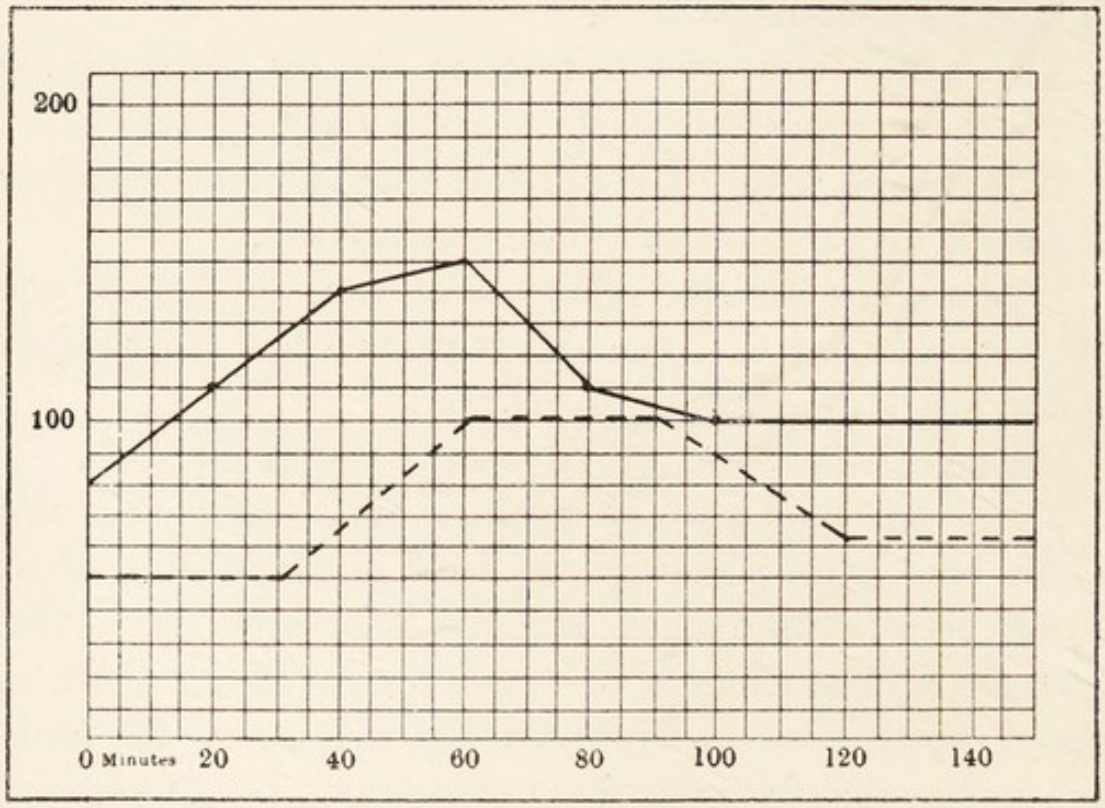
These life-long glycosurics pass sugar in their urine because their renal threshold for sugar is low. The condition is negligible, for which reason I think the term

* Appendix I.

" negligible glycosuria " an apt one, being less lengthy than glycosuria without hyperglycæmia.

The first few cases described had albuminuria as well as glycosuria, and Salmonson thought therefore that it was due to a peculiarity in the kidney, and termed the

DIAGRAM I.



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

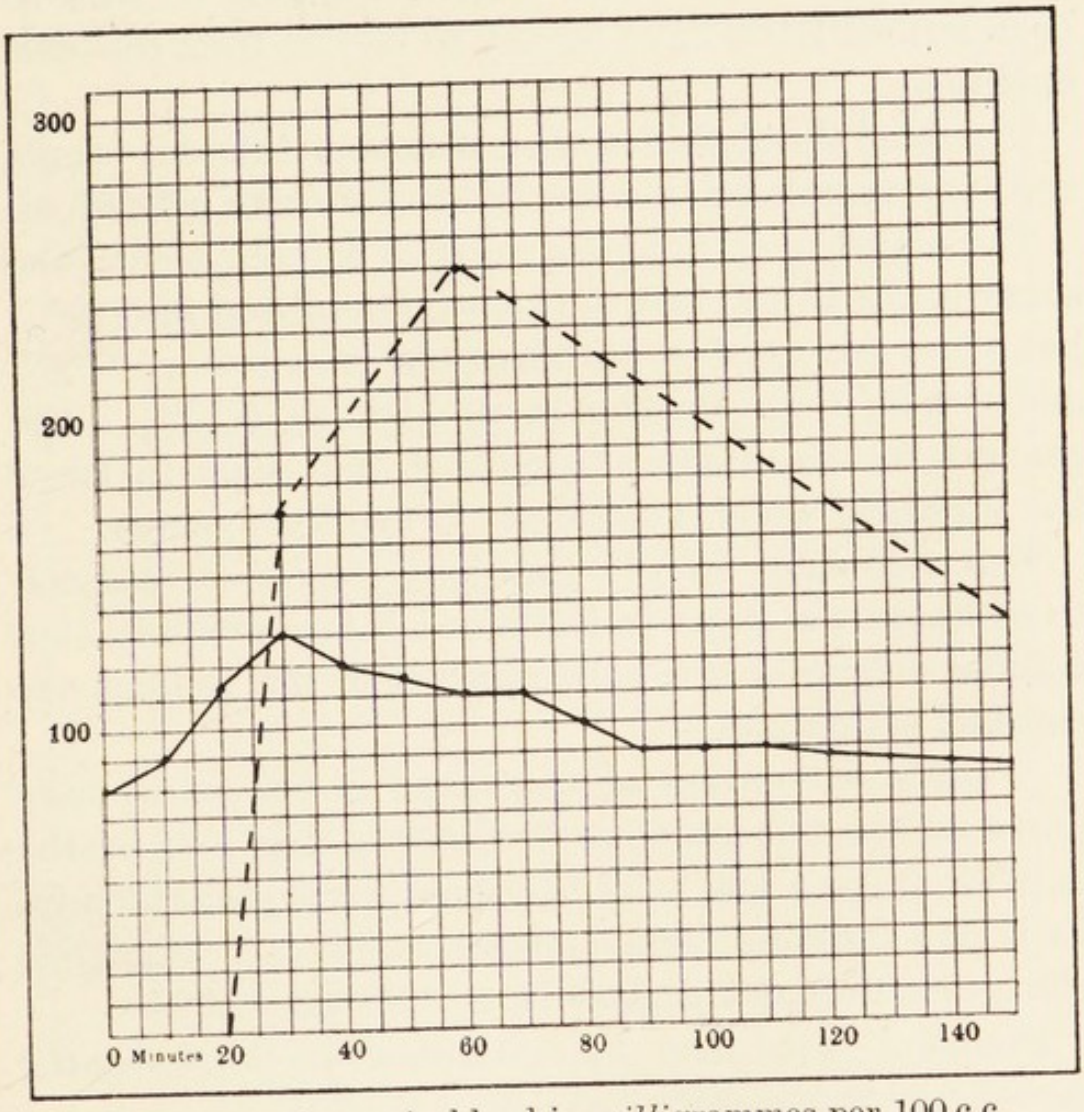
Sugar in blood after the administration of 50 grm. dextrose by mouth did not rise above 0·15 %, whilst the sugar in the urine rose to 10%. This seemed extraordinary. Two samples of blood and two samples of urine were examined in different laboratories and by different observers.

condition " renal glycosuria." We have reason to believe that the peculiarity does not reside in the kidney, and therefore the term is misleading.

Because there is sugar in the urine, but the condition

is harmless, it has been called diabetes innocens—an unhappy name, because there is no diabetes (polyuria); glycosuria innocens would be a more reasonable name.

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.

Until a few years ago I took the view 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 has proved incorrect.

I have met patients who have passed up to 10% of dextrose in the urine and who have not had any excess of sugar in the blood, and when submitted to tests to be described later, have proved to be free from diabetes mellitus.

The renal threshold for sugar differs in different people and may vary from time to time in the same individual.

The majority do not pass sugar in the urine until the sugar in the blood rises to the neighbourhood of 0·20%, but there are some whose threshold is as low as 0·09% and others with thresholds as high as 0·25%. The changes in the plasma during digestion seem to lower the threshold when it is already below the average.

This difference in the threshold makes it essential to estimate the sugar in the blood before arriving at a definite diagnosis in a case which does not present the cardinal symptoms.

A single estimation of the sugar in the blood may prove useless. It must not be assumed that because the individual has a low renal threshold for sugar, therefore he is not suffering from diabetes mellitus. Negligible glycosuria does not protect from diabetes mellitus.

Doubtful cases may be submitted to the following carbohydrate tolerance test :

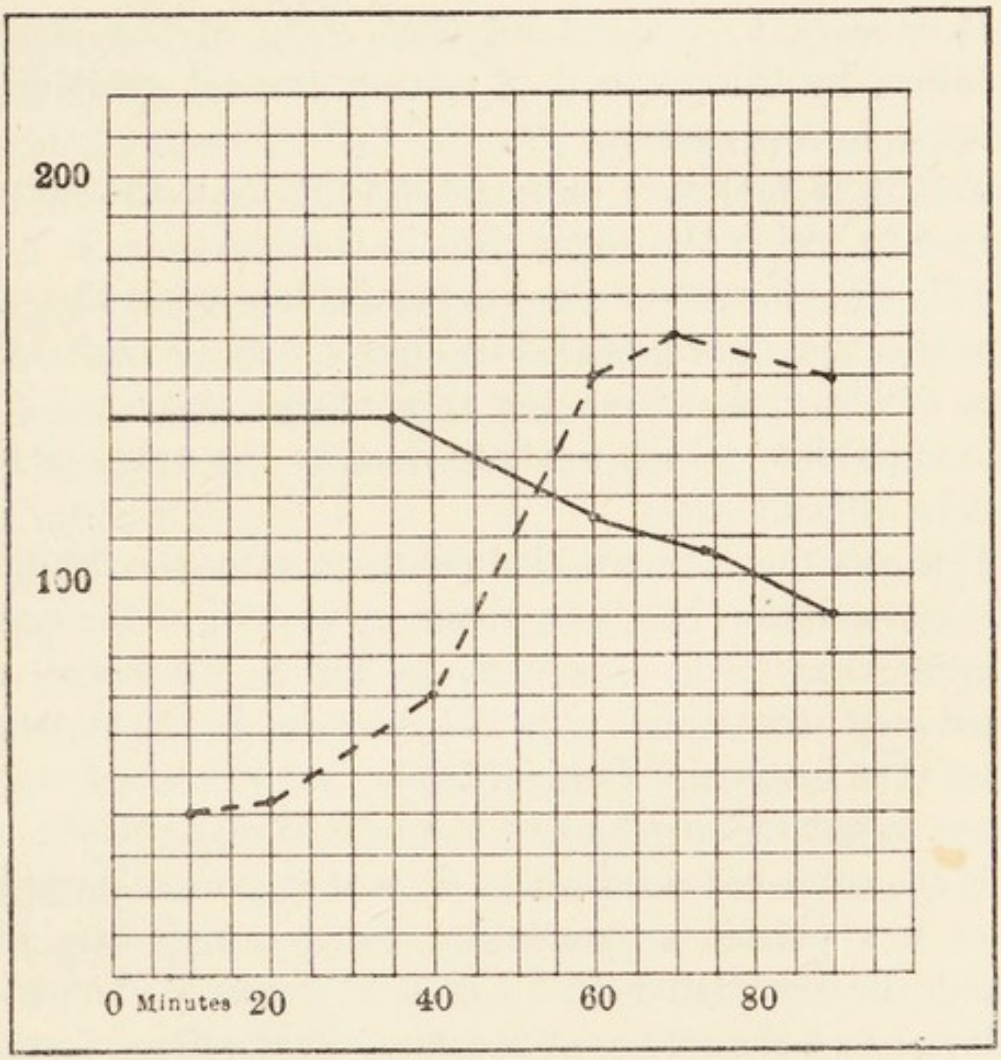
The patient is told to fast for 8 hours ; a sample of blood is taken. Then 60 grm. of dextrose dissolved in 200 c.c. of water with the juice of one lemon is administered by the mouth.

Samples of blood are taken at intervals of 20 minutes for the following 2 hours.

The sugar in the samples of blood is estimated and the curve drawn.

In the normal individual the fasting blood-sugar is

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.

about 0·09%; after the drinking of the sugar solution the sugar in the blood should not rise above 0·20%, and should have fallen to or below 0·09% within 100 minutes.

It has been recorded that in some men not suffering from diabetes mellitus the sugar in the blood rises to 0·24% for a short period of a quarter of an hour or so. Although I have examined many hundreds of glycosurics, I have not met any with this peculiarity.

It is easy to understand that some of the curves obtained by this method of testing present great difficulty in interpretation.

The time factor is more important than the actual height to which the sugar rises in the blood.

This time factor does not depend solely upon the rate at which the sugar is stored and burnt, but also upon the rate of absorption from the alimentary tract, and it is this variability which tends to destroy the value of the test in difficult cases.

If the stomach be emptied one hour after the draught of sugar solution has been given, up to 40% of the sugar may be recovered. There is, as far as we know, no constancy; sometimes only 10% remains in the stomach after that interval. It is probable that the blood-sugar curve is not independent of the rate of absorption.

If the curve obtained with a dose of 60 grm. of dextrose does not permit a conclusion being drawn, the test should be repeated with 75 grm. of dextrose, but with this amount the return of the sugar in the blood to that found during fasting may be extended to 120 minutes.

