CLINICAL PATHOLOGY IN GENERAL PRACTICE

TESTS OF RENAL FUNCTION

BY

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Assessment of renal function begins with an appraisal of the patient's past and present history, particularly in respect of oliguria, polyuria, nocturia, haematuria, and oedema; continues with the physical examination and urine analysis; and ends with special tests designed to provide information from which the extent and severity of the renal damage can be judged and the prognosis made. It is perhaps unfortunate that the term "renal-function tests" has come to be restricted to certain biochemical investigations of renal activity, because in practice much can be learnt about renal function from simple clinical observation and urine analysis. For example, the development of oedema, which may be insufficient to cause pitting of the skin at the ankles or over the sacrum and yet enough to cause a sudden increase in body weight, indicates impairment of at least one aspect of renal function—the ability to eliminate excess sodium.

The function of the kidneys is to maintain the volume and the concentration of the various constituents of the body fluids within narrow limits. To achieve this constant *milieu intérieur* the kidneys regulate the urinary excretion of water, sodium, chloride, and potassium; eliminate from the body the waste products of metabolism, such as urea; and maintain the acid-base balance by disposing of the acid substances usually present in a normal diet. Because the kidneys have so many functions, no single biochemical investigation will test all aspects of renal activity. Many tests have been evolved, and in recent years great progress in the understanding of renal physiology in health and disease has been achieved by investigations, too complicated for ordinary use, which measure the volume of fluid filtered through the glomeruli per minute and the volume of blood flowing through the kidneys per minute.* In this article only three tests of renal function—the water-concentration test, the blood urea, and the urea clearance—will be discussed. These have been chosen because they are simple, easily carried out, and within the scope of any laboratory.

Indications

Tests of renal function may be helpful in answering any of the following questions. Is renal disease present in this patient who gives a history suggesting previous renal disease but in whom nothing or little abnormal is found on physical examination and urine analysis? What is the extent and severity of the renal damage in this patient who clearly has renal disease, and what is the prognosis? What measures can be taken in this patient with renal failure to ease the load on the kidneys? Only the first and second of these questions are considered, the last being a matter of therapeutics.

The value of renal-function tests as an adjunct to diagnosis is limited because the kidneys have considerable powers of reserve; although large amounts of renal tissue may be

destroyed or removed, the remainder will continue to serve the functions of the body satisfactorily provided an excessive strain is not imposed. Tests of renal function are designed to provide such a strain, but even then extensive bilateral damage must be present before the tests show any abnormality, and by this time there are often protein and casts in the urine to indicate kidney disease. Nevertheless positive evidence of renal damage in some patients with glomerulo-nephritis in a quiescent phase, prostatic hypertrophy, bilateral pyelonephritis with sterile urine, and polycystic disease of the kidneys may not be obtained until tests of renal function are applied. In cases of unilateral disease, such as calculi and tumours, intravenous pyelography is a more useful adjunct to diagnosis.

In assessing the extent and severity of renal damage, and in making the prognosis, tests of renal function are of value when there is bilateral involvement and when applied at a suitable time in the course of the disease. For example, there is little indication for renal-function tests in acute glomerulo-nephritis when the patient's general condition and the degree of oedema, hypertension, proteinuria, haematuria, and oliguria are all indicative of the severity of the renal damage at the time. But when the acute phase is passed tests of renal function may indicate the extent of the residual damage. In those unfortunate patients in whom the disease proceeds to the chronic form, renal-function tests repeated at intervals are helpful in judging the tempo of progression.

Water-concentration Test

This test has much to recommend it, because, apart from a urinometer costing about three shillings, no special apparatus is required, and the test can be carried out in a few seconds in the patient's home or in the surgery. Although a more sensitive index of renal damage than the urea-clearance test, the water-concentration test is a qualitative rather than a quantitative index of renal function, and does not measure the extent of renal damage or distinguish between moderate and severe degrees.

Physiological Basis.—The kidneys are made up of nephrons, each comprising a glomerulus, its tubule, and the accompanying blood supply. The glomerulus acts as a filter, and as blood flows through the glomerular capillaries fluid of the same composition as protein-free plasma enters the tubular lumen. As this filtrate passes down the tubule some 98 to 99% of the water and lesser amounts of the substances dissolved in it (so-called solutes such as sodium, chloride, and urea) are reabsorbed by the tubular epithelium and passed back into the blood stream. Because relatively more water than solutes is reabsorbed, the fluid contains at the end of the tubule more sodium, chloride, and urea per ml. of water than it did at the beginning. As the concentration of solutes increases, the osmotic pressure of the tubular fluid also increases, and this resists the further reabsorption of water. Thus to excrete a concentrated urine (and therefore a urine of high specific gravity) the tubular epithelium has to work against the osmotic pressure exerted by the tubular fluid. If the tubular cells are damaged the ability to reabsorb water will be impaired and the specific gravity achieved will be lower than normal.

