Medical.

THE CLINICAL IMPORTANCE OF BLOOD-SUGARS—HIGH AND LOW.¹

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THERE are three diseases in which of recent years the centre of interest has shifted considerably from an examination of the urine to an examination of the blood—jaundice, nephritis and diabetes. It has been generally realized that the kidney may offer an obstacle of varying degree to the passage of normal or abnormal constituents of the blood into the urine, and that the examination of the urine gives us information which may be incomplete and even positively misleading. This is due to the fact that the kidney has a *threshold*, and that this threshold is capable of variation. The term threshold is now generally accepted, though as thresholds are not built above the level of the floor, it has become somewhat meaningless, and the French term “sill” is more rational. The term “leak point” is also sometimes used, and has the advantage of clarity.

Ambard classified the substances excreted by the kidney as follows :—

- (1) Substances like alcohol or acetone which merely diffuse out.
- (2) Substances which are incapable of playing any useful part in cellular metabolism, i.e., waste products, which the kidney excretes in a more concentrated state than they are present in the blood. Urea is the best example.

Since the amount of this in the blood is normally 20 to 40 mg. and in the urine 2 per cent., it has been concentrated fifty to one hundred times in the process of excretion. This involves much work on the part of the kidney, but there is no question of “threshold.”

As long as the concentrating power of the kidney is normal, it will continue to excrete urea whatever the percentage of it present in the blood. A rise of blood-urea, then, is evidence of a failure of concentrating power in the kidney.

(3) Substances which are capable of playing a useful part in cellular metabolism, such as sugar, salt, hæmoglobin, bile. Against the excretion of these the kidney imposes a threshold, so that the blood shall not be denuded of them. As Ambard puts it, the body is a Free Trader as regards the second group, but imposes an export tariff on this third group. If this tariff were a fixed one, our task would be simplified, but as it may vary both in different healthy individuals, and at different times in the same individual if diseased, we may have to control our urine analysis by blood-analysis from time to time. There are three variables, the blood, the urine and the kidney ; we require a knowledge of two of these before we can form an opinion as to the state of the remaining one. In nephritis, we chiefly compare the blood and the urine to form an estimate of the state of the kidney ; in glycosuria, having formed some estimate of

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the state of the kidney, we are principally concerned with the blood-sugar as a guide to the metabolic state.

Ever since the days of Claude Bernard, it has been known that the blood always contains sugar, and estimations of the amount were made from time to time by researchers. But it was not until twenty years ago that such estimations began to be made for clinical purposes, and it was not till 1913 that Ivar Bang published a convenient method for making such estimations from very small quantities of blood. Still simpler methods are now available. Even then it was not realized at first how important it is in any doubtful case to have a curve of sugar tolerance worked out. In those days, in common with many others, I was guilty of assuming that because a normal or subnormal blood-sugar was found on a single examination, therefore the patient had no impaired carbohydrate tolerance. For we were still under the influence of Pavy's teaching that the amount of sugar in the general circulation was not influenced even by a heavy carbohydrate meal, so responsive was the liver to changes of sugar in the portal blood. Now we know that the sugar in the blood begins to rise within five minutes of its ingestion, reaches its maximum of 0.16 to 0.18 per cent. in fifteen to twenty minutes, and has returned to its fasting level in an hour and half. The normal leak point may be taken as just over this maximum.

A standardized method was quickly evolved and 50 grm. of dextrose used as the test meal, though if it is considered advisable to use the test in a severe diabetic, 25 grm. is more usually employed. Indeed, it is curious to see how little difference is made in the form of the curve whether 25, 50 or 100 gr. of dextrose are given.

The form of the curve may vary within the limits of health. Thus Graham found that ingestion of carbohydrate produced a higher and more prolonged rise when he was tired before he had a holiday, than when he returned from that holiday. But the curve did not reach his leak point, so there was no glycosuria. The mechanism by which the kidney varies its threshold or leak point is not really understood, but Hamburger and Brinkman's perfusion experiments indicate that it is bound up with the concentration of the calcium and potassium in the blood, and with the H-ion concentration.