If this curve, too, is on the borderline, the choice of two procedures remains open:

(1) To send the patient away for six months with the advice to eat and drink whatever he likes during that period and repeating the test after that interval.

If the curve obtained then shows exactly the same

carbohydrate tolerance or suggests a greater capacity for storing and burning sugar, it may be assumed that the patient is not suffering from early hypoglycopyresis ; on the other hand, a curve which suggests by rising higher or falling less rapidly that the carbohydrate tolerance has fallen indicates that the patient should restrict his diet.

(2) The most critical test with which we are acquainted may be performed. The patient is fasted for 24 hours, and then a sterile aqueous solution of 18% dextrose should be injected intravenously at the rate which will introduce into the patient 0·8 grm. dextrose per kilogramme body-weight per hour for 3 hours.

During these three hours samples are taken at 20-minute intervals.

If the sugar in the blood does not rise above 0·20%, it is safe to assume that the patient can metabolize carbohydrate at the normal rate and is not suffering from hypoglycopyresis.

If this test be adopted it must be remembered that the distilled water must be free from all toxins, either quite freshly distilled, or autoclaved immediately after being distilled and kept hermetically sealed.

The dextrose, too, must be pure, and free from any moulds which grow in it if it be not kept absolutely dry.

Many of my patients have received these injections, and only once was there any subsequent rise of temperature ; this I believe was due to the dextrose having become contaminated.

If the sugar in the blood rises above 0·20%, it may be worth while determining the efficiency of the carbohydrate metabolism by repeating the test with a smaller

dose of dextrose, say 0·6 grm. per kilogramme body-weight. If the sugar in the blood rises to 0·20% and remains there it shows that the pancreatic efficiency is $\frac{600}{8}$%, *i. e.* 75%.

If the blood-sugar remains under 0·20% probably the pancreatic efficiency is over 75%.

The dose given upon the second injection is decided by studying the first curve. If the rise above 0·20% is early the dose given the second time should be comparatively small.

This method suffers from at least one defect, namely, that the very nervous patient needs much reassuring, otherwise emotion acting through the suprarenals will cause the blood-sugar to mount too high and vitiate the result.

Unfortunately the tolerance tests are affected by the same factor.

In arriving at a diagnosis one must remember that the metabolism is affected adversely by anything which lowers the general vitality, such as overwork, anxiety, infection, and therefore the repetition of a test may be necessary before coming to a definite conclusion.

The greater the experience of the observer, the less dogmatic he will be in his statements.

HOW TO ESTIMATE THE SEVERITY OF THE DISEASE.

When the diagnosis has been decided and the patient informed, he will ask if his condition is mild or severe.

A reply to this question can be made after making the following observation.

The patient is fasted for 24 hours and the sugar in the blood estimated; if it be above 0·18% the condition cannot be termed mild, whilst if it be below 0·09% the tolerance of the patient will be found to be good.

If the sugar in the blood be 0·12% to 0·14% then 25 grm. of dextrose may be given by the mouth, and samples of blood taken at intervals of 20 minutes until the sugar in the blood has fallen to its original value between 0·12% and 0·14%.

The urine secreted during that time is collected and the amounts of sugar and urea that it contains are estimated.

Assume that the time is taken 4 hours, and the amount of sugar excreted is 5 grm. and the urea 4 grm.

Then the carbohydrate stored and burnt during the 4 hours is $25 - 5 + (4 \times 1{\cdot}7)$ equals 26·8 grm., or 6·7 grm. per hour. This may be interpreted as about a 10% efficiency.

There is some doubt as to whether all the potential carbohydrate in the protein katabolized during the time should be added—whether some cannot be burnt without being converted into dextrose.

In my opinion the error in adding it, is much less than omitting it, for the following reason.

It is generally accepted that all the potential carbohydrate in protein is changed to dextrose in the metabolism of the complete diabetic, whilst in the normal individual the percentage converted into dextrose is unknown; it may be all, it may be none.

When the individual is able to burn and store carbohydrate at the normal rate of, say, 60 grm. per hour, the addition due to the potential carbohydrate would be

but 2%, whilst in the severe diabetic in whom we know most of the potential carbohydrate is converted to sugar the percentage due to it rises to 20 or more.

It is true that this method would be made more accurate by injecting the sugar into a vein, but that would make it less suitable for consulting-room work.

The method may be used for the purpose of diagnosis and also to determine the benefit derived by treatment.

A girl had been rejected by a bank because her urine contained sugar. At 10 a.m. the sugar in her blood was 0·10%. At 10.10 she was given 60 grm. of dextrose by the mouth: the sugar in her blood rose to 0·16%, but fell to 0·13% in one hour and remained about that level for an hour. One may assume, therefore, that it fell to her normal within an hour. During that time she excreted 334 c.c. urine containing 0·63% sugar and 0·5% urea.

During the hour she burnt or/and stored 60 − 2 + 1·8 grm. dextrose—practically 60 grm., which is the normal. The diagnosis, therefore, was "negligible glycosuria."

In July Mr. L—, with a history of recent onset of diabetes mellitus, at 9.50 a.m. had a blood-sugar of 0·17%, having fasted 24 hours. After 25 grm. of sugar by the mouth it rose to 0·30%, and fell to 0·17% after 160 minutes; allowing for sugar excreted and katabolized from protein, one found that he burnt and/or stored 9 grm. carbohydrate per hour, or a carbohydrate metabolism efficiency of 7%.

At the end of September, *i. e.* after two months' treatment, this observation was repeated four days after he had ceased to take insulin, and he was found to

have a blood-sugar of 0·09%, which rose to 0·16%, and fell again to 0·09% in 80 minutes.

Repeating with 50 grm. dextrose instead of 25, one found that he was able to burn and/or store 50 grm. dextrose in one hour, showing a carbohydrate metabolism efficiency of over 80%.

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 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 patient suffering from diabetes mellitus comes under treatment sufficiently early to permit of the correct treatment, 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.

Upon determining their tolerance it 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 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 occurred.

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, but 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.

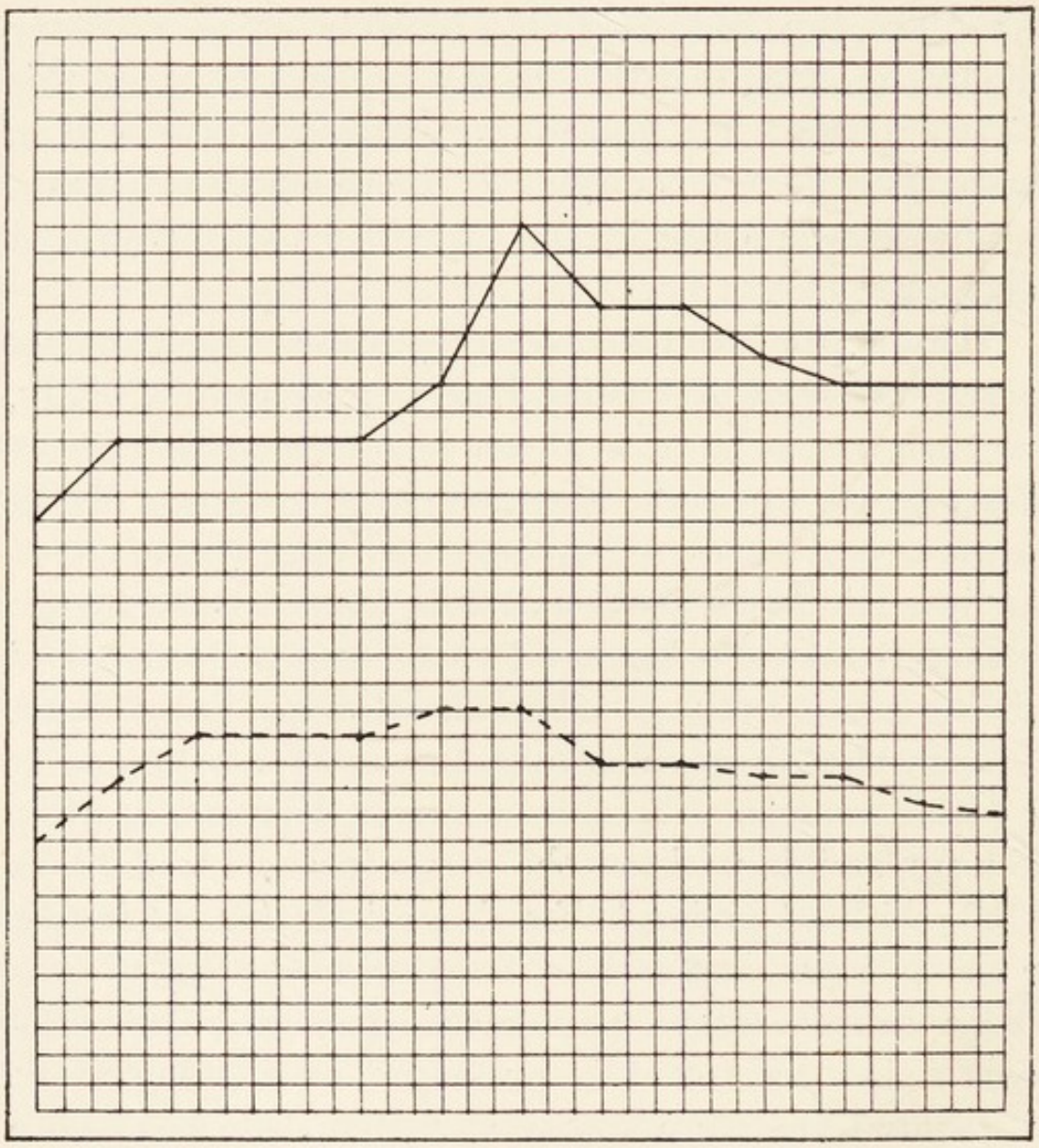
One cannot expect any great regeneration in these cases unless treatment is prolonged over many years. It is only when the evidence of regeneration has passed beyond doubt that one will be justified in advising a treatment which must interfere with sleep.

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

Diagram No. IV 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.* 6 grm. per hour for 3 hours.

Diagram IV.



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

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 6 grm. 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 V).

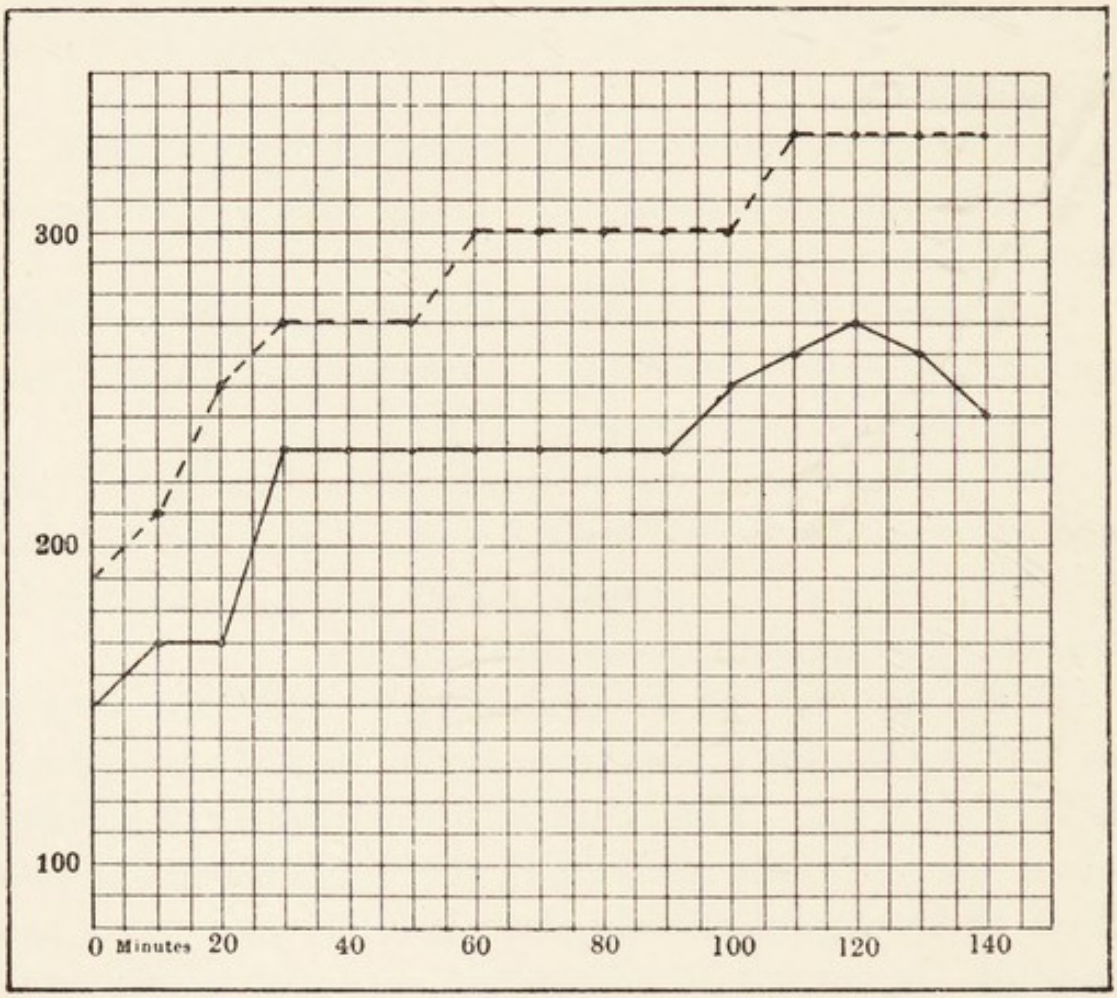
This patient could not be controlled. She stole food, and during the period between the two observations her blood-sugar was usually above 0·15%, although it was rare for her urine to contain sugar.

