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ALBUMINURIA AND GLYCOSURIA.

A POST-GRADUATE LECTURE DELIVERED AT WESTMINSTER
HOSPITAL, SEPTEMBER 18, 1928.

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THERE cannot be one practitioner who at some period or other of his career has not found reason to regret the omission to perform the elementary tests for albumin and sugar in the urine; and he is fortunate indeed if the omission occurs on a relatively unimportant occasion. This examination is in fact a fundamental precaution, whatever

the condition from which the patient is suffering or the complaint he advances; and although I make no pretence to advance any new information, and can only claim the attempt to provide a convenient summary, there is no need to apologize for the elementary character of my subject. This is logically considered under two heads: the identification of albumin or sugar in the urine; and secondly, the significance of their presence.

ALBUMINURIA means the passage into the urine of protein that is coagulable on boiling. The protein substances that may be encountered are serum proteins—serum albumin and globulin; compound proteins, nucleo-albumin and mucins; and proteolytic products—albumoses.

The familiar tests which have successfully withstood the attempted introduction of others, perhaps more delicate and less equivocal, are the application of heat and the addition of nitric acid, or, as they are popularly termed, the coagulation and the nitric acid tests. A urine with turbidity due to urates becomes clear on being heated; a cloudy precipitate which may subsequently form will be due to earthy phosphates or to coagulated albumin. The former is at once dissolved by a few drops of acetic acid, the latter becomes denser. It is well to add a few drops of acetic acid to the urine before boiling to ensure sufficient acidity. This precaution is in itself a test, as a precipitate which forms with acetic acid in the cold, as it is termed, is identified as nucleo-protein, which may be mistaken for albumin, but is of no pathological significance. A final precaution is to recognize an unusual phenomenon, a precipitate which appears at a comparatively low temperature and disappears on further heating. This is the Bence Jones albumose, which is an accompaniment of multiple myelomata, and is also found in some cases of leukæmia. It may be said that the average onset of coagulation of albumin is 75°C .; the Bence Jones body begins to precipitate out at 50°C ., at 58°C . it is well developed, at 70°C . clearing has already begun, and on boiling the liquid should again be nearly if not quite clear. It is a rare phenomenon, but it is peculiarly striking. I once identified it in a routine examination of a medical man, who believed himself to be in perfect health and in whom three months later symptoms first appeared.

The nitric acid test is, in my opinion, less convenient. An excess of urates may be precipitated, and so may nucleo-protein. There are also other fallacies, e.g., precipitation of copaiba resin, if the patient is taking this drug, and urea itself may be precipitated as the nitrate.

As regards genuine albuminuria, the percentage is usually below 1 and rarely exceeds

2. The actual loss to the body is therefore of little importance and is easily replaced. It is the significance which is of consequence. It may at once be said that the presence of albumin is not necessarily pathological, still less is it an indication of diseased kidneys. It is convenient to speak of pathological and non-pathological albuminuria; the latter may conveniently, if perhaps unscientifically, be called physiological.

Pathological albuminuria occurs in nephritis, in other diseases of the kidney, e.g., tuberculosis and new growth, in suppurative conditions of the lower urinary tract—cystitis, urethritis; in hæmorrhage from any part of the urinary tract; in damage to the renal epithelium by toxins, exogenous or autogenous; this category will naturally include a very large number of conditions, e.g., alcoholism, burns, diabetes, gout, lead, mercury and arsenic poisoning, syphilis, foetal products in pregnancy. Albuminuria occurs in many of the acute specific fevers, particularly scarlet, diphtheria, variola, erysipelas, also in pneumonia and typhoid, less so in influenza and measles. In certain nervous disorders, apoplexy and convulsions; in circulatory disturbances, whether due to heart or lung disease, or to pressure on or obstruction of the inferior vena cava; ascites, ovarian tumours or cysts may be mentioned in this category. It is clear that a variety of causes may be responsible for the albuminuria of pregnancy, pressure of the uterus on veins, excessive strain on the placental circulation, the direct action of foetal products on the kidneys, not to mention the possibility of contamination of the urine by small hæmorrhages or vaginal discharges.

It will be evident that the significance of albuminuria in any one of these numerous conditions will depend upon the recognition of a cause which is primarily responsible. In some instances a clinical examination suffices, in others a microscopical examination revealing the presence

of casts, blood-cells, pus, organisms, will indicate the line along which further investigation should extend. It is impossible to consider such a vast subject even superficially, nor for the present purpose is it necessary.