However, once the form of the normal curve was agreed upon, it became obvious that cases of glycosuria fell into two great categories. For *renal glycosuria* is sharply demarcated off from all the rest. The name was given on the analogy of the effect of phlorhizin poisoning, which seems to act directly on the kidney, causing it to secrete sugar, even when the sugar in the blood has been reduced below normal. Although there is no evidence of renal or indeed of any other disease, "since it is the threshold of the kidney, however it is regulated, which determines whether sugar is excreted at a certain level of blood-sugar, it seems better," Graham says, "to connect the name of 'renal glycosuria' with this condition." The subject of renal glycosuria has no symptoms and is usually quite well, until he is worried by the discovery of sugar, generally on examination for life insurance. I may take as a typical example of this a young lady in whom glycosuria was detected in the course of routine examination. On further observation, I found that she always passed about the same amount of sugar whatever the diet, the percentage usually lying between 1 and 2 per cent. Her blood-sugar was low and never reached the normal leak point of 0.15 per cent., even after 50 grm. of glucose were administered in one dose, nor did this increase the glycosuria. One may conclude that a glycosuria which keeps at 1 to 2 per cent. independently of diet is of

the renal type, and a practical deduction is that such patients should not be put on a restricted diet. It is very difficult, if not impossible, to get them free from glycosuria, but it is easy to cause them to waste and become ill if such an attempt is made. Doubtless some of the cases of persistent glycosuria without symptoms that are described from time to time are of this class. But I have also had instances of intermittent glycosuria of the renal type. Thus, a young man of 21 had glycosuria detected on examination for life insurance and on one occasion afterwards. He had no other symptoms. His blood-sugar was 0.064 per cent., and after 50 grm. of dextrose it never rose above 0.12 per cent., falling again to 0.065 per cent. in one and a half hours, without any glycosuria. He evidently had a low leak point, but when 50 grm. of dextrose were given this was not necessarily reached. Another young man, aged 20, showed traces of sugar in the urine on three occasions on examination as to the fitness for work in the East. His blood-sugar was 0.1 per cent. and did not rise above this figure at any time after 50 grm. of dextrose. At the end of an hour and a half he passed 0.46 per cent. of sugar and his blood-sugar was as low as 0.05 per cent.

I do not see how it is possible to recognize renal glycosuria of this intermittent type without observing the blood-sugar curve after the ingestion of 25 to 50 grm. of dextrose. Maclean has pointed out that the question may be further complicated by the passage of ketones with the sugar. But whereas in true diabetes ketones can be passed without sugar, in this type it is merely when the sugar is being drained off that there is not sufficient available to oxidize the fats completely. In other words, in renal glycosuria, ketosis is due to direct loss of sugar, while in diabetes, ketosis is due to loss of the power to utilize sugar.

A patient with renal glycosuria needs no treatment, but, as Graham says, if he is treated as a diabetic, little harm will ensue; sooner or later he will abandon the treatment with no ill-effect. But if a mild diabetic is treated as a case of renal glycosuria he will inevitably grow worse. It is a curious fact that hot climates occasionally seem not to suit the subjects of renal glycosuria. It is not a very common condition, but routine blood-sugar examinations have shown that it is considerably more frequent than was previously suspected. In insurance work I have come across quite a fair number and am now prepared to recommend their acceptance at ordinary rates for an endowment assurance if the blood-sugar curve is typical. As we have only had about twenty years' experience of the condition I hesitate to recommend acceptance for a whole life policy.

Before dealing with the other types, all of which show a raised blood-sugar after 50 grm. of dextrose, even if they do not when fasting, it will be helpful briefly to consider the ordinary mechanisms of carbohydrate metabolism. Although carbohydrate forms more than 70 per cent. of our ordinary diet, it seldom constitutes more than 1 per cent. of our body weight. This simple consideration alone shows that it must be the most easily metabolized of the foodstuffs. The body can do four things with ingested carbohydrate:—

- (1) Some may be consumed at once by muscular energy.
- (2) Normally much of it is stored in the liver or muscles as glycogen.
- (3) Some of it may be stored in the more stable form of fat. As Von Noorden showed, some cases of obesity are really ones of latent glycosuria. An impaired glycogenic function is compensated for by a deposit of fat, and the loss of a valuable

foodstuff is thus avoided. But like all pathological substitutes for a physiological method, it is an inferior one.