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 in 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 redeveloped although the diet and dose of insulin were 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.

Diagram V.



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

In addition to the causes of deterioration mentioned above there is the administration of anæsthetics, traumatic damage of tissues resulting from accident and 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 of bacterial origin.

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 in guinea-pigs, 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 blood-sugar fell again to 0·25%, and later after the removal of the septic stump the blood-sugar became normal and the dose of insulin was reduced.

The factors which determine whether insulin will reduce blood-sugar 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 infections 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 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 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 the majority 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.

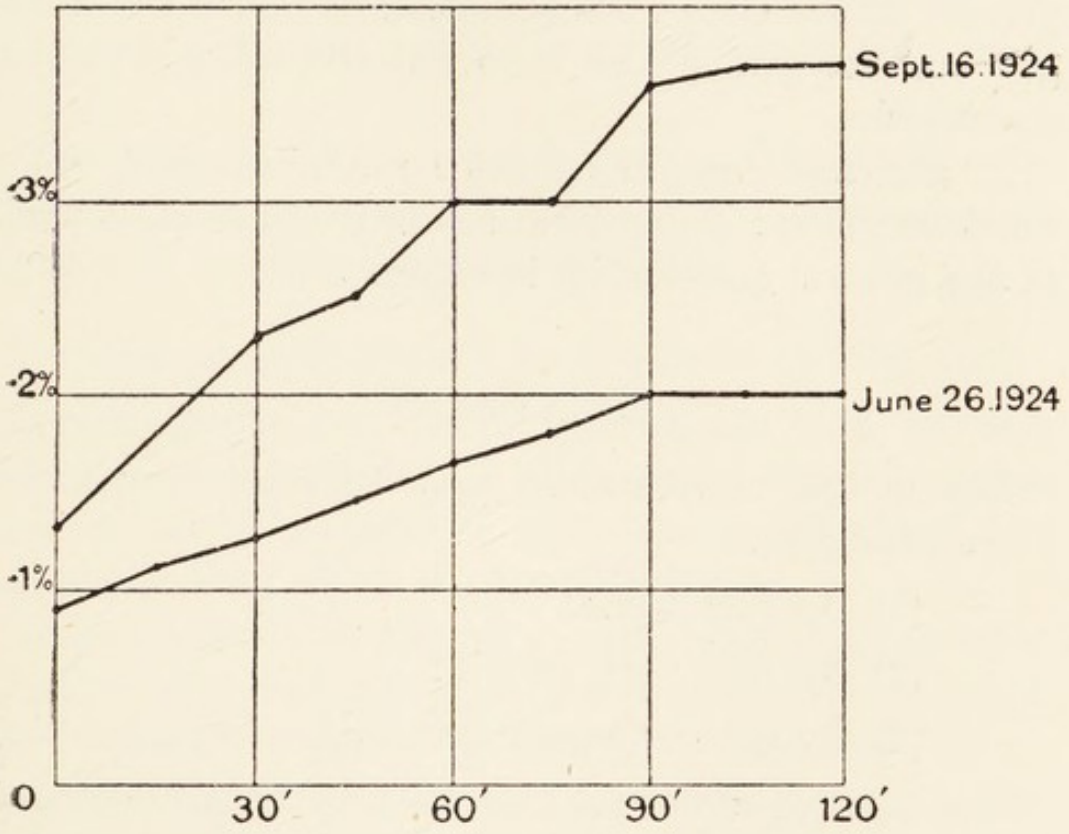
Some time ago opportunity offered to determine the deterioration in the pancreas following an operation for which ether was administered.

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 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

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

Diagram VI.



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.

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.

The details of treatment may be considered under three headings :

(1) By diet alone.

(2) By diet with insulin.

(3) By other preparations with or without diet.

The basis of successful treatment is the avoidance of throwing excessive work upon the internal secreting cells of the pancreas—a proceeding which would lead to a further degeneration of those cells.

Until we know better, we may assume tentatively that the substance in the blood which stimulates the β cells of the islands of Langerhans is dextrose. (There are some reasons to doubt this, but nothing conclusive.)

When the dextrose in the blood rises above a certain percentage, these cells manufacture insulin.

In the less severe cases of diabetes mellitus, the sugar

in the blood can be kept below the appointed level by limiting the food. It is found that the amount of food which can be utilized by the patient is increased by subjecting the pancreas to a short rest.

Before insulin was obtainable this rest was accomplished by fasting the patient for a few days until the sugar in the blood fell to normal. Now one has the choice of fasting the patient or giving insulin for a short period.

The latter is the more satisfactory method, but some patients have a rooted objection to hypodermic injections, and must be treated accordingly.

Preparation of the Patient for Treatment by Diet alone.

Years ago the majority of medical men took the view that their patients should obey orders implicitly, and that it was ill advised to tell them much about the complaint from which they were suffering.

Time has modified this view, and to-day it is generally accepted that diabetic patients should be told sufficient about their complaint to let them understand how necessary the restrictions are, and how they can collaborate with their medical adviser in combating their disability.

The patient should have explained to him that he is unable to utilize the food he takes owing to a gland in his body having been partially destroyed, and that the destruction will proceed unless treatment be adopted.

That as time passes it is quite probable he will be able to increase his diet provided he adheres most strictly to orders.

That when the optimum diet has been found, and

found to be meagre, it is not the doctor's fault. That the magnitude of the diet does not rest with the medical adviser, and that he cannot increase it if he will, but that it rests entirely with the efficiency of the gland in the patient's body.

The method adopted to induce the patient to obey must depend upon his education and intelligence. Those of low intelligence and but little education are made to obey through fear of punishment, a somewhat higher type by promise of reward, whilst the fully educated by the desire to do what is right.

One is loth to coerce a patient by frightening him, but it may be necessary. Diabetics often feel well and are free from discomfort, and suggest postponing treatment until symptoms develop.

These must be told what may happen to them, and how a hæmorrhage into the retina may destroy sight irreparably.

Hesitation in arousing the fears of the patient may be rewarded by the patient returning when blind and upbraiding the physician for not having told him what might occur if he did not follow advice.

This is illogical on the part of the patient, but how many patients are logical ?

When the patient has decided to undergo treatment and has expressed the desire to avoid insulin if possible, he should either enter some institute or engage a hospital nurse to look after him.

A goodly pile of amusing books along with a wireless apparatus will assist to keep his mind occupied and prevent him brooding over his disease.

In the evening he is given an aperient if necessary,

but only if necessary. The routine administration of aperients is a medical impertinence.

Occasionally patients have said to me, "Kindly give orders that only what you prescribe shall be given to me." I have replied, "That goes without saying," and then I have heard how they have been submitted to great discomfort in the past in nursing homes by the nurse insisting upon their taking purgative pills.

In many cases rest in bed along with a very meagre diet leads to constipation, and therefore a mild laxative such as a Seidlitz powder may be required during the first few days of treatment.

The following morning the patient remains in bed, and is given unlimited weak tea, soda-water and plain water.

In the majority of cases the sugar disappears from the urine after two days' fasting; when it does not, the sugar in the blood should be estimated to decide whether the patient has an abnormally low threshold for sugar.

I have met one case in which fasting was continued for 9 days because glycosuria persisted; the patient had a renal threshold for sugar of 0·08%.

If the patient possesses a low renal threshold for sugar, all adjustments of diet must be made dependent upon the amount of sugar in the blood.

During the period of fasting, small quantities of acetone and diacetic acid may be excreted; as a rule this is unimportant, but if any symptoms of diabetic coma develop, the patient must be given insulin and carbohydrate.

If the sugar in the blood persists above 0·15% after

4 days' fast, insulin must be given, because the carbohydrate metabolism of the patient is so low that it cannot utilize the potential carbohydrate in the protein katabolized.*

When the urine has been free from sugar for 24 hours, or the sugar in the blood has been below 0·14% for that period, a progressive diet is begun.

The first object is the determination of the amount of carbohydrate which can be utilized by the patient without causing hyperglycæmia.

If a progressive diet purely of carbohydrate were given, increasing by 5 grm. daily, the process of finding the optimum diet might take weeks, and during the period of low nutrition the patient would lose several kilograms.

There is yet another reason for modifying the apparently ideal method.

A certain amount of protein is essential in the diet even of the adult. The tissues must be repaired, and for this purpose approximately $\frac{3}{4}$ grm. per kilogram bodyweight per diem is the minimum required, and therefore that quantity may be added to the diet fairly early.

At the same time it must be remembered that 58% of the protein is potential carbohydrate.

The following progressive diet has been in use for a number of years and proved useful in many hundreds of cases :

* Theoretically and practically the administration of fat will spare the protein and reduce the sugar in the blood in some cases of severe diabetes ; but a diet rich in fat is loathed by most, and is no longer a necessity where insulin is available.

Dr. Leyton's Table for Finding Tolerance of a Patient weighing 112 lb.

First day after urine is free from sugar.

The numbers given in these tables are the nearest whole numbers. The omission of fractions leads to apparent errors in arithmetic.

Seidlitz powder upon awakening if required.

		Carbo-hydrate.	Pro-tein.	Fat.
Breakfast.	Weak coffee, 300 c.c. (10 oz.)* Cooked F. beans or asparagus or sea-kale, 75 grm. (2½ oz.) . . .	1	1	1
Lunch.	Weak coffee, 300 c.c. (10 oz.). Cooked asparagus or seakale or F. beans, 100 grm. (3 oz.)	2	1	1
Tea.	Weak tea, 300 c.c. (10 oz.)			
Dinner.	Weak tea, 300 c.c. (10 oz.). Cooked seakale or F. beans or asparagus, 75 grm. (2½ oz.) . .	1	1	1
	Calories, 55.	4	3	3

Second day after urine is free from sugar.

Seidlitz powder upon awakening if required.

Breakfast.	Weak coffee, 300 c.c. (10 oz.). Cooked F. beans or asparagus or seakale, 150 grm. (5 oz.)	3	1	2
Lunch.	Weak coffee, 300 c.c. (10 oz.). Cooked asparagus or seakale or F. beans, 200 grm. (7 oz.)	4	2	2
Tea.	Weak tea, 300 c.c. (10 oz.)			
Dinner.	Weak tea, 300 c.c. (10 oz.). Cooked seakale or F. beans or asparagus, 150 grm. (5 oz.)	3	1	2
	Calories, 110.	10	4	6

* Assume for convenience 30 c.c. = 1 fluid oz. 30 grm. = 1 ounce.

Dr. Leyton's Table for Finding Tolerance of a Patient weighing 112 lb.

Third day after urine is free from sugar.

Seidlitz powder upon awakening if required.

		Carbo-hydrate.	Pro-tein.	Fat.
Breakfast.	Weak coffee, 300 c.c. (10 oz.); thin cream, 5 c.c. (1 teaspoonful) .			1
	One egg		6	5
	Raw lettuce, 200 grm. (7 oz.). .	6	2	1
Lunch.	One egg		6	5
	Cooked cucumber, 200 grm. (7 oz.) .	6	2	0
Tea.	Weak tea, 300 c.c. (10 oz.); thin cream, 5 c.c. (1 teaspoonful) .			1
Dinner.	One egg		6	5
	Cooked F. beans or asparagus or seakale, 200 grm. (7 oz.) . .	4	1	2
	Calories, 336.	16	23	20

Fourth day after urine is free from sugar.

Seidlitz powder upon awakening if required.

Breakfast.	Coffee, 300 c.c. (10 oz.); thin cream, 10 c.c. (1 dessertspoonful) . .			1
	One egg		6	5
	Raw lettuce, 200 grm. (7 oz.). .	6	3	1
Lunch.	One egg		6	5
	Cooked cabbage, 200 grm. (7 oz.) .	11	3	1
Tea.	Weak tea, 300 c.c. (10 oz.); thin cream, 10 c.c. (1 dessertspoonful) .			1
Dinner.	One egg		6	5
	Cooked F. beans or asparagus, 200 grm. (7 oz.)	4	2	2
	Calories, 377.	21	26	21

Dr. Leyton's Table for Finding Tolerance of a Patient weighing 112 lb.

Fifth day after urine is free from sugar.

Seidlitz powder upon awakening if required.

		Carbo-hydrate.	Pro-tein.	Fat.
Breakfast.	Coffee, 300 c.c. (10 oz.); thin cream, 10 c.c. (1 dessertspoonful) . .			1
	One egg		6	5
	Raw lettuce, 200 grm. (7 oz.) . .	6	2	1
Lunch.	Cooked lean meat, 30 grm. (1 oz.) .		8	3
	Stewed cabbage, 200 grm. (7 oz.) .	11	3	1
Tea.	Weak tea, 300 c.c. (10 oz.); thin cream, 10 c.c. (1 dessertspoonful) .			1
	One egg		6	5
Dinner.	Clear broth, 240 c.c. (8 oz.) . .		5	0
	One egg		6	5
	Cooked F. beans or seakale, 200 grm. (7 oz.)	4	2	2
	Calories, 452.	21	38	24

Sixth day after urine is free from sugar.

Seidlitz powder upon awakening if required.

