THE CLINICAL AND COMPARATIVE VALUE OF RENAL FUNCTION TESTS

R. H. McDonald, M.D.

Renal function has to do in general terms with the preservation and maintenance of an optimum environment for body cells. In the unicellular organism where the entire body is in contact with its environment, the process of excretion is a simple matter of diffusion, but in multicellular body masses it becomes necessary that certain specialized cells excrete the waste products of metabolism, excessive water, and salts in order that the chemical composition of the body fluid and cells may remain constant. Specifically, the kidney excretes the waste products of nitrogen metabolism and the excessive inorganic salts, exercising, however, a certain amount of selective action in regard to those salts necessary for the animal economy and excreting others which have no threshold *in toto*. Therefore, these functions are of prime importance in maintaining the viscosity or tonicity of the blood and body fluids and are directly concerned in the maintenance of the hydrogen ion concentration of the body within the narrow limits of fluctuation consistent with health. The kidney undoubtedly acts in accordance with nervous and probably hormonal influences and is profoundly affected by disturbances of endogenous metabolism in other portions of the body. Metabolic disturbances incident to general infections of the body and surgical operations increase the renal load and may be factors which cause insufficiency. Thus some method which will be an index of renal reserve is highly desirable.

It is hardly conceivable that any single ideal test for renal function, especially in the diseased kidney, can ever be attained. It cannot at present be assumed that all the many partial functions of the kidney are equally depressed in a given renal lesion. In fact, there is abundant clinical evidence to show that in one renal lesion the difficulty consists in excretion of the nitrogenous metabolites, whereas in another the difficulty seems to be in regard to the inorganic salts and water. In the past twenty-five years numerous tests have been proposed, each of which has been based on some phase of renal physiologic activity, and many are of definite value if their limited significance is appreciated. It must be recognized that our knowledge of both the pathologic and physiologic processes in the kidney is inadequate. Prognosis must be based on the summing up of a large number of variables of which the functional efficiency of the kidney at any given time is only one. The course of the disease process in nephritis cannot be predicted accurately from a knowledge of the renal efficiency at any one time or even from a knowledge of the rate at which this efficiency is changing over a given period. Furthermore, individual patients differ in the way they withstand a given

degree of renal impairment. The constitutional variables which cause such differences are not within the scope of any renal function test, but can only be gauged in the light of clinical opinion and any other related data. It must be remembered, therefore, that the results obtained from any test are not to be regarded as absolute measures of renal efficiency but rather as relative or comparative values.

Stieglitz and Knight[1] suggest certain criteria by which the value of a renal function test should be judged.

(1) It should be so simple that it requires a minimum of time, both for the patient and the doctor, as well as a minimum of equipment, chemical analysis, etc.

(2) It is a prime consideration that it should cause no harm.

(3) It should, as far as possible, be a specific test of the structures or functions which are to be studied. This admittedly is difficult in view of the inadequacy of our knowledge and difference of opinion as to which portions of the renal unit excrete different substances.

(4) In order to measure accurately the renal ability, the kidney should be placed under stress. It is well known that the total number of functional glomeruli is considerably less in a resting condition than the maximum number which can be called into play. In this respect the renal tissues act in exactly the same way as other tissues.

(5) The test should yield uniform results in normal subjects. No absolute unanimity of results is, of course, to be expected because of the variability of the factors concerned, but it should be possible to establish results within certain limits in normal individuals, deviations from which can safely be regarded as being abnormal.

Despite the difficulties involved in a complex biological problem of this type, a number of tests of renal function have been devised which successfully meet the criteria cited above for the study, prognosis, and treatment of renal lesions. These fall naturally into three general classifications as suggested by Freyberg.[2]

1. Those which test the ability of the kidney to concentrate or dilute the urine.

2. Those which test the ability of the kidney to excrete introduced foreign substances.

3. Those which test the ability of the kidney to excrete normal metabolic wastes.

Concentration and Dilution Tests

It has been recognized for a considerable period that one of the initial evidences of decreasing renal efficiency is to be found in the inability of the kidney to secrete urine of high concentration or conversely of high dilution. The application of this knowledge to the study of

renal function appears to have been made first, by Volhard[3] in 1908. In the test he devised, the renal function is estimated from its ability to excrete urine of large volume and low specific gravity after one and one-half liters of water are drunk and to execrete urine of high specific gravity after a subsequent period in which no fluid is drunk. The test was somewhat modified by Lundsgaard[4] in 1920, and in 1927 Rosenberg[5] added certain precautions to make certain that the body was in a normal and steady state of hydration. For two days before using the concentration or dilution tests which were done on different days, the subject had a controlled diet without unusual variations in salt and with 1500 cc. of water. The weight of the subject was taken during the days before and after the test in order to detect instability of the water balance due to the invalidating factors of extrarenal influences of endocrine, nervous, or metabolic origin.