(4) Some of it may pass out in the urine. Except for the minute trace, not exceeding 0.1 per cent. of sugar normally present in the urine, the amount of sugar which can be assimilated is remarkable. A normal individual has to take at least $\frac{1}{4}$ per cent. of his body weight, which means as much as 150 to 200 grm. (5 to 7 oz.) dextrose at one time before any will appear in the urine. It is therefore very difficult to raise the blood-sugar above the leak point in a normal individual by giving him sugar by the mouth.

From the foregoing observations it is clear that sugar is normally stored rapidly. It is unnecessary here to go into the proofs that this storage is effected through the agency of insulin. It is of more interest to inquire how the output of insulin is regulated to the need of the body.

At the outset we must notice that the adjustment is not immediate, for as we have seen, blood-sugar rises for about half a hour after a meal and then proceeds to fall again, although sugar is still pouring from the bowel into the portal vein. This suggests that a preliminary rise of blood-sugar is necessary to start the mechanism, but it is only since recent work by McLeod and Le Barre that we have been able to appreciate how this acts. It appears that the cell-islets of the pancreas are under nervous control and that their secretory activity is regulated by the level of the blood-sugar. These islets receive a rich innervation from the vagi, and section of the vagi causes a transient rise, while stimulation of them produces a considerable fall of blood-sugar. Venous blood drained from the pancreas of a normal animal A into a depancreatized animal B, definitely lowers its blood-sugar. If now sugar is injected into animal A, a further striking and prolonged fall of blood-sugar occurs in the recipient B, suggesting that this procedure has stimulated the production of insulin in A. But if the vagi are cut in A this does not happen. Further, if insulin hypoglycæmia is produced in animal A, its pancreatic venous blood can no longer lower the blood-sugar in the depancreatized recipient B. The most reasonable explanation of this is that a rise of blood-sugar stimulates the vagal centres to excite a secretion of insulin from the cell-islets.

There is a close analogy between this and the way in which an increased H-ion concentration in the blood stimulates the respiratory centre, and even a suspicion of cerebral anæmia stimulates the vasomotor centre. Setting aside, for the moment, the question as to whether all diabetes is pancreatic in origin or not, it is clear that if there is any lack in the cell-islets, they cannot adequately respond to the vagal demand for insulin; the blood-sugar therefore remains high and the inadequate or damaged islets have a continued demand made upon them. At any rate Allen has shown that if a dog has a partial excision of the pancreas, but not enough to cause glycosuria, and the blood-sugar is then kept raised by an ample carbohydrate diet, the remaining cell-islets swell up, vacuolate, and finally burst their basement membranes. When this last stage is reached permanent degeneration results. But if insulin is given at the same time, overwork of the pancreas is prevented and these changes do not occur. We may conclude, then, that whether the process starts in the pancreas or not, anything which maintains hyperglycæmia will damage the pancreas sooner or later. For this reason some years ago I suggested as a modification of Naunyn's phrase, everyone with a resting hyperglycæmia is a potential diabetic. To-day I am almost prepared to go

further and to assert that everyone with a resting hyperglycæmia is a diabetic. The vicious circle has been started and can only be broken by insulin. In a discussion held in this room some ten years ago, I posed the question, "Is hyperglycæmia the enemy?" but answer came there none. To-day it can hardly be doubted that a persistent hyperglycæmia keeps up such a continued strain on a damaged organ that disaster is inevitable sooner or later, because it renders the damage progressive. In the past several symptoms of which the diabetic often complains, cataract, neuritis and liability to septic complications, have been referred with more or less show of reason to hyperglycæmia. Lawrence has recently called attention to a type of case where a very high blood-sugar may cause symptoms resembling an acute abdomen accompanied by a considerable leucocytosis. Cairns Forsyth points out that a valuable diagnostic sign is that the vomiting precedes the pain in this type, whereas it follows the pain in acute abdomen. It is a very important thing to recognize since apparently it yields to insulin, whereas a laparotomy may have serious results. But in general we may say that the disadvantages of a high blood-sugar are slow and cumulative, while the disadvantages of too low a blood-sugar are swift and dramatic.