Breakfast.	Coffee, 300 c.c. (10 oz.); thin cream, 10 c.c. (1 dessertspoonful) . .			1
	One egg		6	5
	Raw lettuce, 200 grm. (7 oz.) . .	6	2	1
Lunch.	Cooked lean meat, 100 grm. (3 oz.) .		24	9
	Cooked asparagus or F. beans, 100 grm. (3 oz.)	2	1	1
	Boiled potatoes, 45 grm. (1½ oz.) .	10	1	0
Tea.	Weak tea, 300 c.c. (10 oz.); thin cream, 10 c.c. (1 dessertspoonful) .			1
	One egg		6	5
Dinner.	One egg		6	5
	Stewed cabbage, 100 grm. (3 oz.) .	5	2	
	F. beans or seakale, 100 grm. (3 oz.) .	2	1	1
	Calories, 565.	25	49	29

Dr. Leyton's Table for Finding Tolerance of a Patient weighing 112 lb.

Seventh day after urine is free from sugar.

Seidlitz powder upon awakening if required.

		Carbo-hydrate.	Pro-tein.	Fat.
Breakfast.	Weak coffee, 300 c.c. (10 oz.)			
	Clear broth, 200 c.c. (7 oz.)			
Lunch.	Weak coffee, 300 c.c. (10 oz.)			
	Clear broth, 200 c.c. (7 oz.)			
Tea.	Weak tea, 300 c.c. (10 oz.)			
Dinner.	Weak tea, 300 c.c. (10 oz.)			
	Clear broth, 200 c.c. (7 oz.)			

Eighth day after urine is free from sugar.

Seidlitz powder upon awakening if required.

Breakfast.	Coffee, 300 c.c. (10 oz.); thin cream, 30 c.c. (1 oz.)	1		3
	One egg		6	5
	Cooked fat bacon, 20 grm. (¾ oz.) .		3	10
	Raw lettuce, 200 grm. (7 oz.) . .	6	2	1
Lunch.	Cooked lean meat, 60 grm. (2 oz.) .		16	6
	Cooked F. beans or asparagus, 100 grm. (3 oz.)	2	1	1
	Boiled potatoes, 45 grm. (1½ oz.) .	9	1	
Tea.	Weak tea, 300 c.c. (10 oz.); thin cream, 30 c.c. (1 oz.) . . .			3
	One egg		6	5
Dinner.	Clear broth, 240 c.c. (8 oz.) . .		5	
	One egg		6	5
	Stewed cabbage, 100 grm. (3 oz.) .	5	2	
	Seakale or beans, 100 grm. (3 oz.) .	2	1	1
	Calories, 556.	25	49	40

Dr. Leyton's Table for Finding Tolerance of a Patient weighing 112 lb.

Ninth day after urine is free from sugar.

Seidlitz powder upon awakening if required.

		Carbo-hydrate.	Pro-tein.	Fat.
Breakfast.	Coffee, 300 c.c. (10 oz.); thin cream, 30 c.c. (1 oz.)	1	0	3
	One egg		6	5
	Cooked fat bacon, 30 grm. (1 oz.) .		5	15
	Raw lettuce, 200 grm. (7 oz.) . .	6	2	1
Lunch.	Cooked lean meat, 60 grm. (2 oz.) .		16	6
	Fat, 15 grm. (½ oz.)			12
	Cooked seakale or beans, 100 grm. (3 oz.)	2	1	1
	Boiled potatoes, 45 grm. (1½ oz.) .	9	1	
Tea.	Weak tea, 300 c.c. (10 oz.); thin cream, 30 c.c. (1 oz.) . . .			3
	One egg		6	5
	Boiled potatoes, 25 grm. (¾ oz.) .	5	0	0
Dinner.	Clear broth, 240 c.c. (8 oz.) . .		5	
	One egg		6	5
	Stewed cabbage, 120 grm. (4 oz.) .	7	2	
	Cooked F. beans or seakale, 75 grm. (2½ oz.)	2	1	1
	Calories, 925.	32	51	57

Tenth day after urine is free from sugar.

Add 30 grm. (1 oz.) of fat as butter; distribute this amongst the vegetables.

Dr. Leyton's Table for Finding Tolerance of a Patient weighing 112 lb.

Eleventh day after urine is free from sugar.

		Carbo-hydrate.	Pro-tein.	Fat.
Breakfast.	Coffee, 300 c.c. (10 oz.); thin cream, 30 c.c. (1 oz.)	1	0	3
	One egg		6	5
	Cooked fat bacon, 30 grm. (1 oz.)		5	15
	Raw lettuce, 200 grm. (7 oz.)	6	2	1
Lunch.	Cooked lean meat, 60 grm. (2 oz.)		16	6
	Fat, 15 grm. (½ oz.)			12
	Cooked beans or seakale or asparagus, 100 grm. (3 oz.)	2	1	1
	Boiled potatoes, 45 grm. (1½ oz.)	9	1	
	Butter, 15 grm. (½ oz.)			12
Tea.	Tea, 300 c.c (10 oz.); thin cream, 30 c.c. (1 oz.)			3
	One egg		6	5
	Boiled potatoes, 45 grm. (1½ oz.)	9	1	
	Butter, 15 grm. (½ oz.)			12
Dinner.	Clear broth, 240 c.c. (8 oz.)		5	
	One egg		6	5
	Stewed cabbage, 100 grm. (3 oz.)	5	2	
	Cooked seakale or beans, 100 grm. (3 oz.)	2	1	1
	Butter, 30 grm. (1 oz.)			25
	Calories, 1298.	34	52	106

Twelfth day.—Same as eleventh day.

Calories, 1415.

Dr. Leyton's Table for Finding Tolerance of a Patient weighing 112 lb.

Thirteenth day after urine is free from sugar.

		Carbo-hydrate.	Pro-tein.	Fat.
Breakfast.	Coffee, 300 c.c. (10 oz.); thin cream, 30 c.c. (1 oz.)	1	0	3
	One egg		6	5
	Cooked fat bacon, 30 grm. (1 oz.)		5	15
	Raw lettuce, 100 grm. (3 oz.)	3	1	
	White bread, 15 grm. (½ oz.)	10	1	
Lunch.	Cooked lean meat, 60 grm. (2 oz.)		16	6
	Fat, 15 grm. (½ oz.)			12
	Cooked beans or asparagus, 100 grm. (3 oz.)	2	1	1
	Boiled potatoes, 45 grm. (1½ oz.)	9	1	
	Butter, 30 grm. (1 oz.)			25
Tea.	Tea, 300 c.c. (10 oz.); thin cream, 30 c.c. (1 oz.)			3
	White bread, 15 grm. (½ oz.)	10	1	
	One egg		6	5
	Butter, 15 grm. (½ oz.)			12
Dinner.	Clear broth, 240 c.c. (8 oz.)		5	
	One egg		6	5
	Stewed cabbage, 100 grm. (3 oz.)	5	2	
	Cooked seakale or beans, 100 grm. (3 oz.)	2	1	1
	Butter, 30 grm. (1 oz.)			25
	Calories, 1450.	42	52	118

Fourteenth day.—No carbohydrates and only half quantities of protein and fat (patient may take less, but not more than this).

Dr. Leyton's Table for Finding Tolerance of a Patient weighing 112 lb.

Fifteenth day after urine is free from sugar.

		Carbo-hydrate.	Pro-tein.	Fat.
Breakfast.	Coffee, 300 c.c. (10 oz.); thin cream, 30 c.c. (1 oz.)	1	0	3
	One egg		6	5
	Cooked fat bacon, 30 grm. (1 oz.)		5	15
	Raw lettuce, 100 grm. (3½ oz.)	3	1	
	White bread, 15 grm. (½ oz.)	10	1	
	Butter, 15 grm. (½ oz.)			12
Lunch.	Lean cooked meat, 60 grm. (2 oz.)		16	6
	Fat, 15 grm. (½ oz.)			12
	Cooked F. beans or seakale, 100 grm. (3 oz.)	2	1	1
	Boiled potatoes, 45 grm. (1½ oz.)	9	1	
	Butter, 15 grm. (½ oz.)			12
Tea.	Tea, 300 c.c. (10 oz.); thin cream, 30 c.c. (1 oz.)	1		3
	White bread, 15 grm. (½ oz.)	10	1	
	One egg		6	5
	Butter, 15 grm. (½ oz.)			12
Dinner.	Clear broth, 240 c.c. (8 oz.)		5	
	One egg		6	5
	Stewed cabbage, 100 grm. (3 oz.)	6	2	
	Cooked F. beans or asparagus, 100 grm. (3 oz.)	2	1	1
	Butter, 30 grm. (1 oz.)			25
	Potato, boiled, 20 grm. (¾ oz.)	5		
	Calories, 1461.	49	52	117

Every seventh day must be a half-ration day.

The tables must be modified for patients, depending upon their age and weight.

The minimum protein required by an individual who has ceased to grow, and is not abnormally fat, is about 0·75 grm. per kilogram body-weight per diem; but a child needs 4 times that amount, and if too meagre quantity is given it may fail to grow.

The best results can be obtained only by keeping the blood-sugar below 0·15%, but occasionally it is not possible to estimate the sugar in the blood.

It will be noted that the midday meal contains a greater amount of carbohydrate than any of the others; the reason for this is that the diurnal variation of sugar in the blood indicates a rise in the early morning, and therefore it is unwise to give much carbohydrate at breakfast.

It is essential to find out whether glycosuria follows the meal richest in carbohydrate, and therefore in order not to keep the patient awake late at night, the midday meal is chosen.

The urine is passed 2 and 4 hours after lunch and tested for sugar; if these and a specimen of the 24 hours' specimen are all free from sugar, an increase in diet is permitted.

When sugar appears in the urine a few days' fast is indicated, and then a diet up to that given 3 days before the sugar was passed.

When it is possible to keep a close eye upon the sugar in the blood, samples are taken 1 hour after breakfast, at half-hour intervals after lunch, starting 1 hour after and taking three samples. If all these are below 0·15% an increase is permissible.

As soon as the highest blood-sugar estimated reaches 0·15%, no further increase in carbohydrate should be made.

If the diet supplies sufficient energy and satisfies the appetite of the patient, he should adhere to it for months; if the diet is insufficient, an addition in the quantity of fat may be tried so long as the total quantity of fat does not exceed twice the weight of the carbohydrate added to that of the protein.

The final adjustment of the diet must depend upon the idiosyncrasies of the patient.

Very many attempts have been made to standardize diets based upon the height and weight of the patient; this is of great use when time does not allow the patient to be studied individually.

In the treatment of patients one must remember that although all human beings are built upon the same plan, the details of their metabolisms probably differ as much as their personal appearances.

That the metabolisms differ is shown by the fact that dogs are able to recognize different people by their scent; this means that the fatty acids made by different people either differ in quality or in relative quantities.

It is not necessary to labour the point; so many arguments could be quoted in evidence without reference to the so-called congenital faults in metabolism.

The energy in the diet of the patient should be the least which will allow the patient to maintain his weight and to carry on his work.

Hunger may be appeased by choosing foods which are bulky.

If it be found that upon raising the value of a diet

by adding fat, the sugar in the blood rises above 0·15%, and that without the fat the patient loses weight, treatment with insulin becomes imperative.

THE ADMINISTRATION OF INSULIN.

Insulin must be injected; if given by the mouth it fails to act.

Hundreds of experiments have been performed with the hope that some other method of administration might be found, but so far with negative results.

It seems unlikely that any substance occurring in vegetables or in the tissues of the animals which possess insulin-like properties would be absorbed unchanged from the alimentary canal; if it were, primitive man would have run the risk of dying from hypoglycæmia. In prehistoric days the hunter killed his animal and ate it raw, and would have died in hypoglycæmic coma if he had absorbed the insulin contained in his meal. No doubt man and all carnivorous animals have developed a defensive mechanism which allows them to take sugar-burning substances by the mouth with impunity. There is no evidence that this mechanism fails in the diabetic, much as we should like it to.

Absorption of insulin through the nasal mucous membrane or through the skin is so slight and variable that it is of no practical value.

At present insulin can be administered in three ways, and in three ways only:

1. Intra-venously.
2. Intra-muscularly.
3. Hypodermically.

When given intravenously its action is rapid, and therefore this method of administration is of use in diabetic coma; but in the routine treatment with insulin, it is wiser to give the injection of insulin either hypodermically or intramuscularly some 15 minutes or more before carbohydrate is introduced into the stomach. The actual time should be determined by trial; it differs in different individuals, and may increase when, after months of treatment, the injections have led to some hardening of the subcutaneous tissues, which seems to delay its absorption.

There are a number of makers of insulin, and the methods adopted by the different makers are not all the same, and it will be found that if one brand of insulin causes inflammation and discomfort, it may be replaced by another, which may prove satisfactory. As far as I can find out, this is not due to the difference in raw material. The American insulin is said to be prepared from the pancreas of pigs chiefly, while the greater part of the English insulin is made from the pancreas of oxen. One firm of manufacturing chemists was good enough to prepare a batch from pig's pancreas, and I found that a patient who was sensitive to various British makes, but not to the American insulin, was nevertheless sensitive to that prepared by them. On the other hand, I have come across patients who are sensitive to American insulin and not to some of the British brands; this is rather an exception, but the point is that if one brand of insulin causes discomfort, then try another.

The standard strength of insulin is that 1 milligram of the dried powder shall contain at least 8 units of the

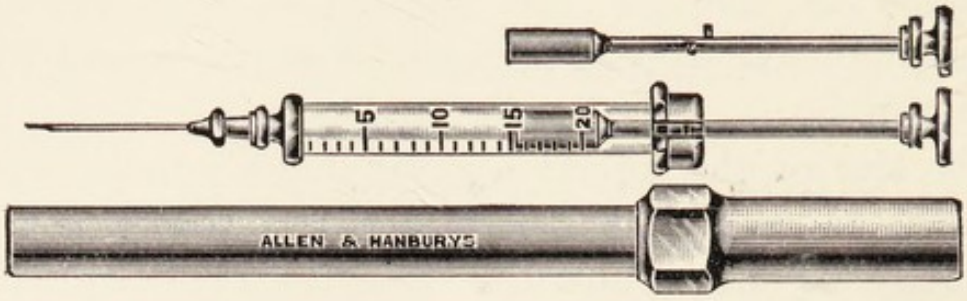
active material; it seems probable that a milligram of pure insulin would correspond to 240 units.