In this country Mosenthal[6] in 1915 introduced the test which bears his name and which is dependent upon the same general principles. Restriction of diet was found to be unnecessary and the patient is allowed to follow his own desires concerning the intake of foods and fluids. The test depends upon the fact that, with an ordinary fluid intake even at a constant rate per hour, the hourly volume and specific gravity of urine vary markedly during the day in normal subjects and that the extent of the variation diminishes in the presence of nephritis. The urine is collected in 2-hour periods from 8 o'clock in the morning until 8 o'clock at night and in a 12-hour period from 8 at night until 8 the next morning. The specific gravities of the 2-hour specimens and the volume of the 12-hour night specimen are measured. The normal values given by Mosenthal[7] in 1932 are a specific gravity of 1.020 or above in one or more of the 2-hour specimens, a specific gravity difference of not less than 0.009 between the highest and lowest specimens and a volume less than 725 cc. for the 12-hour night urine.

The dilution portion of the test was discarded by Addis and Shevky[8] in their concentration tests in 1922. It had been shown that the dilution test gave less constant findings, was less sensitive, and added no information which was not supplied by the concentration test. The concentration test of Addis and Shevky is performed by having the subject abstain from fluids of all sorts from after breakfast, 8 a. m., until after arising the following morning, 24 hours later. During the last 12 hours of the dry period from 8 at night to 8 in the morning, the urine is collected and the specific gravity of this specimen is measured. No preparatory period or special diet is suggested. Addis and Shevky have found that, in normal individuals who previously have followed an ordinary diet, the average specific gravity of the urine obtained as described above was 1.032, that 95 per cent of tests on normal subjects on ordinary diets showed values of 1.028 or above and 100 per cent were above 1.026.

In making the original concentration tests which Lashmet and Newburgh[9] devised in 1930, the subject remains in bed four days and during the first three a special diet is given consisting of 45 grams of protein, 106 grams of fat, and 180 grams of carbohydrate. The sodium chloride intake is from two to three grams daily and the fluid intake 1500 cc. At 6 p. m. after the patient has had supper on the third day, all intake, both fluid and food, is stopped until noon the following day; all urine is discarded except the specimen obtained from 10 o'clock until noon on the fourth day. The specific gravity of this 2-hour specimen is determined. Lashmet and Newburgh found that all normal subjects concentrated the urine to 1.026 or above on this regimen. In 1932 Lashmet and Newburgh[10] altered their test, omitting the three day preparatory period but the period of desiccation was increased to 24 hours (Table 1).

TABLE 1

LASHMET AND NEWBURGH CONCENTRATION TEST, 1932

All foods and fluids except special dry diet are discontinued for 38-hour period beginning at 10 p. m.

Urine collected from 8 a. m. next morning (second day) to 8 a. m. following morning (third day).

This is specimen 1.

Urine collected from 8 a. m. to 10 a. m. (third day).

This is specimen 2.

Urine collected from 10 a. m. to 12 noon (third day).

This is specimen 3.

Diet is 40 gms. protein Total calories 1900
104 gms. fat 1 gm. sodium chloride added
204 gms. carbohydrate
Total water available, 700 cc. in 24 hours.

Normal subjects concentrate urine to specific gravity 1.029—1.032.

In all these concentration tests, the specific gravity of the specimen must be determined accurately. Any significant amount of protein in the urine will, of course, increase the specific gravity. It has been found that for each per cent of protein in the urine the specific gravity is increased by 0.003. All the concentration tests are based on the ability of the kidneys to excrete urine of high specific gravity and it has been shown that this is a sensitive index of early renal damage. It was pointed out by Koranyi[11] as early as 1899 that the kidney does thermodynamic work in concentrating urea and other solids in the urine to many times their concentration in the blood. The amount of urea contained in 50 liters of blood, for example, is likely to be concentrated into one liter of urine. It takes about as much calculated work to do this as to compress six liters of gas at atmospheric pressure into one liter at six atmospheres. A damaged kidney cannot accomplish this concentration.