So far, however, we have only considered the question of the vagus and the pancreas. But there is another side, for the visceral or vegetative nervous system consists of two mutually antagonistic parts, the *sympathetic* which mobilizes the body for defence, converting potential energy into kinetic, and the *parasympathetic* or extended vagus which stores up energy, especially the energy derived from the assimilation of food. Each of these co-operate with endocrine glands, the sympathetic with the adrenals, thyroid and pituitary; the parasympathetic with the pancreas, and possibly the parathyroids. An important way in which the first group prepare for defence is by mobilizing sugar into the blood-stream. Here it is normally utilized for muscular energy if the organism has to defend itself by fight or flight, or it is used for the production of fever. Cramer has shown that this is at any rate one of the ways in which fever is produced. If carbohydrate metabolism is normal the sugar is utilized at once, but if it is not there will be hyperglycæmia, though not necessarily glycosuria. Thus hyperglycæmia in pneumonia and rheumatic fever was observed some years ago before its significance was realized. I think we have in this fact the explanation of the influence of focal sepsis in aggravating diabetes. Sepsis will not necessarily cause hyperglycæmia. Thus in six consecutive cases of recurrent boils I found hyperglycæmia in one but not in the other five. The occurrence of recognizable hyperglycæmia in sepsis indicates an imperfection in the sugar-storing mechanism, and if such an imperfection is already definitely present it will increase it. But it is defensive in origin.

The view which I therefore wish to put forward is that the normal regulation of blood-sugar is accomplished thus: (1) A rise in blood-sugar is met by an increased secretion of insulin mediated through the vagus and pancreas; (2) a demand for increased blood-sugar is met by an increased conversion of glycogen into sugar through the sympathetic acting on the adrenals, pituitary and/or thyroid. The first two antagonize the action of insulin on the liver while the last acts as a general accelerator of metabolism.

I will take the example of the thyroid first. Within a short space of time I had two striking examples of rapid enlargement of the thyroid in lads, apparently due to a reaction against infection from septic tonsils; in each case the swelling went down considerably

immediately after the enucleation of the tonsils, and although there was never glycosuria and no resulting hyperglycæmia, the blood-sugar rose to 0·233 in one case, and to 0·21 per cent. in the other, an hour after 50 grm. of sugar were given ; yet there was no glycosuria.

This is still more marked in exophthalmic goitre. I have never investigated the carbohydrate metabolism in this disease without finding a marked rise of blood-sugar following the administration of sugar. There may be no glycosuria because of the rise of threshold, but even the level of the raised threshold may be exceeded and then glycosuria follows. This may occur temporarily from a purely emotional cause.

Do cases of hyperthyroidism ever develop true diabetes ? I think they do if they have hyperglycæmia prolonged enough to damage their cell-islets. A girl developed Graves' disease when her father became prisoner of war in the hands of the Turks. Her condition grew worse as information as to his sufferings arrived, and when he died she was found suffering from glycosuria. After preliminary dieting the urine became free from sugar, but I found she had a resting hyperglycæmia of 0·198 per cent. which rose to 0·46 per cent. an hour after 50 grm. of dextrose, when she passed 5·25 per cent. of sugar. In other words, she had become a true diabetic, and she died in coma as the result of an intercurrent infection about a year later. This was before the days of insulin.

In hyperthyroidism there is usually no resting hyperglycæmia, but according to Mackenzie Wallis the typical response to the ingestion of 50 grm. of dextrose is a sharp rise reaching its maximum in an hour and then usually a rather sharp fall again, but not reaching normal in one and a half hours. Graham more cautiously says that the blood-sugar curve of hyperthyroidism merely shows a lowered carbohydrate tolerance.