To turn now to the condition regarded as non-pathological albuminuria. Some idea of its uncertain ætiology is afforded by the extensive terminology attached to it—physiological, adolescent, intermittent, remittent, cyclical, postural, functional, alimentary, the albuminuria of exercise.

In many instances there is a high percentage of globulin or euglobulin, and precipitation by acetic acid in the cold may be produced. In some instances the albumin may be detected only at certain hours of the day, being usually absent during recumbency, to appear during the active hours of the day. It is associated therefore with the erect attitude and also with exercise. In some cases there is also a paroxysmal hæmoglobinuria. In some cases the albuminuria is induced by a cold bath or even a surface chill. All kinds of explanations are forthcoming. That posture has a distinct effect is indubitable, and it appears that lordosis of the spine is of consequence, as this exerts its influence when the subject is erect. The left renal vein is then compressed between the spine and the aorta, and it has been shown on occasion that such albuminuria may be derived from the left kidney only. Such a mechanical effect may be partly responsible for the albuminuria of pregnancy.

But even if posture and corresponding circulatory disturbance play a more or less indispensable part in the production of albuminuria, there must be an appropriate condition of the blood plasma. The subject usually displays many manifestations of vaso-motor instability, and the albuminuria may often be checked by the administration of calcium lactate. Certainly it may be checked by no other means short of perpetual recumbency, and the chief importance

is to recognize the innocence of the condition, and not to restrict the subject's activities or in any way to prejudice him. This circumstance acquires particular importance in relation to exercise. The albumin which so commonly results after exertion is now regarded as negligible. It is found to be invariable in oarsmen and in boys after any form of exercise; in my experience it is less common in adults who indulge in track athletics. As casts and blood are sometimes found with albumin, it is, perhaps, going too far to include these circumstances as functional only, but any nephritis which results would appear to be of the most trivial character. There appears to be no evidence that a so-called alimentary albuminuria ever occurs as a leakage when an excess of protein, e.g., eggs, has been taken.

GLYCOSURIA.

That glycosuria is not diabetes is nowadays an elementary truism. Our eminent predecessors, notwithstanding the lack of assistance from blood-sugar estimations, which are a comparatively recent introduction, realized the existence of several conditions in which glycosuria was a transitory and trivial phenomenon, and even of conditions in which sugar was excreted in comparatively large quantities, yet without the usual pathological accompaniments of diabetes mellitus. To the latter the term *diabetes innocens* was sometimes applied, a term which has now been replaced by "renal glycosuria," as removing any suggestion of a real diabetic condition and introducing a renal possibility, a consideration to which I shall shortly return.

Dextrose (or glucose) is the important carbohydrate excreted. Its identification as a substance which reduces Fehling's solution permits confusion with other reducing substances which may also be found in urine, some of which are carbohydrates, such as lactose, lævulose, maltose, and pentose. Lactose may be found in the urine of pregnant or puerperal women, lævulose and

maltose as rare metabolic disturbances, and pentose still more rare. Another substance which reduces Fehling's solution is glycuronic acid, which may result from the administration of large doses of chloral hydrate. In addition, an imperfectly performed test may result in reduction from the presence of uric, hippuric, homogentisic and salicylic acids, of creatin, creatinin, xanthin, and other bodies of this composition. So far as the identification of glucose is concerned, the result of fermentation with yeast will exclude lactose and pentose, a rare product which may occur after the ingestion of certain fruits rich in arabinose, cherries, plums, and pears, and also spontaneously as a metabolic freak, particularly in Jews. Fermentation will also exclude the large variety of non-carbohydrate substances above enumerated. If any doubt still remains as to whether glucose or some other sugar is present, subsidiary tests may be employed, rotation of the plane of polarized light, or production of appropriate osazone crystals. But this is really within the realm of the laboratory worker and not of the clinician. As a general reduction of Fehling's or Benedict's solution means glycosuria, it will be well to spend a few moments discussing the performance of these tests.

First of all, it should be remembered that glucose is present normally in urine in perhaps 0.01 per cent., that Fehling's test will detect 0.02 per cent., and Benedict's considerably less. The delicacy of the last-named is indeed an objection to its clinical application, although it is immune to fallacies. As a rule, a urine containing an appreciable quantity of sugar has a specific gravity above 1.025, but discovery of a lower specific gravity must not be interpreted as evidence that glycosuria is absent. It has been shown that 1 per cent. glucose may be present in a urine of specific gravity 1.007, and even 1.003. Another practical consideration is the advantage of employing a twenty-four hours' specimen for examination, since an isolated specimen may be free

from an abnormality present only at certain times of the day.