Excretion of Introduced Substances

The chief representative of the second group cited above is the phenolsulphonphthalein test which was introduced by Rowntree and Geraghty[12] in 1911. It was pointed out by Rowntree that the evidence of decreasing renal function was a flattening of the excretory curve and it has been demonstrated by several workers that the total 2-hour excretion is a poor index of renal ability since even a damaged kidney may excrete from 50 to 60 per cent of the dye in the 2-hour period. However, the use of the fractional phenolsulphonphthalein test has, to a large extent, improved the efficiency of the test. The technique is shown in Table 2.

Table 2

Fractional Phenolsulphonphthalein Test

Patient drinks 600 cc. water and empties bladder 30 minutes before test is commenced.

6 mg. (1 cc.) of sodium salt of phenolsulphonphthalein is injected intravenously.

Specimens of urine collected at 15 minutes, 30 minutes, 45 minutes, 60 minutes, and 120 minutes.

Estimation of dye content with Duboscq colorimeter using freshly prepared standards with phenolsulphonphthalein.

Normals, (Chapman and Halsted[13])

2 hour totals varied from 63—84 per cent
15 minute excretion 28—52 per cent
30 minute excretion 12—24 per cent

Excretion of Normal Metabolic Wastes

The third group of renal function tests are those which are based on the excretion by the kidney of normal metabolic waste. It has been shown repeatedly that the absolute level of the urea, uric acid, creatinine, and other nitrogenous metabolites, or of the inorganic salts of the blood is of no value in determining the extent of renal damage, since increased concentration of these substances in the blood does not occur until approximately five-sixths of the renal units have been rendered functionless. Thus normal blood urea is a common finding during the greater part of the course of any renal lesion, even in the face of overwhelming clinical evidence and urinary signs of severe renal damage. In the acute phase of hemorrhagic Bright's disease, uremia may be noted due to the temporary disturbance of a large proportion of the kidney. With recovery from the acute phase, these excessive nitrogenous wastes are reduced to a normal level and continue at this level unless further acute phases occur. This continues until progressive degeneration reduces the number of renal units to a number below that absolutely necessary for excretory function, and the stage of renal insufficiency or terminal Bright's disease is reached. This may cover a period of many years. Further-

more, increased nitrogenous metabolites of the blood may be distinctly increased in conditions entirely apart from renal disease and in the presence of normal kidneys. In severe dehydration, the level of the blood urea may be considerably increased, due to a concentration of the blood. In obstructions of the upper intestinal tract, the level of the nonprotein nitrogen of the blood may be increased rapidly to uremic levels. In this instance, beside the factor of dehydration, there is also in all probability a factor of increased production of nonprotein metabolites due to an increased endogenous catabolism, perhaps related to the production of toxins from the gastro-intestinal tract. In both these cases, the condition subsides quickly provided the etiological factors can be corrected. In severe grades of urinary obstruction it is also very common to see high blood urea readings without uremic manifestations, but this subsides within a few days when the obstruction is relieved. These blood chemistry readings are, therefore, of little value in themselves as far as the degree of renal function is concerned, although they are indicative of severe renal damage if nonrenal sources can be eliminated.

However, it has been possible by a simultaneous study of the concentration of nitrogenous metabolites in the blood and in the urine to develop tests which have been exceedingly important and useful in determining renal function. It has been found that the excretion in the urine of several substances of widely different chemical nature have one property in common; that is, for each of them the rate of excretion in the urine is, under proper conditions, directly proportional to the concentration of the blood. From this it follows that the ratio of excretion rate to blood concentration is a figure independent of the actual concentration in the blood over a wide range. It is this figure which is believed to indicate the excretory efficiency of the kidney toward the subject under consideration. By clearance, therefore, is meant the rate of excretion of a substance, expressed in milligrams per unit of time divided by the average concentration of the substance in the blood plasma during that time, expressed as milligrams per cubic centimeter. The clearance figure represents that volume of blood which would contain an amount of the substance under consideration equal to the quantity excreted in unit time in the kidneys. It is assumed, merely for convenience, that the blood flowing through the kidney is completely freed or cleared of this substance before leaving by the renal vein, although actually, it has been shown that only a small percentage (10.5 per cent—Van Slyke) of the blood content of the substance is actually eliminated during its renal circulation.

The most important of these clearance tests is the urea clearance of Van Slyke[14] although the same principles may be applied in regard to uric acid and creatinine and also to the inorganic salts. The technical

difficulties of estimating these latter substances have made the use of urea by far the most common test substance.