It used to be stated that there is increased carbohydrate tolerance in the opposite condition of hypothyroidism. Samson Wright objects to the use of such a term at all, maintaining that the limit of tolerance for sugar is the amount that the stomach will receive without vomiting, and that this is usually about 500 grm. But I think the meaning of the phrase is clear, it means that sugar goes into storage quicker than usual, so that the rise of blood-sugar is less than normal. Now, although one would expect that the blood-sugar curve in hypothyroidism would be the opposite to that of hyperthyroidism, Gardiner Hill and others have shown that this is not the case. I have found a similar state of affairs and had regarded it as exceptional, due to some other cause, but it is apparently the rule for the blood-sugar in myxœdema to rise slowly to a greater height than normal, so that the resulting curve closely resembles that of patients with hyperthyroidism. Glycosuria may not occur, however, which explains the reason for the former view, which was based more upon a study of the urine than of the blood. This lowered tolerance would account for Garrod's observation that out of eleven consecutive cases where myxœdematous patients had been on thyroid treatment for some time, four had glycosuria. I saw in 1923 one of G. R. Murray's original cases of myxœdema who had developed diabetes. She had been taking thyroid extract for over thirty years, and, as she objected to insulin, she died about a year later, apparently as a direct result of the diabetes. One can only conclude that excess of thyroid raises the blood-sugar by mobilizing more sugar into the blood, while lack of thyroid raises it by diminishing the storage of sugar by the liver. Evidently in treatment by thyroid extract the happy mean must be aimed at, and the blood-sugar curve kept as normal as possible.

But the following case raises the question in a different and an interesting form. The wife of a medical man, aged 32, was worried because she was putting on weight rather rapidly. She therefore started taking 5 gr. of thyroid extract daily, one Christmas, and lost over a stone in weight. By the following May she suffered from palpitations and shortness of breath, so she stopped taking thyroid, but her weight continued to fall, in spite of rest. In September she became thirsty, had pruritus vulvæ and was found to be passing sugar in large amounts. I found her resting blood-sugar was 0·38 per cent. I put her on 2½ gr. of quinine hydrobromide three times a day, and dieted her. She became free from sugar on the first day of fasting, and when her diet contained 63 grm. of carbohydrate her blood-sugar was 0·144 per cent. When I last saw her she was still free from sugar on 90 grm. of added carbohydrate, but her resting blood-sugar was 0·153 per cent. and she was still losing weight, so she was starting a course of insulin. The pulse was still rapid and she was a little tremulous, but she had no other signs of hyperthyroidism. What is the explanation of the case? Personally, I think her increasing weight was the first sign of impaired carbohydrate metabolism, and that taking the thyroid extract converted her from a case of latent to one of consecutive glycosuria by still further upsetting her metabolism. One thing, however, to which I would specially call your attention is that as a case of Graves' disease improves the threshold may fall faster than the hyperglycæmia, so that I do not worry particularly about the appearance of a certain amount of sugar in the urine if the general condition of such a patient is obviously improving. Thus, a woman of about 40 had Graves' disease and developed leukoderma. Her resting blood-sugar was 0·069 per cent., but after 50 grm. of dextrose it rose to 0·323 per cent. at the end of an hour, yet she had no glycosuria. She improved very much under treatment, and as she did so she occasionally passed sugar. I saw her frequently for about four years after this and she apparently kept quite well.

Adrenal Glycosuria.—The antagonism between the pancreas and the adrenal medulla is well known. It is expressed in such phenomena as Loewi's adrenalin pupillary reaction, and in the dribbling secretion of pancreatic juice which follows removal of the adrenals, a secretion which can be checked by injections of adrenalin. But it is shown most clearly in the opposite effects of adrenalin and insulin on carbohydrate metabolism. That adrenalin injections could produce glycosuria was shown by Blum more than twenty years ago. Later it was seen that the diabetic puncture produced its effect through the adrenals and possibly the pituitary in addition. Severance of the nervous channels between the medulla and the adrenals renders diabetic puncture inoperative. J. H. Burn has proved that there is no direct antagonism between adrenalin and insulin, and he agrees with the accepted view that adrenalin turns the glycogen of the liver into sugar, thus interfering with the storage mechanism.

