CLINICAL PATHOLOGY IN GENERAL PRACTICE

GLYCOSURIA AND HYPERGLYCAEMIA

BY

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Glycosuria and hyperglycaemia are closely related because, except in those patients with a lowered renal threshold, glycosuria is always an indication that the blood sugar is higher than normal. While recent advances in our knowledge of renal physiology have invalidated the concept of a renal threshold as an unvarying and characteristic concentration of glucose in the blood—above which glycosuria occurs, and below which it does not—there is no doubt that from the clinical point of view this concept is justified and of real value. In most people the renal threshold is about 180 mg. per 100 ml., a value which the blood sugar normally never exceeds; glycosuria does not therefore occur. Hyperglycaemia with a blood-sugar concentration exceeding the normal threshold, as occurs in diabetes and in a few other pathological conditions (see below) leads to the appearance of sugar in the urine. In patients with a normal renal threshold glycosuria is absent when the blood sugar is below 180 mg. per 100 ml., a trace is detectable when the sugar concentration is around 200 mg. per 100 ml., while a complete reduction of the usual clinical testing reagents is given when the blood sugar is 300 mg. or more per 100 ml.

Glycosuria can, however, also occur without a raised blood sugar in renal glycosuria, in which condition the renal threshold is lower than normal, being sometimes as low as 80 mg. per 100 ml. The threshold is sometimes raised, especially in diabetes; hyperglycaemia with blood-sugar concentrations above the normal threshold can then occur without glycosuria.

Tests for Reducing Substances in Urine

The presence of a reducing substance in the urine may be investigated by Benedict's test* or by the recently developed "clintest" tablet test. Fehling's test is less sensitive and less specific and has little to recommend it. Benedict's test is less easy to perform properly than the clintest, which has many advantages in general practice because no external source of heat is required. The very rapid and convenient screening test using clintest with undiluted urine is especially valuable, but a positive result should always be confirmed by the standard technique recommended by the manufacturers.

Significance of Reducing Substances in the Urine

The urgency with which the general practitioner must act upon finding that the urine of his patient reduces Benedict's solution or the clintest tablet must depend entirely upon the clinical condition. Most patients with diabetes mellitus give a clearly defined history of the disease, and if a positive test for reducing substances in the urine is found in a patient with loss of weight, pruritus, thirst, and polyuria there is no point in arranging elaborate investigations to decide whether or not the reducing substance is glucose. The problem of the moment is whether the patient has diabetes, and, if so, whether the condition is an urgent one requiring immediate treatment with insulin. This will depend on the presence or absence of severe ketosis.

Reducing Substances and Ketone Bodies in the Urine.—As soon as a urine is found to contain a reducing substance,

Rothera's test* for acetone and aceto-acetic acid should be performed. If it is strongly positive it should be followed by Gerhardt's ferric chloride test* for aceto-acetic acid. The Rothera reaction is much more sensitive than the ferric chloride reaction, and when the latter is positive the ketosis is more severe. Much care, however, must be taken in the interpretation of the ferric chloride test; patients who have been unwell have often taken salicylates or aspirin previously, and the distinction between the colour reaction given by salicylates in the urine and that given by aceto-acetic acid is by no means as clear-cut as many books suggest. The classical means of distinguishing the ferric chloride reaction due to salicylates from that due to aceto-acetic acid is that the latter reaction becomes negative after boiling the urine, but this is hardly ever necessary, because the patient himself will be able to say whether he has had aspirin or salicylates. A positive ferric chloride reaction due to aceto-acetic acid will be accompanied by an extremely intense Rothera reaction which will be negative if the reaction is due to salicylates.

Some difficulty might be expected if there is severe ketosis and the patient has had either of these drugs, but the presence of heavy glycosuria and ketone bodies in the urine, together with such evidence of pre-coma as recent vomiting, shortness of breath, abdominal pain, giddiness, and acetone in the breath, must be taken as an indication for immediate treatment with glucose and insulin. It may indeed be dangerous to wait for a blood-sugar determination unless facilities for this investigation are readily available. It is the opinion of those with special experience that patients in diabetic coma or pre-coma are best treated in centres with facilities for the control of this condition. All that is required, therefore, is that the patient should be given a dose of 40 units of insulin, together, if possible, with 50 g. of glucose by mouth, and then sent to hospital. In the absence of clinical signs of pre-coma a blood-sugar determination may also be dispensed with in reaching a diagnosis of diabetes if the history is typical and reducing substances and ketone bodies are present in the urine.