In all probability the inflammation following the injection is due to the impurities, and that the different makes contain different quantities and kinds of impurities.

The site of the injection must depend upon several points. In my opinion the ideal site is that which was selected for intra-muscular injections of salvarsan, namely the upper part of the gluteus maximus. This area is sparsely supplied with nerves and therefore somewhat insensitive; care should be taken not to inject more than $2\frac{1}{2}$ inches below the iliac crest lest nerves be involved. When injecting in this region the needle should be held at right angles to the skin and plunged in for at least an inch. This region may not be found suitable in female patients for two reasons: (1) It may entail considerable disrobing; (2) the corset may press upon the area and lead to discomfort. Alternative areas are the muscles of the upper arm and the outer part of the thigh. Some patients find that the discomfort is less if the injection be given hypodermically, and others if it be given intra-muscularly. A sharp, clean needle is essential, the less sharp the needle the greater the pain. The syringe used for injections should be one which can be easily sterilized; for the convenience of those who travel, I have designed a syringe which can be charged with a dose of insulin and then kept in a metal case so that the injection may be given before a meal, without carrying any complicated paraphernalia.

Since the success of the treatment of diabetes mellitus

with insulin depends upon maintaining the sugar in the blood between 0·08% and 0·15%, I shall describe first the treatment, assuming that the sugar in the blood



can be examined as often as thought advisable, and later the modification which should be adopted if blood-sugar estimation is impossible.

TREATMENT WITH INSULIN.

The treatment will depend upon the view taken by the medical adviser. If he be of the opinion that diabetes mellitus is essentially a progressive disease and that treatment does not arrest the complaint, and cure is beyond hope, then the advice to the patient would be to eat and drink whatever he likes, but when he has eaten food containing starch or sugar he must give himself an injection of 20 units of insulin, provided that that dose does not render the urine sugar-free.

Fortunately the majority of medical men do not take that view.

Those who had experience of the treatment of diabetes mellitus by the restricted diet as suggested by Allen learnt that in many cases the disease could be arrested, and in some the carbohydrate tolerance could be increased.

From the time that insulin has been available it has

been my practice not to fast the patient, but without delay to fix a diet which will supply him with sufficient energy, and then find the dose of insulin required to allow him to utilize it.

The object of this is to allow the pancreas to regenerate by giving it rest and nourishment.

The patient must enter a hospital or a nursing-home, or have a nurse who has been taught how to take the measured quantity of blood if samples are to be taken at frequent intervals.

The diet should supply at least 25 Calories per kilogram body-weight, and as far as possible this diet should approximate that to which the patient is accustomed, but the carbohydrate should not exceed 60 grm. per diem ; the main amount of carbohydrates should be given at breakfast and the evening meal.

The general principles guiding one in the diet are :

(1) An individual who is still growing requires considerably more protein than an adult.

(2) An obese patient should receive a diet of comparatively low energy value and only a small amount of fat.

(3) The lean patient suffering from over-activity of the thyroid or infected with the tubercle bacillus needs a diet of high energy value.

(4) The patient with very advanced diabetes mellitus may not be able to utilize 60 grm. of carbohydrate daily, except when receiving enormous doses of insulin.

(5) A patient with very high blood-pressure along with diabetes mellitus must have a diet containing only traces of sodium chloride.

One rule applies to all diets, namely that fats burn

satisfactorily only in the flame of carbohydrate; for this reason it is unwise to allow the quantity of fat in a diet to exceed twice the weight of the carbohydrate added to half the weight of the protein.

A typical diet for a man weighing 10 stones would be :

		Carbo-hydrate.	Pro-tein.	Fat.
Breakfast.	Unlimited tea			
	3 oz. cream	3		18
	½ oz. oats made into porridge . .	10		
	2 oz. fat bacon weighed raw . .		10	30
	One egg		6	5
	½ oz. bread	10		
	¼ oz. butter			6
		23	16	59
Lunch.	4 oz. lean meat, weighed cooked .		32	12
	½ oz. fat of meat „ „ . .			12
	1 oz. butter			24
	8 oz. green vegetables, weighed boiled	5		
		5	32	48
Tea.	Cup of tea			
Dinner.	Clear soup			
	6 oz. fish, weighed raw . . .		30	
	1½ oz. butter.			36
	2 oz. boiled potatoes, weighed cooked	12		
	8 oz. green vegetable, „ „ .	5		
	3 oz. apple, weighed raw . . .	10		
	2 oz. cream	2		12
		29	30	48
	Totals . . .	57	78	155

The energy of a diet can be estimated quite easily. 1 grm. carbohydrate, on being burnt, supplies 4 Calories. 1 grm. protein, on being converted into urea, supplies

4 Calories. 1 grm. fat, on being burnt, supplies 9 Calories. Therefore the energy value of the diet is :

$$4\ (57 + 78) + 9\ (155) = 1935.$$

Since the patient weighs 62 kilo, that means that he receives 31 Calories per kilogram body-weight.

It is, in my opinion, essential for the diet to be expressed in grammes of carbohydrate, protein and fat, in order that the patient may be able to vary the actual food-stuffs at will, so long as he maintains each meal unaltered as to quantities of carbohydrate, protein and fat.

I have designed a chart (see p. 50) upon which the essential data may be recorded. In that illustrated, the diet mentioned above is recorded.

When the diet has been fixed the effect of it upon the sugar in the blood is observed. If the sugar in the blood after breakfast and after the evening meal is found to remain under 0·15%, insulin will not be required.

If the sugar in the blood is too high 1 hour after breakfast, 5 units of insulin is given before breakfast and before the evening meal, and the effect noted.

The dose of insulin should be increased gradually until the sugar in the blood 1 hour after breakfast is not more than 0·15%.

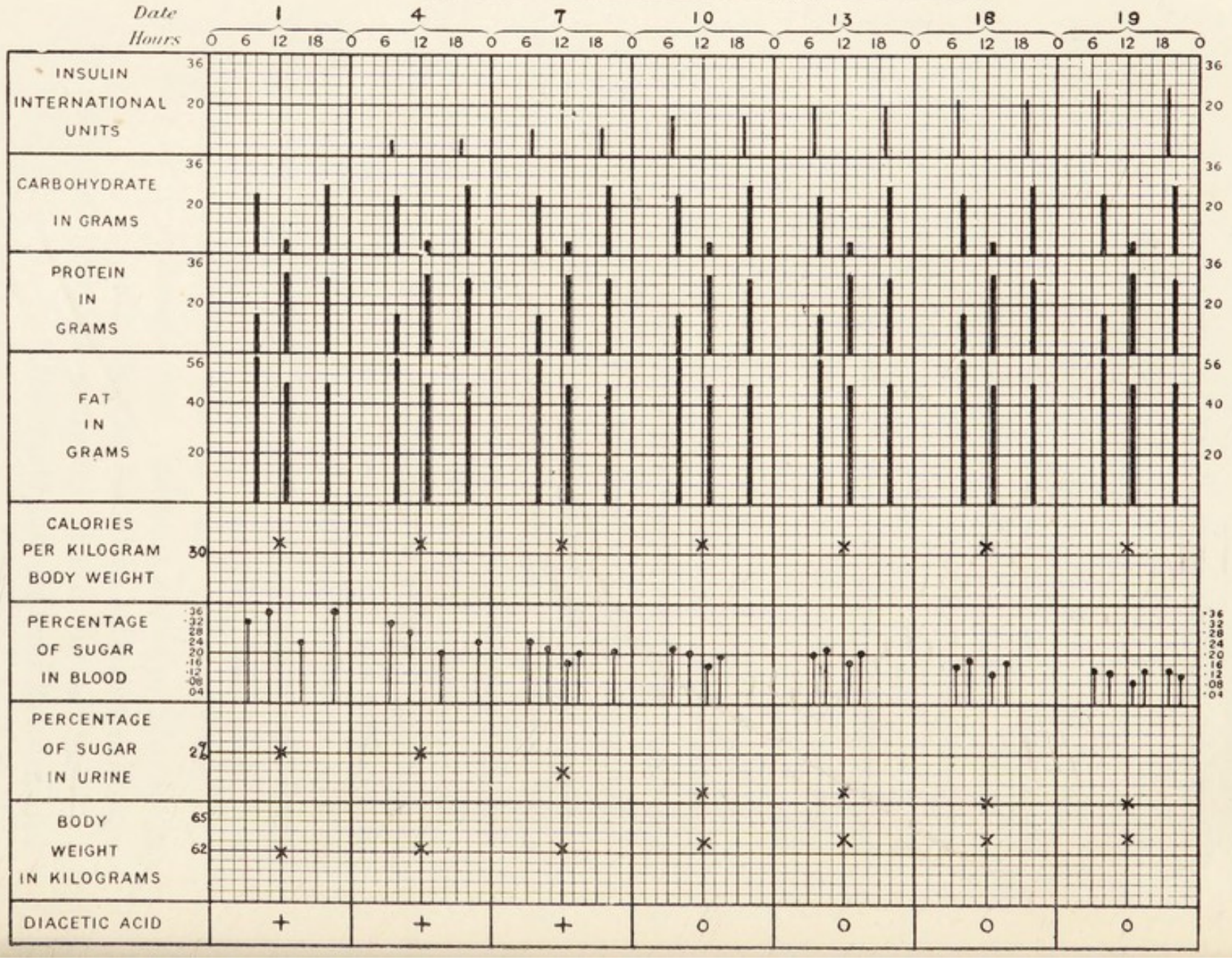
This dose may lead to the development of hypoglycæmia towards midday, and therefore it is wise to examine samples of blood at that time.

There is no fixed optimum interval between the injection of insulin and the meal.

If it be found that the sugar in the blood rises too high an hour after breakfast and then falls rapidly to

LEWIS'S CHART FOR RECORDING TREATMENT OF DIABETES

Name _____ *Age* _____



under 0·08%, it is wise to increase the time between injection and the meal.

Care must be taken not to make the interval so great that hypoglycæmia develops before the meal can be absorbed, but short of this there are advantages in a long interval.

If, in spite of adjusting the time, the minimum of insulin to keep the blood-sugar below 0·15% leads to the sugar in the blood falling below 0·075% at 12 o'clock, two courses are open: either a small carbohydrate meal such as biscuit must be taken at 11.30, or the dose of insulin before breakfast must be reduced along with a corresponding reduction of carbohydrate. The former is preferred as a rule.

Occasionally in very severe cases the dose of insulin required to store and/or burn 60 grm. carbohydrate daily is so immense, that it is wise to reduce the carbohydrate to that which can be metabolized by the injections of 75 units daily given in three doses of 25 units each.

If the best results are to be obtained, the sugar in the blood must be kept below 0·15% for months or even years. In order that this may be accomplished it is my custom to offer to teach my patients how to estimate the sugar in their blood. Quite a number avail themselves of the offer, and, having learnt, take several samples of blood on one day a month and report progress.

The method they are taught is a modification of that of Folin and Wu*; since great accuracy is not essential, those who cannot afford a colorimeter carry out the

* Appendix II.

estimation with graduated tubes, similar in many respects to those used in a Gower's hæmoglobinometer.

Experience has taught me that it is unwise for the patient to test his urine for sugar, because in time he forgets that the test, when positive, is only an indication of a serious advance in his disease, and he thinks that so long as his urine is sugar-free, all is well, and then begins to experiment and increases his diet.

When there is undoubted evidence that the disease has made progress due to this increase in diet, he seeks advice and says, "But doctor, the increased diet did not lead to sugar appearing in my urine."

When he is told that he had received orders not to alter his diet without consulting a physician he replies that he did not understand, illustrating the statement made by Pope, "A little learning is a dangerous thing." Either let the patient estimate the sugar in his blood or make no examinations at all, but keep rigidly to diet and dose of insulin.

TREATMENT WITHOUT BLOOD-SUGAR ESTIMATION.

The administration of insulin without observation of the sugar in the blood cannot be recommended, but when estimations of sugar are impossible the mixed proverb about insulin, "half a dose is better than no bread," may be true.

It is only with luck that one can arrest the disease, and the hope of a cure is very small indeed.

Two main methods may be adopted, depending upon—

(1) The absence of glycosuria.

(2) The development of hypoglycæmic symptoms.

Although I expect that only a few will agree with me, I believe that the latter method is the safer.

This view is based upon an experience which includes at least a dozen diabetic patients with quite low renal thresholds for sugar; in these the former method would have proved not only useless but dangerous, in so far that glycosuria would have given a false sense of security against hypoglycæmia.

(1) The diet is fixed in the same way as if the sugar in the blood could be estimated when desired.

The patient is told to pass urine every 2 hours.

All these samples are examined for sugar.

Before beginning the administration of insulin the patient is told about the symptoms of hypoglycæmia.

A dose of 5 units is injected about half an hour before breakfast and half an hour before dinner. If all the samples of urine contain sugar after 3 days, the doses are increased to $7\frac{1}{2}$ units. If all the samples continue to contain sugar a further increase is made of $2\frac{1}{2}$ units per dose every third day until some of the samples are sugar-free or symptoms of hypoglycæmia develop.