As adrenalin raises arterial tension as well as producing glycosuria, it is tempting to assume that the glycosuria associated with high tension in later life may be adrenal in origin, especially as it is apt to occur in overworked, worried people. But there is no proof of this. I should, however, like to call attention to the form of the blood-sugar curve in this nervous type of glycosuria. It is characterized by a sharp peak just where the normal curve is rounded. This peak exceeds the threshold, and this is when the glycosuria occurs. It suggests a delay in the sugar storage mechanism of the liver coming into action. There is merely a delay, because later on when sugar is still

entering into the blood-stream, the blood-sugar is falling, and there is no glycosuria, so storage must be proceeding normally. For these reasons Maclean has called this the "lag curve."

Now adrenalin is activated through the emotional nervous system, and in its turn acts on the sugar-storing process, so that there is at least a *prima facie* case for investigation of such cases along the line of adrenal glycosuria. It is usually sufficient to deprive these patients of sugar as such, while allowing them to take a reasonable quantity of starch. In this way the mechanism for storage of sugar as glycogen is not suddenly overtaxed immediately after food. The process of starch assimilation is a more gradual one. But the most important part of treatment is a holiday and attention to general hygiene.

Pituitary glycosuria is due to overaction of the posterior lobe of the pituitary. It is often associated with signs referable to other portions of the gland. If the pituitary is enlarged there may be optic atrophy and bitemporal hemianopsia, some interference with the third nerve and X-ray evidence of enlargement of the pituitary fossa. If the anterior lobe is overactive there will be signs of acromegaly as well; if it is underactive there will be diminished sexual development. The glycosuria may be intermittent since the pituitary is rhythmic in its functions, while the characteristic change in the blood is said to be the slow rise of sugar in it, and an equally slow fall, giving a rounded form to the curve.

Mackenzie Wallis called attention to the frequency with which signs of pituitary disease occur in intermittent glycosuria, and also pointed out the close resemblance between the blood-sugar curve in such pituitary cases and in the glycosuria, as distinct from the lactosuria, of pregnancy. This accords with the view that the glycosuria of pregnancy is due to the stimulating effect of pregnancy on the pituitary.

J. H. Burn found that although the pitressin fraction of pituitrin does not in itself cause hyperglycæmia, it inhibits the fall of blood-sugar which would otherwise have followed the injection of insulin. It would appear, therefore, that an excess of post-pituitary secretion can hardly excite glycosuria unless there is some shortage of insulin. Graham has made use of this antagonism to prevent hypoglycæmic reactions after insulin in cases where the margin between the therapeutic and the toxic dose is a narrow one; for if 1 unit of pituitrin is added to 10 of insulin the fall of blood-sugar is slower and more prolonged.

Pancreatic Glycosuria.—No difficulty is experienced in recognizing cases of glycosuria associated with frank pancreatic disease. There is fatty diarrhœa due to an excess of unsplit fats, and there may be creatorrhœa. In the early stages the output of urinary diastase is increased to 50 units or more and the adrenalin eye test may be positive. Yet how often are such signs found in ordinary diabetes? It is true that they may be present in the early stages or even before glycosuria occurs, and subsequently subside. Thus I saw a case of a young lady who had symptoms of pancreatitis and then glycosuria. She cleared up with dieting for a time and then unfortunately returned to ordinary food. After that she showed no evidence of pancreatitis but the ordinary symptoms of diabetes, which subsequently proved fatal. Unless one had seen this case in the early stages its pancreatic origin would have been missed.