Reducing Substances Without Ketone Bodies in the Urine.—Matters may be very different when there are no ketone bodies in the urine. Even then the case with a classical clinical history of diabetes requires little in the way of further investigation, although it is wise never to treat a patient as a diabetic without at least one definitely abnormal blood sugar. For this reason it is unwise to institute treatment in those cases without ketosis before confirming the diagnosis. A blood sugar should be done one and a half to two hours after a full carbohydrate meal, when a figure greater than 180 mg. per 100 ml. is certainly indicative of true diabetes. However, as is shown below, the value of the single blood-sugar determination, although excellent when the blood sugar is definitely raised, is of less value when the concentration is only slightly above the upper limit of normal or when the relationship between the collection of the blood and the time and nature of the previous meal is uncertain.

On the other hand, if on clinical grounds the practitioner thinks that the diagnosis of diabetes mellitus is unlikely, a single determination of the blood sugar *may* help, but it is usually essential to carry out a glucose-tolerance test. It is always worth while looking for glycosuria in two samples—the early morning sample passed before breakfast and the

*See also the article in this series by Dr. H. E. Archer on "Urine Testing in the Surgery" (November 28, p. 1211).

sample taken one and a half hours after a full carbohydrate meal; glycosuria is most likely to be present and heaviest in this second sample. If in a patient not receiving insulin the amount of reducing substance in the urine is not greatly increased about one and a half hours after a carbohydrate meal, the reducing substance is unlikely to be glucose.

The identification of a reducing substance in urine is very seldom required. The value of the osazone test and of the yeast fermentation tests in distinguishing glycosuria has been over-emphasized. The osazone test is difficult to carry out, and even in the hands of the experts is not always as reliable as has hitherto been believed. Fermentation tests, too, are not always satisfactory, for many of the common varieties of yeast ferment sugars other than glucose. The recently developed paper chromatographic method of detecting and identifying reducing substances in the urine is by far the most satisfactory yet devised. With this technique it has recently been shown that in pregnancy lactosuria is twice as common as glycosuria, the former being found in as many as 50% of the antenatal patient attendances. All things considered, the identification of a reducing substance in urine should be undertaken by laboratories specializing in this kind of investigation.

A Single Determination of the Blood Sugar

In many cases of diabetes, even in those in which the clinical history is not entirely typical, the diagnosis may be definitely established by the determination of the blood sugar. The interpretation of the result obtained depends upon the knowledge of the effect of the previous meal upon the blood-sugar concentration. It is shown below that after 50 g. of glucose in the fasting condition the blood sugar normally rises from a fasting level of 80–100 mg. per 100 ml. to not more than 180 mg. per 100 ml. and returns to normal within two to two and a half hours of the beginning of the test. When instead of having 50 g. of pure glucose the food consists of an ordinary mixed meal the blood glucose will not rise quite so high but will take a longer time to return to normal. After a breakfast consisting of eggs and bacon and two or three slices of bread with butter and marmalade, the blood sugar may rise to 140 or 150 mg. per 100 ml. and yet take up to three hours to return to the fasting concentration, whereas after a typical tea of bread, butter, jam, and cake, conditions will approximate more closely to the events occurring in the glucose-tolerance test. It is clear, therefore, that with a typical clinical history a single blood-sugar determination, taken one and a half to two hours after a meal, giving a result above 150 mg. per 100 ml. will almost certainly establish the diagnosis. On the other hand, a blood sugar well below 150 mg. per 100 ml. is not diagnostic of diabetes, and further investigation is necessary by the glucose-tolerance test.

Glucose-Tolerance Test

This test is more often used to exclude the diagnosis of diabetes mellitus than to establish its presence, for it is necessary only in those mild cases free from all symptoms of diabetes in which a single determination of the blood sugar gives an equivocal result.

It is essential to give the patient a full carbohydrate diet for seven days before carrying out this test. If not, a mildly diabetic type of curve may be found in a normal person.

After a full carbohydrate regime the patient is fasted overnight, blood and urine specimens are collected and analysed quantitatively and qualitatively for sugar before and half, one, one and a half, two, and two and a half hours after 50 g. of glucose dissolved in 200 ml. of water. The urine specimens should also be examined qualitatively for ketone bodies. In the normal curve the fasting blood sugar is below 110 mg. per 100 ml.; there is a rise to less than 180 mg. per 100 ml., and a return to the fasting level within two to two and a half hours. A second type of curve which is found in normal persons is the so-called lag storage curve in which the half-hour blood analysis shows an abnormally high concentration of sugar (up to 250 mg. per 100 ml.), but

the specimens at one and a half and two hours have returned to the fasting level. Such a curve found in patients free from symptoms of diabetes is of no pathological significance and may account for the presence of sugar in the urine between half and one hour after a high carbohydrate meal, because of rapid absorption.