When some of the samples of urine are sugar-free the increase in the dose of insulin should be small and gradual until all the samples become sugar-free.

Hypoglycæmic symptoms are commonest about 4 hours after the injection of insulin.

The absence of glycosuria means that the patient is utilizing all the carbohydrate in the food, but it does not mean that the sugar in the blood does not rise to 0·21%—a level at which neuritis and many other complications of diabetes mellitus may develop.

(2) If the dose of insulin is regulated by the

development of hypoglycæmic symptoms, the patient must be nursed by someone who is conversant with the symptoms and recognizes the condition fairly early. The nurse should be instructed how to give hypodermic injections of glucose solution in case medical advice could not be obtained in an emergency.

The morning dose when increased is kept at least 20% greater than the evening dose. This, along with the somewhat greater allowance of carbohydrate at the evening meal, will make it probable that hypoglycæmic attacks will develop during the day rather than at night.

When undoubted hypoglycæmic symptoms occur, the dose of insulin is not increased further. If the symptoms recur with great regularity, either a little carbohydrate is given about three-quarters of an hour before the time they are expected, or the dose of insulin is decreased by a few units.

As time passes the hypoglycæmic attacks may redevelop, which indicate a further decrease of insulin. Occasionally by this method of adjusting the dose of insulin, as in the method based upon the sugar in the blood, a slow regeneration of the pancreas occurs, and in time the patient is able to dispense with insulin.

In order to allow patients to vary their diets, tables have been arranged showing how 5 grm. of carbohydrate and protein may be taken. In the table I prepared in 1916, I included only those substances which did not vary to any great extent.

In those days there was not insulin, and therefore some of the patients had to be content with very small quantities of carbohydrate, and any variation in the

quantity might have led to disastrous results, but now, when the diabetic has an average allowance of 60 grm. of carbohydrate, an error of 3 or 4 grm. in either direction is comparatively unimportant, therefore I am adding to the list very materially, indicating which substances vary considerably.

Five Grammes of Carbohydrates may be taken as—

Grm.	Oz.		Protein.	Fat.
30	1	Almonds, edible part	6	15
*60	2	Apples, raw	0	0
5	⅙	Arrowroot, raw	0	0
120	4	Artichokes (Jer.), boiled once	½	0
30	1	Artichokes (Jer.), steamed	0	0
210	7	Asparagus, boiled once	3	0
20	⅔	Bananas, edible part	0	0
250	8½	Beans, French, boiled once	2	1
250	8½	Beans, scarlet runners, boiled once	2	1
*60	2	Beetroot, boiled once	1	0
*90	3	Bilberries, raw.	0	0
*60	2	Blackberries, edible	0	0
*50	1¾	Black currants, edible	1	0
10	⅓	Bread, white, fresh	1	0
7	¼	Bread, white, stale	1	0
10	⅓	Bread, brown, fresh	1	0
160	5½	Brussels sprouts, boiled once	2	0
120	4	Brussels sprouts, steamed.	2	0
250	8½	Cabbage, boiled in 3 waters	1	1
180	6	Cabbage, boiled in 1 water	1	1
90	3	Cabbage, steamed or stewed	1	1
*150	5	Carrots, boiled once	½	0
*50	1¾	Carrots, steamed or stewed	0	0
250	8½	Cauliflower, boiled once	1	0
90	3	Cauliflower, steamed or stewed	2	0

* Indicates of variable composition.

Grm.	Oz.		Protein.	Fat.
150	5	Celery, raw or stewed	1	0
250	8½	Celery, boiled in 1 water	1	0
*30	1	Cherries, edible part	0	0
150	5	Chicory, raw or stewed	2	0
*50	1¾	Cokernut, fresh edible part	3	25
*60	2	Cranberries	0	0
100	3	Cream, thin	2½	20
150	5	Cream, thick, fresh	3	35
150	5	Cucumbers, raw or steamed	1	0
250	8½	Cucumbers, boiled once	1	0
*60	2	Damsons	0	0
150	5	Endive	2	1
30	1	Figs, edible part, raw fresh	½	0
60	2	Gooseberries, raw	½	0
90	3	Grape fruit, edible part	½	0
*30	1	Grapes, fresh	½	0
*30	1	Greengages	0	0
*7	¼	Jam	0	0
150	5	Kale, boiled once	3	0
80	2¾	Leeks, stewed	1	0
150	5	Lemons, edible part	1	0
180	6	Lettuce, raw	2	1
7	¼	Macaroni, raw	1	0
5	⅙	Marmalade	0	0
150	5	Marrows, vegetable, steamed	0	0
*60	2	Melons, edible portion	0	0
70	2½	Milk, fresh	4	3
40	1⅓	Mulberries, edible part	0	0
30	1	Nectarines	0	0
60	2	Nuts, Brazil, edible part	12	40
10	⅓	Chestnuts, edible part	1	0
30	1	Filberts, edible part	5	20
20	⅔	Peanuts, edible part	5	7
20	⅔	Pistachio, edible part	4	10
20	⅔	Walnuts, edible part	5	12
7	¼	Oatmeal, raw	1	0
60	2	Olives, edible green	0	10
*100	3	Onions, raw	1	1
*50	1¾	Onions, boiled once	½	½

Grm.	Oz.		Protein.	Fat.
45	1½	Oranges, edible part	0	0
*150	5	Parsnips, boiled once	1	1
30	1	Parsnips, steamed or stewed	0	0
70	2½	Peaches, fresh, edible part	½	0
40	1⅓	Pears, edible part	0	0
30	1	Peas, green, boiled fresh	2	½
7	¼	Peas, dried	1	1
*100	3	Pickles, without sugar	0	0
*50	1¾	Pineapples, fresh, edible part	0	0
*30	1	Plums, edible part	0	0
30	1	Potato, raw or boiled once	½	0
80	2¾	Radishes, raw	1	0
*40	1⅓	Raspberries	½	0
*60	2	Red currants	½	0
120	4	Rhubarb, raw	½	0
6	⅕	Rice, raw	0	0
100	3	Seakale, steamed or stewed	0	0
210	7	Seakale, boiled once	0	0
150	5	Spinach, boiled once	3	0
60	2	Strawberries, fresh	½	0
6	⅕	Tapioca	0	0
7	¼	Toast	½	0
120	4	Tomatoes, raw	1	0
*90	3	Truffles, cooked	4	0
*200	6½	Turnips, boiled once	1	0
70	2½	Turnips, steamed	3	0
180	6	Watercress, raw	1	0

Five Grammes of Protein may be taken as—

Grm.	Oz.		Fat.
30	1	Bacon, raw fat	15
15	½	Beef, roast lean	2
20	⅔	Beef, boiled lean	4
60	2	Brains, raw	5
15	½	Caviare	3
30	1	Cheese, Brie	7
15	½	Cheese, Cheddar	6
20	⅔	Cheese, Camembert	5
15	½	Cheese, Cheshire	6

Grm.	Oz.		Fat.
25	¾	Cheese, cream	8
15	½	Cheese, Dutch	2
25	¾	Cheese, Roquefort	7
20	⅔	Chicken, roast	1
60	2	Eggs, hens'	5
15	½	Fish, brill, raw	1
25	¾	Fish, crab, boiled	1
20	⅔	Fish, cod, raw	0
30	1	Fish, eels, raw	5
50	1¾	Fish, hake, raw	2
20	⅔	Fish, herring, grilled	2
25	¾	Fish, halibut, raw	1
45	1½	Fish, lemon sole	0
25	¾	Fish, lobster, grilled	1
45	1½	Fish, mackerel, raw	3
45	1½	Fish, plaice, raw	1
25	¾	Fish, salmon, raw	2
40	1⅓	Fish, sole, raw	0
25	¾	Fish, trout, raw	0
25	¾	Fish, salmon, raw	2
45	1½	Fish, whiting, raw	0
20	⅔	Ham, boiled	5
15	½	Hare, cooked	1
30	1	Kidneys, cooked	2
22	¾	Lamb, roast	2
20	⅔	Mutton, roast	5
60	2	Oysters (4% carbohydrate)	1
40	1⅓	Pâté de Foie Gras (3% carbohydrate)	12
15	½	Partridge, cooked	1
15	½	Pheasant	1
20	⅔	Pigeon	1
15	½	Pork, roast	3
15	½	Rabbit, cooked	1
20	⅔	Sardines, tinned	4
30	1	Sweet-breads, boiled	½
30	1	Tongue, fresh boiled	3
30	1	Tripe, boiled	3
20	⅔	Turkey, roast	2
15	½	Veal, cooked	2

The slogan for successful treatment is "Keep the sugar in the blood between 0·08% and 0·16%," but naturally the methods by which this is accomplished must differ, depending upon the temperament and occupation of the patient.

The man of leisure can regulate his life by the clock, receive insulin a definite number of minutes before his meal, and the meal can be composed of a definite number of grammes of carbohydrate, protein and fat. He can avoid anxiety by limiting his horizon, and his relatives may guard him from emotional disturbance; but when a man earns his living, the regularity of his life may be disturbed.

Amongst my patients is a pilot: he can keep the sugar in his blood between the limits on a fixed diet on 15 units of insulin twice a day. Experience has taught him and me that a fixed diet with a fixed dose of insulin would prove disastrous. For instance, he may be on the bridge and expecting a meal in half an hour's time, and therefore gives himself 15 units of insulin; the boat runs into a fog; even if he has the meal brought to him and eats it, anxiety may prevent it being absorbed, and he may develop an attack of hypoglycæmia, which might prove disastrous to many.

For this reason, whilst at work the man drops his insulin and goes on a protein diet; this prevents a hyperglycæmia and a hypoglycæmia.

Some patients become hypersensitive to the probe of the hypodermic needle; these may be better served by one injection of insulin daily, and the diet arranged so that most of the carbohydrate is taken at the meal following the injection.

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

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 showing the salt content of some foods is given to allow the choice to be made of those which contain very little. 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.

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

I have seen the pressure fall 60–70 mm. by adopting this treatment, and as far as I can tell hæmorrhages postponed

In my experience resumption of salt has led to the pressure rising again.

INSULIN FAILS.

Insulin fails to lower the sugar in the blood in a small percentage of patients who appear to be suffering from diabetes mellitus.

The commonest cause is an infection, not necessarily accompanied by pyrexia. We are not acquainted with the determining factor; I have seen patient with extensive carbuncles react normally to insulin, also patients with extensive pulmonary tuberculosis who were expectorating large quantities of sputum teeming with acid-fat bacilli.

These tuberculous patients become immune to insulin when the pneumococcus and *Diplococcus catarrhalis* appear in their sputum.

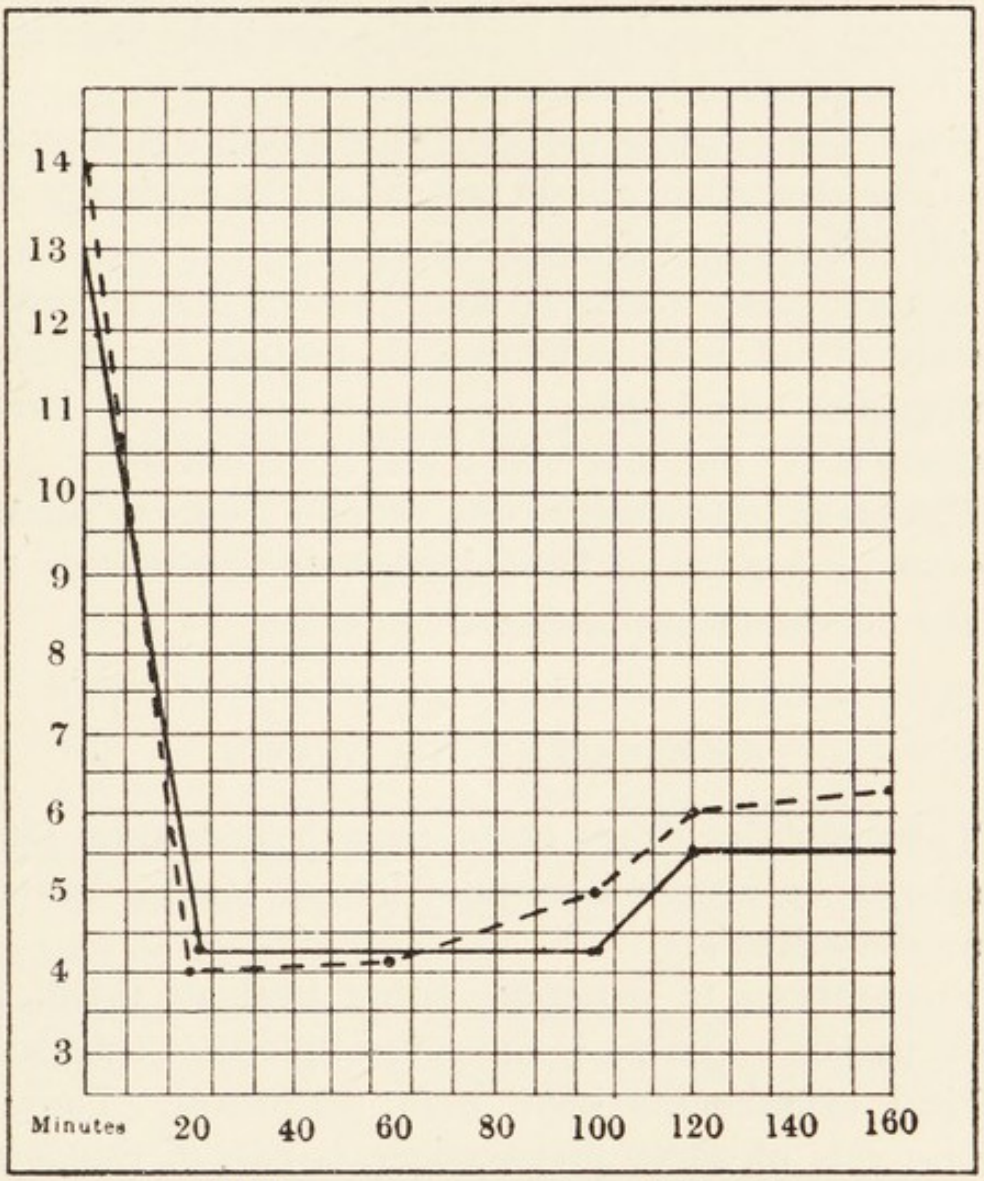
The toxins arising from bruising the tissues in some cases neutralize insulin. It occurred to me that perhaps the substance was the product of protein decomposition, histamine.