Diabetes.—But when full allowance is made for all this, one must admit that the pancreatic origin of true diabetes is still unproven. My own view is that it is usually

due to a more profound metabolic disturbance than that evoked by one endocrine gland. Eppinger, Falta and Rudinger put forward the hypothesis of a disturbed endocrine balance as the cause. If one endocrine gland were diseased we could understand a loss of balance comparable to that which occurs when a group of muscles is paralysed. But such signs of endocrine disease are lacking in ordinary diabetes even if carefully looked for. It will be noted that the sympathetic stimulates all the endocrine glands which mobilize sugar into the blood, i.e., the thyroid, adrenal and pituitary, while it probably inhibits the pancreas, either directly or by antagonizing the vagus, thus checking sugar storage. Overaction of the sympathetic at any rate means increased katabolism and usually hyperglycæmia. And as hyperglycæmia, if not caused by deficiency of the pancreatic cell-islets, will at any rate damage them in time, we may admit that all cases of diabetes are ultimately associated with insufficiency of pancreatic internal secretion. The other view is that some toxin exercises a selective action on the cell-islets. But there is no direct evidence of this.

The blood-sugar curve starts above normal, rises very sharply and keeps at a high level for at least two hours, so that it differs materially from the other curves I have discussed. But to my mind it is seldom necessary to do a full blood-sugar curve in what appears to be a clear case of true diabetes, nor is it usually advisable.

It is important to remember that in general the dietetic treatment of diabetes renders the urine free from sugar more readily than it lowers blood-sugar. Indeed, before the discovery of insulin, the usual course of events was for the renal threshold to rise, so that although no sugar escaped the blood-sugar remained high. It was not uncommon to find a resting blood-sugar of 0.25 per cent. without glycosuria. Of course this was an attempt at compensation, an attempt to hold the sugar in circulation long enough for it to be utilized, but it had the great disadvantage of allowing the cell-islets to be damaged further. This is where insulin is such an enormous help.

The following table, adapted from Lawrence, gives a very concise picture of the state of affairs in some of the conditions I have been speaking of:—

			Hyperglycæmia.	Glycosuria.
Normal	...	...	o	o
Renal glycosuria	...	...	o	+
Untreated diabetes	...	...	+	+
Treated diabetes	...	...	+	o

In concluding this part of my subject I should like to refer to three special instances: the influence of encephalitis; of age; and of mental states on the blood-sugar curve. McCowan and others have found that the majority of post-encephalitics show a hyperglycæmia after ingestion of dextrose, and that this is markedly sustained in 50 per cent. of the cases. A return to a normal curve is a good prognostic sign. Hyoscine has been found to improve the clinical condition in some such cases, and these are the ones where the drug modifies the curve so as to approximate more nearly to the normal. The fact that the levulose test is normal is against the idea of a permanent hepatic insufficiency in those cases.

F. W. Marshall has recently (*Quart. Journ. Med.*, January, 1931, p. 257) made an interesting study of the effect of age on blood-sugar. The ages in his series varied from 65 to 94, the average being 72.

He found only 14 per cent. showed a curve within what might be regarded as

normal limits, while 39 per cent. of normal healthy people over 65 showed a prolongation of the curve which failed to reach its normal fasting level within two hours, indicating a storage defect. Although this would be regarded in younger people as an indication of potential diabetes, we may apparently disregard it after 65. A "lag" curve was found in 25 per cent., and although we have no statistics as to its frequency in earlier years, it certainly is not at all common. It is probably an indication of commencing fatigue of the mechanisms for dealing with carbohydrate. A "flat" curve, implying diminished absorption of carbohydrate, was found in 7 per cent. Most striking of all is the fact that the diabetic curve was found in 14 per cent. of healthy old men. So that defects of one sort or another in dealing with carbohydrates occur in 86 per cent. of healthy old men. The threshold for sugar is also raised and may be taken as 200 mg. Doubtless this is again a conservative process to compensate to some extent for the metabolic difficulties of old age. Such difficulties may well be a factor in the loss of weight which is common after 65. The moral is, do not take blood-sugar curves too seriously in old age.

McCowan and Quastel have also made interesting observations on the variations in the blood-sugar curves of psychotic patients which show an association between a state of emotional tension and hyperglycæmia. They attach most importance to a sustained level in the curve.