If Fehling's solution is used, the two solutions should be kept separately and mixed only at the time of testing, as the mixed solution tends to become self-reducing. At the time of performing the test, equal parts are mixed and boiled, an equal quantity of urine is separately boiled and added, and preferably a few drops at a time to gain some impression of the quantity of sugar present. Prolonged boiling with Fehling's solution of a urine containing uric acid or creatinin may lead to reduction which will not occur if the reagent and the urine are separately boiled and then mixed.

Benedict's solution requires exactness in use. Five c.c. of the reagent must be measured, and eight to ten drops of urine added. The mixture is boiled for two minutes. A green, yellow or red precipitate forms, according to the quantity of sugar present. An important advantage is that the other substances which reduce Fehling's solution give a negative result with Benedict's.

Fermentation by yeast has already been mentioned as a confirmatory test of the presence of sugar. It also affords a method of estimating the quantity. The rationale of the test is that owing to decomposition of the sugar the specific gravity falls; every degree of specific gravity lost represents one grain of sugar per ounce.

Now, admitting the existence of glycosuria, let us turn to the circumstances in which it occurs. In the majority of subjects sugar appears in the urine as soon as the blood-sugar exceeds about 0.17 per cent., and if an opportunity is afforded to estimate the percentage of sugar in the blood, the comparative importance of glycosuria becomes known. For, on the one hand, we may find in an established diabetic that the blood-sugar is substantially above 0.17 per cent., and yet sugar does not appear in the urine, so that a dangerous degree of hyperglycæmia may be overlooked because glycosuria is not present. On the other

hand, the opposite condition may be encountered when glycosuria occurs, although the blood-sugar never rises even to the normal maximum, 0.17 per cent. In this case some peculiar condition of the kidneys appears to be present, and the term leaky kidneys or renal glycosuria is employed. In the days which preceded blood-sugar examinations, such cases were regarded as diabetes and treated quite unnecessarily by restriction or deprivation of carbohydrate. Their innocence was identified clinically by astute observers, who expressed their opinion by employing the term diabetes innocens. It may be added that a combination of diabetes with renal glycosuria may occur but rarely.

The occurrence of glycosuria in cerebral tumours, epilepsy and nervous disturbances generally is very familiar. Such cases are the clinical representatives of glycosuria resulting from puncture of the floor of the fourth ventricle; the action is upon the sympathetic nervous system through the adrenals, and explains the temporary glycosuria which may result from excitement and other emotional disturbances.

Intermittent glycosuria is not infrequent in gouty subjects, and especially those addicted to alcoholic excess. It is sometimes (though not often) present in Graves' disease, presumably from antagonism of the thyroid and pancreas. For a similar reason glycosuria may occur in acromegaly.

The association with boils and sepsis is familiar. In children glycosuria sometimes occurs shortly after an attack of pertussis.

Apart from the question of blood-sugar estimations, glycosuria acquires special importance when associated with the presence of acetone, β -oxybutyric and diacetic acids in the urine, and particularly the last two, since acetone may occur in the urine in a large number of relatively innocent conditions. In diabetes the percentage of sugar bears no relation to the amount of diacetic acid excreted, but the presence of sugar encourages the test for β -oxybutyric acid

which, although it cannot in itself intrinsically produce coma, is an essential factor. It is not strictly true to say that one tests for β -oxybutyric acid, for direct identification of this acid is very difficult. But since it is always accompanied by diacetic acid, the test for the latter by the simple addition of ferric perchloride is sufficient. The only fallacy in this test is the close similarity afforded by a urine containing the decomposition products of salicylic acid, which will be present if one of the coal-tar products has been administered. The colour is rather different, but sufficiently like for confusion if the possibility is forgotten. Naturally, prolonged boiling in the case of diacetic acid, which is volatile, destroys the colour which persists in the other instance.

A POST-GRADUATE CLINICAL AND PATHOLOGICAL DEMONSTRATION.

Given at St. Mary's Hospital, October 7, 1928.

By ZACHARY COPE.

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LADIES AND GENTLEMEN,—I have endeavoured to bring together a series of cases and specimens as instructive as they are rare and interesting. All the patients before you have been operated upon, and some have only been asked to come in order that you may be assured of their present condition. From each case I hope we shall be able to draw one or more clinical lessons which may prove of value in future practice.

The first patient is a man aged 57, whom I first saw five years ago on account of a large hard swelling in the posterior part of the left frontal region of the skull. It was hard, painless and appeared one with the bony skull. It had been first noticed between ten and fifteen years previously, and epileptic fits had begun ten years before I saw him,