I asked my first assistant, Dr. Gerald Slot, to carry out a series of observations in that direction, and to my surprise he found that that substance led to a fall of sugar in the blood of the rabbit.

At the moment we do not know which substance prevents the action of insulin, but we do know that often the removal of the infection will lead to the action of insulin being augmented.

I have seen three cases in which insulin had no effect upon the sugar in the blood when given in doses of 50

DIAGRAM VII.



Milligrammes per 100 c.c. of blood.
——— = one unit of insulin.
- - - - - = three milligrammes ergamine phosphate.

units. In these a long and detailed search for evidence of infection failed. In two of these insulin had acted normally for a time.

When insulin fails to act and an infection cannot be discovered, the insulin should be continued in large doses along with a very restricted diet for several weeks.

I have seen several patients who have not appeared to benefit by injections of insulin until the treatment has been pursued for some weeks.

When one is quite satisfied that insulin fails to act, then the treatment should consist of the optimum diet which will supply sufficient energy.

In these cases it may be found that a diet consisting mainly of fat with only enough protein to maintain nitrogenous equilibrium and mere traces of carbohydrate is the only one which will maintain life.

The great restriction of the protein seems to allow a greater proportion of fat being given without the risk of the development of ketosis.

TREATMENT BY DRUGS.

Treatment by drugs other than hypodermic, intramuscular or intravenous injection of insulin has not proved satisfactory.

Preparations of pancreas, either fresh or dried, are quite useless ; this has been proved time after time when critical experiments have been performed. The immense sale of these preparations is one of the many astounding proofs of the inaccuracy of observation. The manufacturers of some of these preparations advertise in a manner which competes with that of proprietors of secret remedies, but none records observations which will bear the attention of a critical investigator.

I recognize that this is a dogmatic statement, and I

hate being dogmatic, but if I can persuade my readers that they should tell their patients to cease taking the preparation (by mouth) unless they can prove to their *own* satisfaction that the preparation is doing good, I shall have saved many patients an expenditure which they can ill afford.

There is no doubt that quite a number of preparations lead to a diminution of sugar in the urine, but this, by itself, must not be taken as evidence that the preparation is beneficial. This diminution can be brought about in at least three ways :

(1) By raising the renal threshold for sugar.

(2) By diminishing the appetite and thus leading to the patient reducing his diet.

(3) By interfering with absorption.

In all probability calcium iodide was introduced as a treatment for diabetes mellitus, because it was noticed that by its administration the sugar in the urine decreased in some cases which happened to have a low renal threshold ; calcium salts are found to raise the threshold in some individuals.

Raw pancreas and the extracts of some leaves upset the appetite and may apparently do good by reducing the diet.

Codeine, morphine and atropine delay absorption.

In certain circumstances this delay may be beneficial, and prevent the concentration of the sugar in the blood rising above the renal threshold for sugar.

None of the preparations increases the power of the individual to burn or store carbohydrate, and therefore the benefit derived is apparent rather than real.

ALCOHOL.

There cannot be any general ruling about alcohol in diabetes mellitus; every case must be considered separately.

At one time it was thought that alcohol was a valuable source of energy for diabetic patients, 1 grm. of absolute alcohol supplying 7 Calories. I was amongst those who at one time believed that having found the maximum amount of carbohydrate, protein and fat which the patient could utilize without the sugar in the blood rising to too high a level, alcohol could be added to the diet with advantage.

A long series of experiments showed that this was incorrect in the majority of cases; the energy supplied by the alcohol could not be added without hyperglycæmia occurring. Alcohol could only replace carbohydrate or fat.

The majority of authorities have discarded alcohol as a source of energy for diabetics.

It is my custom to advise against alcohol because it depresses the highest centres, thereby diminishes self-control, and makes it more difficult for the patient to adhere rigidly to instructions, but one must realize that the diabetic patient has to submit to much deprivation and therefore should not be denied anything which will not do him harm; for this reason, if the patient has been accustomed to taking alcohol and would feel that its absence would diminish his pleasure in living it should be permitted in moderation, provided someone else is responsible for his diet.

The form of alcohol must depend upon the inclination

of the patient. Whiskey, gin and brandy can be obtained free from sugar, but this is scarcely worth while, because the amount in the ordinary good brands is very small. Before there was insulin, when perhaps the daily ration of carbohydrate was only 10 grm., these minutiæ had to be taken into consideration.

Wines and beers vary enormously.

The patient should obtain a dry wine and have the percentage of sugar in it estimated by a chemist, and allow for the amount of carbohydrate taken in it at his meals.

The percentage of carbohydrate in a brand of beer can be obtained from some brewers and allowed for accordingly. I give a short table :

Half a pint of the following beers count as 5 grm. of carbohydrate :

Bottled Beers.

India pale ale (Barclay's).
Export stout (Barclay's).
Light lager (Barclay's).
No. 1 old ale (Barclay's).
English ale (Fremlin).

Draught Beer.

Burton (Barclay's).

Half a pint of the following contain grammes carbohydrate :

Bottled dark lager (Barclay's) . .	6·5
Draught bitter	7·0
Draught mild ale	7·0
Bottled brown ale	7·5

Bottled Russian stout	9·0
Draught pale ale	10·0
Draught stout	11·0

EXERCISE.

When the treatment suggested by Allen in 1913 was put into practice one found that the fasting patients lost their sugar more rapidly when allowed to take exercise than when kept in bed.

Muscular exercise favoured the burning of sugar in the diabetics.

It was my custom to advise my younger patients who could take strenuous exercise to make a slight increase in the carbohydrate of their meal preceding vigorous exercise.

This rule applies exactly in the same way to patients receiving insulin, but they have the choice of increasing the diet or diminishing the dose of insulin.

The converse naturally applies too; if the diet and dose of insulin has been correlated whilst the patient has been taking exercise, upon his ceasing the exercise the insulin must be increased or the carbohydrate diminished.

The quality and quantity of exercise recommended must depend upon the physiological age and general condition of the patient; the fact that he is suffering from pancreatic inefficiency need not be taken into account provided his pancreas is being subsidized adequately, but intense fatigue must be avoided.

If the patient receive a dose of insulin before a meal it is essential for him to absorb that meal. Intense fatigue may delay the absorption of the meal and lead to severe hypoglycæmia.

PREGNANCY.

Before insulin was available it was the duty of the physician to advise the female diabetic patient to avoid pregnancy; now, provided the disease is not very severe, and the desire for a child is great, I believe he is justified in advising his patients to risk pregnancy if they are willing to be under close medical supervision during the whole period of gestation.

The patient should be observed closely to decide whether there is any evidence of further degeneration of the pancreas, which may be shown by the sugar in the blood rising or the development of ketosis. If the change is but slight an increase in the dose of insulin may suffice to re-establish equilibrium, but if the change is progressive, then the pregnancy must be terminated.

If the physician decides that the pregnancy must be terminated he should consult with the gynæcologist, and they jointly should decide which is the best method to adopt in the individual case.

They must take several things into consideration: (1) That a general anæsthetic is contra-indicated because the administration of nitrous oxide, ether or chloroform may lead to further degeneration of the pancreas and aggravate the disease; therefore the only anæsthetics permissible are stovaine, novocaine, benzoyl lactate by intraspinal or regional injection. (2) There is an advantage in sterilizing the patient, since if the present gestation has led to a change in metabolism which is threatening the life of the patient, any future pregnancy probably will produce the same result. (3) The operation of the removal of the uterus performed by a

skilful surgeon has a lower mortality than that of emptying the uterus.

In the majority of cases the decision arrived at will be the removal of the uterus under regional or spinal anæsthesia, depending upon the custom and experience of the surgeon.

This sounds drastic, but is the method which is least likely to give anxiety.

If the obstetrician does not feel capable of performing hysterectomy and the pregnancy is of less than three months' duration the uterus should be emptied and curetted. I am told that this can be performed quite satisfactorily under spinal anæsthesia in spite of the fact that the uterus is firmly contracted.

Later the patient must be told to avoid conception and be instructed in contraceptive methods.

If the pregnancy does 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 stage of labour is prolonged the advisability of Cæsarian section should be considered, remembering that it gives an opportunity of sealing the Fallopian tubes.

Unless the diabetes mellitus is extremely mild the patient should not be allowed to suckle her child.

HYPOGLYCÆMIA.

Hypoglycæmia means less than the normal quantity of sugar in the blood. Like every other term used in

medicine, it is so ill-defined that it conveys different ideas to different people. In order that the reader shall have no doubt about the meaning of the term here, it shall be defined arbitrarily as less than 0·075% dextrose in the blood taken from a finger-tip.

One might define pyrexia perhaps as a condition in which the temperature in the rectum is above 101° F.; symptoms may be absent in pyrexia just in the same way that they may be absent in hypoglycæmia, depending upon the peculiarities of the individual, but if the conditions become really intense, 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 continue to present signs of hypoglycæmia after the sugar in the blood has risen to 0·125%.

It has been assumed that the symptoms following too large a dose of insulin are due to too low a concentration of dextrose in the blood.

Insulin given in therapeutic doses to the diabetic subject 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 sufficient dose to produce hypoglycæmia. It is within the limits of possibility that it is turned into a toxic substance similar to an alcohol, and that symptoms may arise from its presence.

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 of too little sugar in the blood, and when possible those associating with the patient should be informed too, because occasionally the patient fails to recognize the condition in spite of it being obvious to his friends.

The commoner symptoms consist of—

(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 get sight of him.

Often there is an ill-defined sense of coming disaster.

2. Cold sweats are common, but occasionally do not appear very early.

3. Shakiness in my experience is most constant of all the signs.

If the patient is told to stretch out his hands, they are seen to have a very coarse tremor, the excursion being of the order of a centimetre when compared with the fine tremor of hyperthyroidism, which is of the order of a millimetre.

If the patient writes and puts in full stops, dots his i's, there can be but little doubt left in the mind of the observer who inspects the writing.

4. Intense muscular weakness is subjective. The patient is able to walk and move. I am not acquainted with any ergographic tracings which have been taken.

5 and 6. Difficulty in speech shows itself in two ways: actual articulation is affected, due, I expect, to poor control of 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 patient simulates that of a man under the influence of alcohol.

7. Convulsions: I have not seen patients in hypoglycæmic convulsions, but from the descriptions by those who have, I imagine that they are very like those occurring in epilepsy.

8. Coma may be very profound. The heart first becomes rapid, and later slow and feeble.

The patient is pale and the respirations extremely shallow—so shallow that upon first sight it may appear that dissolution has already occurred.

The less important and rarer symptoms are extremely varied, and occasionally it is difficult to interpret the sensations described.

More than one case of hypoglycæmic diplopia has been diagnosed as encephalitis lethargica; the mental symptoms to which reference will be made later, make an error in diagnosis especially easy.

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 skin as if a new woollen vest were being worn, alteration in vision, leading to the golf club striking the earth instead of the ball.

The mental changes are naturally the most alarming, but fortunately not very common. These vary in intensity from slight inebriation to dementia with excitement.

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

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 in a most excellent manner:

"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 10 minutes or a quarter of an hour he appeared to be quite insane.

"He sprang in 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 to 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.

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

It is therefore wise to take samples of blood from patients who have alleged hypoglycæmic symptoms; then to give carbohydrate, and at one's leisure, estimate the sugar in the blood.

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 of the injection nor to carelessness in failing to note the concentration* of the solution; it may be due to the sudden cessation of a toxæmia due to the bursting of an abscess or the elimination of some focus.

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

* American insulin is supplied in 3 or 4 different concentrations.

treatment had had an epileptic fit. The patient was over 40, and had not had any fits previously. Since he was having injections of insulin, it seemed to me wise to give him sugar in spite of the medical adviser asserting that he did not like awakening patients who were sleeping after epileptic fits.

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

Another cause for poor absorption is the hurrying of the food through the bowel too rapidly ; this may be due to emotional disturbance, or to the unwise administrations of aperients.

Excitement due to other causes may upset digestion. Some that have come my way are a game of chess, a political meeting, a deal upon the Stock Exchange, the responsibility of piloting a ship through a fog, and the entertainment of guests after a dinner.

There is yet another cause for hypoglycæmia. The facts may be given without any attempt to explain.

Explanations have been offered, but since the definition of truth is "that which satisfies," the explanations do not appear to be true.

Several cases have been reported, and in my practice, which includes over 500 cases treated with insulin, 2 or

perhaps 3 have occurred. Two of these I have been able to observe.

I give a short record of a typical case :

A man, æt. 29, with a history of diabetes mellitus of 4 years' duration, was admitted to the London Hospital and placed upon a diet of 50 grm. carbohydrate, 90 grm. of protein, and 130 grm. of fat.