Technique.—If a casual specimen of urine, free of protein and sugar, has a specific gravity of 1025 or more, renal function is probably normal, although, of course, renal

*The normal glomerular filtration rate is 100 to 120 ml. per minute; the normal renal blood flow is 1,000 to 1,300 ml. per minute.

disease may be present. If the casual specimen has a specific gravity of less than 1025, a water-concentration test should be carried out. The patient is asked to drink nothing after tea on the day before the test and to have a dry evening meal. The bladder is emptied on retiring and any urine passed during the night discarded. The following morning breakfast and all fluids are omitted, and the bladder is emptied at 8, 9, and 10 a.m. into separate jars. If the volume is too small to measure the specific gravity in the ordinary way, the volume of each specimen is measured and the urine diluted with one or two equal volumes of distilled water. The specific gravity is then measured and the last two figures of the observed value multiplied by two or three respectively to obtain the correct value for the undiluted urine.* Alternatively, a specially small urinometer is available for measuring the specific gravity of small volumes.

Interpretation.—If renal function is normal the specific gravity of at least one of the specimens voided at 8, 9, and 10 a.m. will be greater than 1025. In the elderly the concentrating power of the kidneys is somewhat reduced and a value of 1020 must be regarded as normal. A specific gravity of less than 1020 is evidence of renal damage; in severe cases it may become fixed at 1010 or 1012. A false result may sometimes be obtained if the patient has congestive cardiac failure, because excretion of oedema fluid during the night will simulate inability to concentrate. Failure to excrete urine with a specific gravity higher than 1003 to 1005 is found in diabetes insipidus.

Blood Urea

Physiological Basis.—Urea is formed from the breakdown of proteins, and the level in the blood is largely governed by the rate of excretion by the kidneys. The concentration in the glomerular filtrate is the same as that in the plasma, and as the fluid passes down the tubular lumen some of the urea diffuses back across the epithelial lining into the blood stream, but the amount excreted depends largely upon the amount of fluid filtered through the glomeruli. Hence the concentration in the blood is influenced by the glomerular filtration rate, which depends upon the number of functioning glomeruli and the pressure and volume of the blood flowing through them, and by the rate of urea formation in the body, which depends chiefly upon the protein intake.

Sample Required.—About 5 ml. of venous blood is collected in a clean tube containing a small pinch of potassium oxalate powder. If the specimen has to be sent to the laboratory by post a few drops of formalin should be added.

Interpretation.—Normally the blood-urea concentration varies from 20 to 40 mg. per 100 ml., but values up to 50 mg. cannot be regarded as abnormal in the elderly. Since the urea level is influenced both by diseases of the kidney and by conditions in which the kidneys are not primarily involved, the causes of urea retention are conveniently considered under two main headings—renal and extrarenal.

Renal Causes of Urea Retention

The degree of renal damage that must be present before there is urea retention depends to some extent upon the amount of protein in the diet. On an average intake adequate elimination of urea can be effected by as little as two-thirds of one kidney; therefore widespread bilateral kidney damage must be present before there is nitrogen retention of purely renal origin.

In acute glomerulo-nephritis the blood urea is often raised but rarely exceeds 100 mg. per 100 ml. In 90% of cases the symptoms and signs of the acute phase subside and the blood urea returns to normal, although in a small

proportion proteinuria may persist and chronic glomerulo-nephritis develop many years later. Some 5% of patients die in the acute attack with severe oliguria and a blood urea that climbs progressively to levels of 300 to 400 mg. per 100 ml. In another 5% the disease is a little more protracted: these patients proceed over a year to eighteen months to progressive renal failure with a blood urea that rises steadily until the time of death. In the early stages of nephrotic nephritis, characterized by gross oedema, a normal blood pressure, and heavy proteinuria, the blood urea is normal, but if the condition progresses urea retention due to renal failure occurs in the later stages.