Historically the conception of the urea clearance test goes back to observations made by Bright in 1826 when he noted markedly increased plasma nonprotein nitrogen concentration with reduced urinary concentration in patients with severe renal disease. The conception of the simultaneous studies of the blood and the urinary concentrations of these excretory products has been advanced by many investigators during the intervening period, particularly by Ambard in France and by Addis and Van Slyke in this country. Addis[8] believed the urea excretion ratio to be independent of the volume of the urine, and he recommended its determination, that is, the urea in a one-hour specimen of urine over the urea in 100 cc. of blood, as an index of renal function. Van Slyke has shown that this ratio is valuable where the urinary flow is 2 cc. or more per minute but that with a lower flow of urine, the excretion rates vary more nearly in proportion to the square root of the urinary volume. The idea that the urinary urea excretion is directly proportional to the blood urea content when the urinary output is above 2 cc. per minute has been confirmed by several observers. Below this level which has been fixed as the augmentation limit, the urea excretion rate falls, not in direct proportion to the decrease in volume but, on the average, in proportion to the square root of the volume. Thus two formulas are necessary, one for urinary volume over 2 cc. per minute, the so-called maximum clearance, and the other for lesser urinary volume, the standard clearance. The technic of this test is outlined in Table 3.

Invalidating Factors

A number of factors may invalidate the results of concentration tests. It has been shown by Addis and Shevky[8] that extrarenal influences of endocrine, nervous, or metabolic origin could increase the water output or decrease the solid output during the period of test and thus produce a lowering of specific gravity simulating that caused by renal deficiency. An unusually low nitrogen or salt content of the diet might similarly influence the results. Unusual desiccation or conversely water flooding of the subject during the days preceding the test, storage or excretion of edema fluid in subjects of the nephrotic type during the test, and cardiac decompensation might seriously disturb the results without necessarily indicating renal damage. Mosenthal[15] states that a low fixed specific gravity may be found in many widely varying conditions—marked anemia, elimination of edema, pyelitis, polycystic kidney, prostatic hypertrophy, urethral stricture, cord bladder, and diabetes insipidus. Despite the possible interference of such invalidating factors, however, it has been a matter of experience that when signs

of renal lesions exist or have existed, consistently low results in concentration tests afford presumptive evidence that renal damage exists—in some cases, even in the presence of normal urea clearance tests.

TABLE 3

Bladder emptied. Catheterization if there is doubt regarding complete emptying of bladder.

Specimen of urine collected at end of first hour.

Specimen of blood collected at end of first hour.

Specimen of urine collected at end of second hour.

Specimens of blood and urine analyzed for urea content.

Maximum clearance

$$Cm = \frac{U \times V}{B}$$

Standard clearance

$$Cs = \frac{U}{B} \times \sqrt{V}$$

U = Urinary urea in mg. per 100 cc.

B = Blood urea in mg. per 100 cc.

V = Urinary volume in cc. per minute.

Final result expressed in percentages of normal on basis of average of 75 cc. per minute for maximum and 54 cc. per minute for standard.

Normal result, 80 — 120 per cent.

In regard to the blood urea clearance test, the most important single factor which may tend to falsify results is a failure to obtain all the urine formed by the kidneys during the period of the test. Prostatic obstruction, diverticula of the bladder, cystocele, and incontinence usually account for these failures which may be prevented largely by the use of the catheter. Where there is a constant amount of residual urine in the bladder, the clearance test is only slightly falsified because the urea excretion is compared with the concentration of the urea in the blood which varies but little during short periods of time.

The formulas used in calculating urea clearance contain a factor that corrects for variations in urea excretion at different rates of formation of urine. However, when the urinary flow is very small, the urea clearance calculated as usual fails to indicate correctly the renal efficiency. Thus it has been shown that with a urinary volume of 20 cc. or less, the urea clearance test gives a decidedly low reading whereas in the same individual with adequate urinary output, normal values may be obtained. This difficulty may be obviated readily by administering a sufficient amount of fluid before the test begins.

In the phenosulphonphthalein test, the most obvious cause of error in results is to be found in the numerous opportunities for error in technic. These include the question of exact quantitative injection, accurate timing, and failure to collect all the urine excreted in the given period. Residual urine in this case will result in an error of much greater magnitude than in the urea clearance test because the quantitative recovery of a substance not normally present in the blood and urine is required. Catheterization again will lessen this source of error. In the measurement of renal function during pregnancy, the phenolsulphonphthalein test usually is found to give a decidedly low reading. This has been explained on the basis of several factors: (1) the additional fetal circulation; (2) an altered blood flow through the kidneys due to the tumor of pregnancy, and (3) the hydronephrosis known to exist commonly during pregnancy. In cases of severe hepatic damage, the excretion of the dye through the biliary tract is diminished and that portion of the dye which is excreted in this fashion is thus held in the blood stream. The result is that a higher percentage of the dye is excreted by the kidney and consequently a higher functional result is secured for the phenolsulphonphthalein test than normally would be the case.