A normal curve is found in renal glycosuria, when sugar appears in the urine at times when the blood concentration is not abnormally high. Although renal glycosuria is usually of no pathological significance it should be borne in mind that the condition may be accompanied by other forms of renal tubular dysfunction causing amino-aciduria and, or alternatively, abnormal phosphorus excretion leading to persistent rickets. Such cases are rare, but the condition should be borne in mind when glycosuria without symptoms of diabetes is found in childhood. Indeed, all cases of glycosuria in childhood should be referred for diagnosis to a diabetic clinic.

The glucose-tolerance curve is abnormal and usually due to diabetes when the fasting blood sugar is above 110 mg. per 100 ml., the blood sugar rises to a level above 180 mg. per 100 ml. and fails to return to normal values within two to two and a half hours. However, abnormal curves may also be found in sepsis, carbohydrate starvation, hyperthyroidism, severe liver disease, Cushing's syndrome, and some cases of acromegaly, in all of which glycosuria may occur. Usually the non-diabetic causes of an abnormal glucose tolerance are obvious from the clinical findings and the abnormality is not very great.

Glycosuria and Hyperglycaemia in Known Diabetics

Glycosuria and hyperglycaemia must also be considered in relation to the known diabetic, possibly on insulin treatment, who is being controlled by the practitioner. The insulin requirements may be readily assessed by means of routine urine tests for glucose and ketone bodies, but occasional blood-sugar determinations are of value. The time at which the blood or urine should be collected depends upon the type and number of doses of insulin the patient is receiving. Sometimes an early morning specimen may be the best, sometimes the midday specimen, and in other circumstances both. It is not the purpose of this article to supplant the excellent manuals on the treatment of diabetes, but a few general principles may be useful.

While usually the presence of heavy glycosuria may be regarded as an indication for increasing insulin dosage, this is not always the case. The early morning specimen may contain sugar secreted into the bladder in the early part of the night after the evening meal. Clearly a urine test carried out on such a specimen will give no indication of the dangers of early morning hypoglycaemia. For this reason the bladder should be emptied immediately on waking and a further specimen of urine passed as soon as possible before breakfast. In this way the second specimen will be an indication of the fasting blood sugar; this specimen is the one most useful in controlling the dose of protamine-zinc insulin. Similarly it is better to test the second of two specimens passed before lunch or tea in cases on a morning dose of soluble insulin.

In cases on two doses of soluble insulin the morning specimen may be useless as a guide to dosage because the evening insulin may not act long enough to prevent morning glycosuria, but at the same time any increase in insulin dosage may produce hypoglycaemic attacks during the night.

Blood-sugar estimations make treatment easier but are not always essential. In diabetics with a normal threshold periods of hyperglycaemia will usually be accompanied by heavy glycosuria. Determination of the blood sugar in a diabetic patient receiving insulin treatment and not responding with clinical improvement may show that the patient still has a high blood sugar. On the whole, however, determinations of blood sugar in patients with known diabetes are of particular value in indicating hypoglycaemia and provide an indication for the reduction of the insulin dosage.

In any diabetic it is useful to know the renal threshold, because in patients with a low threshold insulin dosage cannot be adjusted by urine tests alone. Some reasonable control is possible if the insulin dosage is decreased when glycosuria disappears and increased when ketones appear in the urine. The threshold may be estimated by a series of analyses of sugar in the blood and urine. A convenient technique is as follows. Four hours after the morning injection of insulin the patient should empty his bladder. Ten minutes later the blood-sugar level should be determined, and as soon as possible after this, preferably within fifteen minutes, the bladder should be emptied again. No food must be taken from an hour before the first emptying of the bladder to completion of the test. The patient has a low renal threshold if more than slight traces of sugar appear in the second urine specimen and the blood-sugar level is below 160 mg. per 100 ml.

Collection and Preservation of Blood for Sugar Determination

Blood collected for analysis of its sugar content must be preserved with one drop of formalin or by the addition of potassium fluoride. It is best, however, to obtain prepared tubes from a local laboratory.

Most of the methods for determination of blood sugar are not entirely specific and the values are usually 15–25 mg. per 100 ml. higher than the true amounts. The figures for sugar concentration given in this article refer to capillary blood; it is important to remember that the content in venous blood is less than that in capillary blood. The difference is not great during fasting, but after a carbohydrate meal it may amount to as much as 20–70 mg. per 100 ml.

Next article on Clinical Pathology.—"Evidence of Gout," by Dr. Oswald Savage.