During the early phases of chronic glomerulo-nephritis there is no rise in the blood urea. The daily urine volume is normal and renal disease may be revealed only by proteinuria, casts, a raised blood pressure, or a poor water-concentration test. As the disease progresses more glomeruli become damaged. The glomerular filtration rate is decreased and less urea is filtered into the tubules. The blood-urea concentration therefore rises, but this automatically results in more urea being filtered, and despite the diminished glomerular filtration rate the same amount of urea is eliminated but at the price of a higher level in the blood. Thus a balance is struck, and a blood urea which rises from 30 to 100 mg. per 100 ml. and remains stationary at this abnormally high level is compatible with many years of happy and useful life, especially if the patient's blood pressure is normal. As the disease progresses more glomeruli are involved and the blood urea rises higher. The tempo with which the disease advances varies from patient to patient but is usually more rapid in those with hypertension. Estimations of the blood-urea concentration repeated at monthly or bimonthly intervals are helpful in deciding the speed of progression, and a urea level which rises in a month from 60 to 100 mg. and then to 120 mg. a month later usually indicates a worse prognosis than a level which remains stationary at 100 mg. per 100 ml.

The blood-urea level often remains within normal limits during the entire course of essential hypertension but may be raised during episodes of cardiac failure and in the malignant phase of the disease. A raised blood-urea level may occur in chronic infective, neoplastic, or polycystic renal disease and indicates bilateral involvement unless there are additional extrarenal causes of urea retention.

Extrarenal Causes of Urea Retention

Any condition which reduces the volume or pressure of the blood flowing through the glomeruli may cause a rise in the blood-urea level, and this occurs in dehydration and shock due to severe and protracted vomiting, profuse diarrhoea, haemorrhage (particularly bleeding from a peptic ulcer), uncontrolled diabetes, and circulatory failure. In these pre-renal conditions which cause urea retention the raised blood level indicates a disturbance of renal circulation rather than intrinsic renal disease, and, provided the underlying cause can be corrected promptly, does not in itself signify a bad prognosis.

Any condition which obstructs the outflow of urine will cause back pressure on the kidneys and reduce the glomerular filtration rate. These post-renal causes of urea retention include prostatic hypertrophy, bilateral calculi, and carcinoma of the bladder. If the urinary obstruction can be relieved the blood urea returns rapidly to normal unless permanent renal damage has occurred.

Urea-clearance Test

Physiological Basis.—The urea-clearance test is a measure of the renal efficiency in removing urea from the blood stream and excreting it into the urine: it is largely determined by the glomerular filtration rate. Normally the concentration of urea in the blood is about 20 mg. per 100 ml. and the amount excreted in the urine is about 20 mg. per minute. This quantity of urea would be provided if in one minute 100 ml. of blood passed through the kidneys

*If the urine contains enough glucose to give a yellow or orange precipitate with Benedict's solution, or enough protein to produce a thick precipitate on testing with sulphosalicylic acid, abnormally high specific gravities will result. With laboratory help a correction can be made by estimating the exact amount of sugar and/or protein present.

and each millilitre was completely cleared of its urea content. But the blood flowing through the kidneys is not completely cleared of urea and the blood-urea concentration in the renal veins is only slightly less than that in the renal arteries. Thus a clearance of 100 does not mean that 100 ml. of blood has passed through the kidneys and was completely cleared of urea, but that the amount of urea excreted in the urine in one minute is equal to the amount found in 100 ml. of blood. Efficient kidneys will "clear" a larger volume of blood per minute than diseased kidneys.

The rate of urea excretion is influenced by the urine volume. As the glomerular filtrate passes down the tubular lumen some of the urea diffuses back into the blood stream. When the rate of urine flow is slow, relatively more urea diffuses back than when the urine flow is fast. Allowances must be made for different rates of urine flow if the results of urea clearance are to be compared in different patients and in the same patient at different times. It has been found that when the urine output exceeds 2 ml. per minute the clearance of urea is maximal, and even if the urine output rises there is no further increase in the clearance of urea.*

Procedure.—The patient should eat an ordinary breakfast, and, although not essential, should remain in bed during the test. At about 9.30 a.m. he drinks a tumblerful of water: this ensures a high urine output and therefore maximal clearance, and also reduces the significance of any errors in measuring the amount of urine passed. The test begins at 10 a.m., when the patient empties his bladder and discards the urine. The bladder is emptied again at 11 a.m. and the urine saved. A sample of blood is taken about this time for estimation of the blood-urea level. At noon the bladder is emptied again and the urine saved. Urine need not be passed at intervals of exactly 60 minutes: provided the exact time is noted at which each specimen is voided the urinary output can be calculated in millilitres per minute. The volumes of the specimens passed at 11 a.m. and noon are measured, and a small amount (about 5 ml.) of each, together with the blood sample and a note of the urine volumes and exact times of voiding, are sent to the laboratory for determination of their urea content.