It was found that 10 units of insulin twice a day were required to keep the sugar in his blood below 0·16%.

After 10 days of constant diet and doses 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 this interval his blood-sugar at times rose to 0·125%, whilst sugar appeared in his urine in small quantities. In other words, a patient who had been unable to burn 104 grm. of carbohydrate daily without receiving 20 units of insulin, suddenly burnt 65 grm. together with that liberated through protein metabolism without any insulin in 24 hours, and continued to do so until the sugar in the blood was reduced to 0·02%.

If the symptoms in this case had not been somewhat unusual, my house-physician, who doubted the diagnosis of hypoglycæmia, would have continued to administer sugar, which probably would have saved the patient.

TREATMENT OF HYPOGLYCÆMIA.

The manifestations of hypoglycæmia are so varied that it is wise to give a solution of sugar by the mouth to any patient who is receiving insulin and 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% dextrose in his blood who appeared in robust health; the high concentration of sugar followed the administration of 50 grm. of dextrose given to determine the sugar tolerance to an individual who was alleged to possess a low renal threshold for sugar.

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

If the hypoglycæmic patient can swallow, recovery will follow the administration of half an ounce of sugar in a little water. If the patient is comatose, one cubic centimetre of 0·1% adrenalin hydrochloride solution may be injected into a muscle and sugar given by the mouth as soon as consciousness is regained. Adrenalin liberates stored carbohydrate; if none happens to be stored it will prove ineffectual, and an ounce of dextrose dissolved in 5 oz. of water should be injected into the rectum. If a sterile solution of dextrose is available, 150 c.c. of a 20% solution should be injected intravenously, or 30 c.c. in five separate places subcutaneously.

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 to 0·20%.

Insulin should not be given for 24 hours after a hypoglycæmic attack.

It is necessary to bear in mind that a patient may have a second hypoglycæmic attack without having received any further dose of insulin. It is true that it is rare, and the second or further attack must be treated with further doses of sugar.

Several lives have been lost through this not being recognized.

I do not offer any explanation, but record the fact that histamine, when injected into a rabbit, reduces the sugar in the blood.

In all probability other products of protein decomposition have a similar effect, and perhaps one of these is responsible for the hypoglycæmia in the few cases recorded.

DIABETIC COMA.

As a rule there is no great difficulty in diagnosing diabetic coma; the deep breathing is quite regular, and therefore contrasts with the periodic breathing which often occurs in coma of renal and cerebral origin. It is rare for acetone* and diacetic acid to be absent from the urine, whilst it is almost the rule for acetone to be recognizable in the breath by its smell.

The percentage of sugar in the urine and in the blood is high, although an occasional case is recorded in which these have been found to be normal for a brief spell. One must bear in mind that some cerebral lesions lead to glycosuria. I remember seeing a young girl who had suddenly lost consciousness; the presence of sugar in

* Appendix III.

her urine had suggested diabetic coma of sudden onset. Upon examination I found her breathing was shallow; there was no ketosis, but a definite hemiparesis, which suggested either cerebral embolus or encephalitis lethargica. The subsequent history of the case proved the latter diagnosis to be correct.

The ultimate cause of diabetic coma in many cases is a sudden further deterioration of carbohydrate metabolism which causes the production of large quantities of poisons such as diacetic acid. This sudden deterioration is brought about by the action of toxins arising from trauma or infection.

The treatment comes under three headings :

1. The elimination of the poisons in the tissues or circulation.
2. The prevention of the elaboration of more poisons.
3. The elimination when possible of the focus producing the bacterial toxins, which have depressed the carbohydrate metabolism, and will diminish very materially the activity of the insulin which will be injected.

1. The poisons in the circulation, such as diacetic acid and its salts, are excreted through the kidneys, and therefore diuresis should be encouraged by all the methods known.

If the patient is able to swallow, large quantities of well-salted and peppered beef-tea should be given. The object of adding salt and pepper is to make the drink add to, rather than quench the thirst of the patient.

The most active diuretic we possess is urea; half-ounce

doses of this substance may be given in the beef-tea at 2-hourly intervals.

Purges may be given with advantage, but it is obvious that if the fluid passes through the bowel it cannot pass through the kidneys, and it is probable that the excretion of diacetic acid is more rapid through the kidneys than the bowel. The object of the purge is to prevent the production and absorption of poisons formed by putrefaction in the intestine. From time to time we see cases of diabetic coma in which we fail to find any focus of infection, but learn that the bowels have not acted for 5 days or more.

If the coma is so deep that the patient is unable to swallow, fluids of the same tonicity as blood must be introduced into the bowel and under the skin, or into the veins ; to these urea may be added with advantage.

At one time bicarbonate of soda was considered to be the specific for diabetic coma ; this may have been due to the fact that the apparent alkalinity of the plasma is reduced in ketosis.

It is now generally recognized that the salts of diacetic acid are as poisonous as the acid itself, and many believe that nothing is gained by the administration of alkalies.

There is, however, an argument in favour of the treatment, namely that it increases the power of the blood to carry carbon dioxide and thus may diminish the asphyxia.

2. The prevention of the elaboration of more poisons is attempted by the stimulation of carbohydrate metabolism. This may be accomplished by the injection, preferably intravenously, of large quantities of insulin along with the administration of sugar, either by the mouth or rectum.

Hyperglycæmia does not cause coma. A man with 0·9% sugar in his blood may appear to be in robust health, nor is there any conclusive evidence that insulin does not burn sugar so rapidly when the sugar in the blood is high as when it approaches normal. Insulin would be useless in the prevention of the production of ketones in the absence of sugar to burn.

If facilities are available to permit frequent estimation of sugar in the blood, then sugar need not be given unless the percentage falls below 0·16; if, however, the regulation of the sugar has to depend upon other methods, one has the choice of either giving a fixed number of grammes of sugar for each unit of insulin, or examining the urine before each injection of insulin, and giving sugar with the insulin only in the absence of glycosuria.

I favour the former of these alternatives, and take the view that whoever adopts the latter will, in time, come to grief, for some day he will treat diabetic coma in a patient with a really low renal threshold for sugar, say in the region of 0·07%; in this case sugar will be found in the urine even when the patient is hypoglycæmic, and on that account insulin will be given without the administration of sugar. The diabetic coma will pass to hypoglycæmia coma, and the patient die without the true cause of his death being realized.

It is my custom to order an intravenous injection of 50 units as an initial dose, along with 50 grm. of dextrose, to be followed by 20 units of insulin and 60 grm. of dextrose every 2 hours until consciousness returns. This method ensures hyperglycæmia, but the hyperglycæmia stimulates renal secretion, and is not very

detrimental to the tissues if present for a short time only.

As soon as consciousness returns the ordinary treatment of diabetes mellitus may be adopted.

3. The search for the focus of infection must be thorough ; often it is only too obvious, but not removable, such as an invasion of the pneumococcus, or some other micro-organism which finds its way into the circulation.

The search should include an examination of the skin all over, bacterial examination of the urine, examination of the tonsils and the nasopharynx.

It is scarcely necessary to add that if the focus can be removed or the absorption of toxins from it prevented by operation, the surgeon should be called in without delay. This advice applies, too, to those cases of diabetic coma occurring in women in pregnancy ; if no other source of toxæmia be found the uterus should be emptied without delay.

It is generally recognized that occasionally during pregnancy a change in metabolism occurs which shows itself as eclampsia ; so, too, occasionally in the diabetic, gestation leads to a ketosis, which improves rapidly after the removal of the fœtus.

DIABETIC GANGRENE.

The cause of diabetic gangrene remains a mystery.

Endarteritis obliterans is a common complication of diabetes mellitus of long standing ; I am unable to find any direct relation between the extent of the change in the arteries and the severity of the depression of the carbohydrate metabolism. One of the most severe and

extensive cases of endarteritis obliterans had a 50% efficiency of his carbohydrate metabolism, and never, as far as I know, a hyperglycæmia above 0·25%.

For some years now I have recorded, with a Pachon oscillometer, the volume of the pulse at the ankle in all cases of diabetes mellitus with gangrene of toes, and find evidence of endarteritis obliterans in about 50%.

A good pulse at the ankle does not preclude the possibility of obliterative endarteritis of the smaller vessels of one toe, and this change in the vessels perhaps may precede gangrene.

The treatment of early gangrene depends upon the blood-supply to the limb ; if the supply is good and constitutional symptoms are absent, the affected part should be kept in a warm, dry atmosphere ; this can be arranged by placing a few electric lamps under a surgical cradle, the end of which must be left open to allow a good circulation of air ; if electric current be not available, hot bricks or some other source of heat should be used ; warm air from a spirit-lamp is not satisfactory because it is too moist.

The skin over a gangrenous area usually blisters ; it is essential to prevent the tissues becoming sodden with the exudation, because that invites the multiplication of micro-organisms.

The warm dry air helps to maintain the circulation and to keep the tissues dry, and thus prevents them from supplying a pabulum for bacteria.

Occasionally the pain is severe ; this in my experience is more frequent in the cases associated with endarteritis, and since it may occur without gangrene, is, in my opinion, due to the endarteritis and not to the gangrene.

DRUGS.

The drugs selected to relieve the pain must depend upon the condition. If the endarteritis be extensive and the volume of the pulse in the thigh only small when the foot is gangrenous, then morphine may be given in doses of any magnitude, because the chance of prolonging the life of the patient is small and the fear of the development of a morphine habit does not enter into the question.

If the blood-supply be fair and the pain intense, codeine, along with acetyl salicylic acid or veramon, may be given.

Codeine is not as efficient a depressant for the sensory cells as morphine, but perhaps owing to the absence of a power to katabolize it, the human being does not need an increasing dose as time passes, to derive full benefit from its action.

The chief disadvantage of codeine is its constipating effect, but this can be met by suitable aperients.

OPERATION IN DIABETIC GANGRENE.

The decision as to the advisability of operation must rest upon the following data :

(1) Is the blood-supply to any part of the limb sufficiently good to make it probable that the flaps will heal ?

(2) Is the alteration in the tissue so great that return to normal is improbable ?

(3) Is the absorption of toxins from the changed tissues causing constitutional symptoms ?

(1) If the blood-supply contra-indicates operation,

one must realize that the patient's chances are infinitely small, but one must decide whether the end will be less unhappy with gangrenous flaps than with a large mass of evil-smelling gangrenous limb.

It is an undoubted fact that if the limb is left death must occur shortly; there is a chance that the blood-supply to the flaps may be sufficient in spite of being bad.

In my opinion the decision must depend upon the effect of morphine upon the patient and upon many details, such as the inclination of the patient, and his surroundings.

(2) It is not until one is certain that the area is not simply livid, but is really gangrenous, that one should advise removal.

(3) Constitutional symptoms, such as rise in temperature, leucocytosis, malaise, indicate that immediate operation is advisable.

COMPLICATIONS INVOLVING THE SKIN.

There are three types of complexion peculiar to diabetics—(1) pink, (2) yellow, (3) bronzed.

I do not know why many diabetics are of a pinkish hue; it is characteristic, and usually permits of diagnosis at sight. The yellow complexion is said to be due to carotin; the palms of the hands and the soles of the feet are more pigmented than the face. I do not believe that the yellowness is due to carotin, but this is not the place to discuss a matter purely of academic interest. The bronzed complexion is associated with an increase in the size of the liver.

These complexions do not alter, however successful the treatment of the diabetes mellitus.

Eczema is a common complication, usually at the orifice of the urethra. The cause appears to be an irritant formed by a fungus growing on the skin, which is moistened frequently with urine containing dextrose.

I cannot help thinking that the change in the metabolism, too, is a potent factor, because I have still to meet the condition in "negligible" glycosuria, and as I have already stated that occasionally in that condition the urine contains over 4% of sugar.

The treatment is true cleanliness; it, along with the constitutional treatment of the disease, leads to rapid recovery.

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 microbic infection is depressed.

COMPLICATIONS AFFECTING THE EYES.

Three conditions may arise in patients suffering from diabetes mellitus which may be due to that disease: cataract, retinitis, amaurosis.

CATARACT.

The question of maximum importance to us is how far cataract affects the treatment of the patient.

When, in old people suffering from mild diabetes mellitus, detailed examination fails to show that any of their tissues have suffered from the altered metabolism, I am in favour of making no change in their mode of life, but advise them to submit to medical examination every six months.

When the elderly patient presents early cataract, is it one's duty to advise vigorous treatment of the diabetes mellitus? The reply to this question needs some consideration.

As far as I can gather ophthalmologists are not in agreement on the relation between cataract and diabetes mellitus in the aged.

There seems to be no doubt that a true diabetic cataract occurs in the young; characterized by being bilateral as a rule ("always"), it begins by dusty opacities appearing throughout the cortex, increasing rapidly, until the lens becomes completely opaque.

The debatable subject is whether there is a true diabetic cataract in the aged. An explanation of the great difference in the rapidity of development has been suggested, namely, that the relatively slow development in the aged is due to the comparative hardness of the lens.

All agree that in the majority of cases of cataract in elderly diabetics, even the most elaborate methods fail to differentiate between the changes in their lenses and in those of undoubted senile cataract.

For this reason some assume that when cataract occurs in patients of advanced years suffering from diabetes mellitus, it is purely a senile change, and has nothing to do with the metabolic complaint.

In my opinion this assumption is unsound.

I am amongst the many observers who have seen diabetic cataract arrested or even slightly improved in elderly patients who have submitted to vigorous treatment of their diseases, whilst a few have recorded cases in which the cataract has cleared completely.

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

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 unreduced 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 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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