Low Blood-Sugar.—It is perhaps not surprising that until the isolation of insulin, the converse of diabetes was not recognized. Then, through the study of blood-sugars it was seen that just as the thyroid defect of myxoedema is the opposite of the thyroid excess of Graves' disease, so diabetes has its opposite in hyperinsulinism. The symptoms of this condition were recognized through their similarity to those produced by an overdose of insulin. Hector Cameron called attention to the similarity between the nervous symptoms of the child who is liable to ketosis and the child who has had too much insulin. Anyone who has had experience of diabetes in children must be familiar with the outbreaks of uncontrollable temper and other nervous manifestations in the child, with too rapid a fall of blood-sugar after a dose of insulin. The child who is liable to ketosis generally has a loathing for fats and a passion for sugar, which is comprehensible physiologically. There is no doubt that Cameron is right in claiming that such children are much improved in health and temper by giving them more sugar, as dextrose, and less fat. But minor degrees of such a condition are not infrequent in adults. Graham has pointed out that those individuals who become extremely irritable if kept waiting for food (and who does not, if the waiting is sufficiently prolonged?) will be found to have a low blood-sugar at that time. Not only a dose of dextrose itself, but a cocktail is said to raise the blood-sugar, which may account for the vogue of the latter in this nerve-ridden generation, for that a nervous mechanism is at work is very probable.

As we have seen, stimulation of the vagus will produce a fall of blood-sugar. The evidence would be more convincing if atropine checked this fall, but it does not. Graham thinks that the hunger pain of duodenal ulcer and other hyperchlorhydric conditions is in part due to low blood-sugar. This is comprehensible, since hunger is accompanied by contractions of the stomach produced through the vagus, and Pavlov proved the influence of the vagus in exciting a secretion of the acid of the gastric juice, while Cathcart in 1911 showed that vagus stimulation would excite activity in the pancreas.

It may well be that a low blood-sugar is one of the normal excitants of hunger, since it would thus directly lead to its own correction.

But apart from this normal mechanism which may be exaggerated under certain nervous conditions, there are now cases on record where tumours of the pancreas have led to a dangerous degree of hypoglycæmia. Such a condition was first described by S. Harris in 1924, while in 1926 the Mayo Clinic had an example due to carcinoma of the pancreas originating in the cell-islets. Some subsequently reported cases have been malignant, others benign. Some such cases, if mild, can be relieved by more liberal and more frequent food; sometimes sugar must be given every two hours. But in other instances it may be almost impossible for the patient to ingest enough sugar to keep the blood-sugar at an appropriate level. Some have died, and epileptiform convulsions led to the fatal issue in some of these, recalling at once the hypoglycæmic convulsions from a gross overdose of insulin. Thyroid extract has been given in some cases for its antagonistic effect on insulin. In severe cases operation must be considered with the object of removing a tumour if present, or of removing part of the gland on the analogy of operation for hyperthyroidism. The literature of the subject has been recently reviewed and a new case recorded by Moore and others in the *British Medical Journal* for November 7, 1931 (p. 837).

I believe that minor degrees of hyperinsulinism are not so rare, and would agree with Falta and with Poulton that some cases of otherwise unexplained obesity are due to this. Clearly pituitrin lack or insulin excess will have the same effect, as they are antagonistic to one another in their effect upon the liver. Relative hypoglycæmia may produce symptoms in chronic diabetics who have become accustomed to a raised level of blood-sugar. Thus, a patient who had been suffering from diabetes for more than ten years before the discovery of insulin developed hypoglycæmic symptoms when first given it, although his blood-sugar was still 160 mg. And even in recent cases there may be a capricious response, so that quite unexpectedly severe hypoglycæmic reactions may occur with comparatively small alterations in the dose. Fortunately such cases are not common; it is possible that they are related to diurnal variations in the glycogen content of the liver, such as are known to occur in animals. Essentially the symptoms of hypoglycæmia must be due to an intracellular anoxæmia, and the continued study of such conditions is sure to throw interesting light on many obscure metabolic and biochemical problems.

FOR NOTES.