With regard to the application of these tests to urological problems, it is at once apparent that another element is added here—the element of urinary obstruction which may accompany parenchymatous renal disease or if prolonged may produce it. If the factor of urinary obstruction can be removed, the renal function tests are at once applicable for the appraisal of the renal efficiency. It is frequently seen that a low clearance value, for instance in an individual with prostatic hypertrophy, is increased considerably by vesical drainage, although the values are usually still well below normal, due perhaps to both pressure over a period of time as well as to the possibilities of renal damage of other origin. In pure urinary obstruction, many of the usual signs of renal insufficiency of parenchymatous origin are missing, for example, hypertension. There are no retinal changes, there is little difficulty with excretion of water, and edema is rarely encountered. Blood urea values of over 200 mg. per 100 cubic centimeters are common without uremic manifestations and subside quickly on relief of obstruction. Estimation of the function of the two kidneys separately may frequently be necessary in unilateral renal lesions. Concentration and clearance tests are not readily applicable and since quantitative ureteral collection of urine is inaccurate, the divided phenolsulphonphthalein is open to question although still used. Urea concentration of individual specimens may be an index of function. The appearance, time, and intensity of color from injected indigocarmine is widely employed either by use of ureteral catheters or by visual inspection through the cystoscope.

More recently, the use of serial roentgenograms in intravenous urography at five minutes, fifteen minutes, and one-half hour have been used as an index of separate renal function.

In summary, therefore, it appears that the concentration tests done after an adequate preliminary regimen and with correction when necessary for the effect of protein on the specific gravity constitute the most sensitive tests for qualitative detection of damaged renal function. It has been shown that this finding may occur before any reduction is noted by the urea clearance or phenolsulphonphthalein test in patients who have obvious renal damage, as evidenced by urinary signs. Such a condition exists in mild acute nephritis, in nephrosis, and very frequently in the early stages of arteriosclerotic Bright's disease. The concentration test possesses the great virtue of simplicity without quantitative collection of urine and without the necessity for any quantitative chemical analyses. It also most satisfactorily meets the requirement of putting the organ in question under functional strain. It has been suggested that this test measures fairly accurately the tubular ability inasmuch as theoretically at least the tubules are concerned with the absorption of water from the glomerular filtrate, thus concentrating the urine. This point cannot, at the present stage of our knowledge, be accepted as absolutely proved. It may be pointed out that when a concentration test yields urine of more than 1.026 specific gravity, one may assume as a general rule that the renal function is normal and other tests are unnecessary. When the patient is recovering from acute nephritis, persistent low gravities may continue to show some evidence of residual renal abnormality for weeks or months after the urea clearance test has returned to normal. As an aid in determining when recovery is complete, therefore, the concentration test is significant.

For measuring the degree of renal damage, however, concentration tests do not appear to be entirely suitable. Although the extent of fall in urine concentration shows some statistical correlation to the urea clearance and to the severity of renal disease, the disagreement in given cases may be extreme. A patient who has practically recovered from an acute nephritis and regained a normal urea clearance may, by concentration tests, continue to yield urine of low specific gravity for some time just the same as a patient in terminal uremia with a very small proportion of normal clearance. In cases of chronic nephritis sufficiently advanced to show urea clearances of 20 to 30 per cent of normal, concentration tests may already show minimal specific gravity of the urine and then will reveal no further changes during the subsequent progress of the disease while the clearance continues to fall until it reaches the uremic level of 3 to 5 per cent. The urea clearance test appears to mirror more accurately the progress of the renal lesion and offers the best method at present for following the patient's progress. It

is unfortunately more cumbersome and requires the chemical analysis of the blood as well as the urine. It is thus not generally suitable for use in the private office but ought to be available in any hospital where surgery is performed. Against it also has been brought the argument that it does not place the kidney under conditions of stress.

The two-hour phenolsulphonphthalein excretion test is not a sensitive test for renal efficiency. The fractional method as advocated by Young[16] has certainly increased the accuracy of the test, and the 15-minute dye excretion appears to be a sensitive index of renal function. The technical difficulties render it somewhat less reliable. It would appear safe to conclude that when the 15-minute specimen contains 28 per cent or more of the injected dye, the renal function is adequate. With low excretion of the dye, interpretation is somewhat hazardous.

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