Interpretation.—The results are expressed as a percentage of the average clearance in normal subjects. Values of 75 to 100% or more are found in healthy children and adults, but may fall to 60% in the elderly. Values of 40 to 60% suggest mild impairment, 20 to 40% moderate impairment, and below 20% severe impairment of renal function. Diminished urea clearance is chiefly due to a decreased glomerular filtration rate, which may be caused by glomerular changes as well as extrarenal factors reducing the volume and pressure of blood flowing through the kidneys. When interpreting the results the relative importance of renal and extrarenal factors must be evaluated. In acute glomerulo-nephritis urea clearance is diminished but it is not until four to six months after the acute symptoms and signs have subsided that the urea clearance gives an indication of the extent of the residual renal damage. If after this interval the clearance is subnormal and shows no further improvement with time the outlook is poor, but the rate of progress of the disease is very variable from patient to patient. During the early stages of chronic glomerulo-nephritis urea clearance is often within normal limits, although the water-concentration test may be abnormal. Later, although the blood urea level may be within normal limits, urea clearance may be mildly impaired (50 to 60% of normal). With further deterioration the urea clearance is more reduced and associated with a raised blood-urea level, which in itself indicates diminished clearance. A temporary reduction of urea clearance may be due to superimposed hypertensive heart failure or salt

deficiency, and thus the test should be repeated at intervals. In essential hypertension urea clearance is often normal for months or years, and then gradually decreases. In the malignant phase it is diminished at an early age.

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WELLCOME RESEARCH LIBRARY OPENED ROYAL SOCIETY OF MEDICINE EXTENSION

In the presence of a representative company of 300 people Lord Woolton on December 4 opened the extension of the library of the Royal Society of Medicine which is to be known as the Wellcome Research Library. An account of the library and of the events that led up to this enterprise appeared in the last issue (p. 1264). Lord Woolton deputized for Lord Salisbury, who was prevented by indisposition from performing the ceremony. The president of the Society (Sir Francis Walshe) was supported by Lord Webb-Johnson and by Sir Henry Dale (chairman of the Wellcome trustees). Those present included the chairman of the Wellcome Foundation (Mr. M. W. Perrin) and representatives of the Ministry of Health, the University of London, the Medical Research Council, the British Council, and the various medical societies.

Sir Francis Walshe thanked the Wellcome trustees most warmly for their generous gift of £125,000 which had made this venture possible, and spoke with gratitude also of the services of Sir Henry Dale, former president of the Society, whose interest in it had been long-standing and most practical.

Sir Henry Dale said that the Wimpole Street building was originally intended to have four stories, but financial stringency at the time of its construction, in 1911, caused those concerned to adopt a cautious policy and to build only three stories, with a flat roof and a strong enough foundation to support a fourth should this be necessary. After the second world war, with the influx of new Fellows and the great demand on the Society's facilities, there was a new urgency to the situation, and the Wellcome trustees were approached for help in the project for the fourth-floor extension. The trustees decided to offer £80,000 to the Royal Society of Medicine. The offer was accepted with gratitude, and a building committee was appointed. The work had been carried out at a time of steeply rising costs, and the Wellcome trustees finally increased their total benefaction to £125,000.

Lord Woolton said that he had several reasons for pleasure in performing the opening ceremony. One was his friendship for Lord Webb-Johnson; another his gratitude for the help he received from his medical advisers at the time he was Minister of Food; and a third and more personal reason was connected with his recent illness. "I owe so much to your profession. I owe to it the fact that I am here at all."

He had been told that the library contained a quarter of a million books. To house these was a gigantic task. The importance of the service of this library to medicine and medical research could not be exaggerated. He was told that it was the greatest medical library in Europe. It would remain the very proud possession of the present and succeeding generations of Fellows. In opening these beautiful rooms he congratulated the Society upon their possession, and the

*When the urine output is less than 2 ml. per minute the clearance diminishes in proportion to the square root of the urine flow. This is called the standard clearance in contrast to the maximum clearance.