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CHANGES AND PROSPECTS IN MEDICINAL TREATMENT

SIR HENRY DALE'S HARBEN LECTURES

Sir Henry Dale, O.M., delivered the three Harben lectures, 1953, at the Royal Institute of Public Health and Hygiene on December 7, 8, and 9, taking as his subject, "Changes and Prospects in Medicinal Treatment." The chair was taken on the successive evenings by Sir Henry Tidy, Dr. J. Browning Alexander, and Sir Arthur MacNalty.

TREATMENT OF PRIMARY CAUSES, INFECTIONS, IMMUNOLOGY, AND CHEMOTHERAPY

In his first lecture Sir Henry Dale began a review of the remarkable changes which, during the past half-century, and largely in the recent quarter, have so transformed the whole aspect of medicinal treatment of disease that what was earlier recognized, by doctors and patients alike, as one of the more backward and ineffective aspects of medical activity had become one of the most successful and scientifically progressive. Medical men of his own generation hardly needed to be reminded of the days when "doctors' medicine" formed the target for a grim kind of humour. There was then a great disparity of aim and interest between the pharmacology of the laboratories and the therapeutic practice of the wards. What pharmacology had to say even about the action of the few unquestionably valuable drugs at that time had little reference to their therapeutic use. Paul Ehrlich complained of the pharmacologists of his time that if he asked them how quinine produced its effect they

would tell him how it acted on the frog's muscle or on the mouse's brain, when what he wanted to know was how it specifically attacked the malaria parasites, causing them to disappear from the blood of a sufferer from malaria. What he wanted to know was how certain doses would cure the patient, not how large doses would poison him.

The lecturer illustrated some of the conditions which prevented the development of therapeutics as a science at a period well within living memory. He said that he mentioned these bygone anomalies and frustrations only to serve as a background for a discussion of the predominant factors which had brought about an astonishing change, a veritable transformation of the whole therapeutic outlook, in recent years.

The stimulus came largely from what at the time appeared to be an essentially new idea in therapeutics, the idea that a medicine should be used to remove or prevent the cause of a disease or a failure of health, whereas the most that had been previously expected of any medication was the relief or mitigation of symptoms, except perhaps in obvious cases, such as the removal of intestinal worms, where the cause of a disease had been readily visible to the naked eye. Of course, the relief of symptoms might still be the most immediate need for the patient and the most urgent duty of the physician. Nobody would depreciate the value of digitalis because it was essentially a remedy for symptoms, not an agent for the eradication of the cause of them, or because pharmacology might not yet have completed its account of the way in which the active constituents of digitalis produced their effects.

The Fertile 'Nineties

It was, however, to the conception of radical treatment of the primary causes of disease as the initiating stimulus in this new development that he would, in the first instance, ask special attention. The decade beginning with 1890 had a special significance in this respect. During that decade there were also profound discoveries in physics—the discoveries of Röntgen, Becquerel, J. J. Thomson, and Rutherford. The first two years of that decade saw the advent of three new lines of medicinal treatment, all concerned with the eradication, removal, or prevention of the primary causes of disease. These were the discovery by Emil von Behring of the diphtheria and tetanus antitoxins, Paul Ehrlich's first (though not practically successful) trial of chemotherapy, and George Murray's first successful treatment of a deficiency disease, myxoedema, by administering thyroid gland in myxoedema. From these separate seeds, in due course, were to develop the luxuriant growths of a progressive therapeutics based on immunology, chemotherapy, and endocrinology, respectively.

It would be possible, of course, to trace the ultimate origin of all immunological treatment to the inoculation against smallpox, practised originally in the middle of the eighteenth century, and more particularly to Jenner's vaccination introduced as that century was drawing to its close. But the last decade of the nineteenth century was surely the great fertile period. Sir Henry Dale devoted the remainder of the first lecture to a discussion of the two different types of remedial agent which deal directly with diseases due to infections by actions which stop the growth of the infecting organisms and lead to their elimination. These were the natural immunological remedies and the artificial chemotherapeutic agents, including the antibiotics.

Immunological Remedies

From 1892 onwards inoculation with killed cultures of bacilli was undertaken for protection against cholera and later against plague. Afterwards came Almroth Wright's similar immunization against typhoid, effective in the first world war; and then the active inoculations against diphtheria and tetanus. Many years were likely to pass, however, before the antitoxins could be spared from the list of essential remedies; perhaps they never would be spared.

Further advances in the effectiveness of both methods of conferring immunity, active and passive, against bacterial infection seemed most likely to come from a deeper know-