THE VALUE OF THE UREA CLEARANCE TEST

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Renal function has to do with the maintenance of the normal constitution of the body fluid—in other words, with the preservation of an optimum internal environment for the body cells. The kidney, in excreting an excess of water with the end-products of nitrogenous metabolism, must exercise a certain degree of discrimination in regard to the excretion of inorganic salts and other so-called threshold substances, depending upon the body need. The importance of such a basic function renders necessary the development of accurate methods for the estimation of renal efficiency. It is not to be expected that any one simple test can be used as an accurate index of the efficiency of an organ whose task involves multiple processes and whose function is influenced from without through nervous connections and hormone control.

Certain phases of renal activity have been used as a basis for tests which may grossly be classified as excretion and retention tests. Excretion tests may be subdivided into (1) those which utilize the estimation of substances normally excreted, and (2) those in which a foreign substance is employed in making the test. The former includes the water test, concentration and dilution test, Mosenthal test, the creatinine test of Major, the urea concentration test of MacLean and the urea clearance test of Van Slyke. The tests in which a foreign substance is employed include the phenolsulphonphthalein test of Geraghty and Rowntree, the indigo-carmine and all dye tests.

In retention tests, an estimation is made of the level in the blood of the nitrogenous metabolites, urea, creatinine and uric acid. Inasmuch as these are maintained at a constant level until renal reserve is lowered to approximately one-fifth of normal, these retention tests are significant only (1) in the terminal stages of a renal lesion, (2) in the acute stage when renal function is temporarily in abeyance as a result of swelling and inflammation, or (3) in obstructive lesions, especially those associated with prostatic hypertrophy where renal function is at a low level in consequence of back pressure.

For the urea clearance test, simultaneous readings of the blood and urinary urea and the urinary output per minute are required. The urine is collected at two successive hourly intervals, the bladder being completely emptied before the beginning of the first period, and midway between the two periods, a specimen of blood is taken. In this way, two tests of the kidney function are made, the one blood urea estimation serving for both, since this varies little over a considerable period of time. The exact period of the collection of urine need not necessarily be limited to an

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hour, provided an accurate record is kept of the time so that the minute volume of urine can be calculated from this. The urea content of the urine and the blood is then estimated and applied in the following manner: If the urinary flow exceeds 2 cc. per minute, the clearance is calculated according to the formula: Maximum clearance $= V \times \frac{U}{B}$. V is the urinary volume per minute, U the urinary urea per cc. and B the blood urea per cc. If the urinary flow is less than 2 cc. per minute, the clearance is calculated according to the formula: Minimum clearance $= \sqrt{V} \times \frac{U}{B}$ An average normal for the maximum clearance is 75 cc. and for the minimum clearance, 54 cc. Results are usually expressed in percentages of normal, and this may be obtained by multiplying by the factor 1.33 in case of maximum clearances and by 1.85 in case of minimum clearances. For description of the technic of tests and calculations, the original articles by McIntosh,[1, 2, 3] Möller[2, 3] and Van Slyke[1, 2, 3, 4] may be consulted. Recently, minor changes have been made in the technic in that it has been shown that the time of day is of little significance and that, in the majority of cases, the patient may be up and around during the test. The use of moderate amounts of coffee has also been shown to be of little consequence.

The urea clearance test possesses the advantage of utilizing a material normally excreted and one which constitutes approximately one-half of the urinary solids, since the average adult urea excretion for 24 hours is 60 grams out of a total solid of 125 grams. Furthermore, according to the modern theory of renal function, the excretion of urea is a function of the glomeruli; thus, the urea clearance test is a measure of the function of that most essential portion of the renal unit, the glomeruli. It is not assumed that the urea clearance formulas express with mathematical accuracy the complete effect of all factors governing urea excretion; rather, they are only expressions of the effect of two factors—blood urea content and urinary volume—which are in continual action and appear to be ordinarily of most importance in regulating the urea output.

In normal individuals, urea clearance tests at different times may indicate a wide variation in results. Thus in normal persons, Van Slyke found variations of from 35 to 75 cc. per minute in standard clearances and in maximum clearances, variations of from 50 to 100 cc. per minute. Furthermore, in the same individual, tests at different times gave as much as 25 per cent variation in results without any evidence of change in renal function. It is evident that other factors, in addition to blood urea concentration and urinary volume, affect urea excretion. Addis and Drury[5] found that the maximum clearance was increased by ingestion of a mixed meal—milk, caffine and glutamic acid—and de-

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creased by pituitrin and very large doses of adrenalin. On the other hand, small doses of adrenalin increased excretion. These factors may exert their influence by varying the blood flow through the kidneys or they may alter directly the excretory ability of the kidney.

The results of the urea clearance tests which had been done at the Cleveland Clinic in a period of two years were reviewed in an attempt to evaluate the accuracy of the test as compared with other renal functional tests and with the clinical diagnoses. The patients on whom these tests were made included a large number without demonstrable renal lesions, as evidenced either by physical examination or urinalysis. Almost without exception, the patients in whom there was no evidence of renal disease showed clearance values ranging from 75 to 100 per cent of normal. Severe hyperthyroidism appeared to increase the clearance value slightly, perhaps in accordance with the increased flow of blood. Acute infection decreased the results slightly while malignant growths appeared to have no definite effect unless the urinary system was involved. In one such case in which a carcinoma of the pelvis was present involving the ureters, clearance values of 13 and 12 per cent were obtained. From the age of 50 onward, clearance values appeared to be reduced. Peripheral arteriosclerosis also was frequently associated with low clearance values; this suggests that pathological changes in the renal arteries may so reduce the flow of blood that urea excretion is considerably hampered. The study of approximately one hundred patients who had no evidence of renal lesion but who did have a variety of other lesions makes it seem probable that urea clearance values are not affected to any significant degree by conditions external to the kidney or urinary tract.

It is evident that, in common with other organs, there is a renal reserve factor which may be depleted over a long period of time before a point is reached where clinical evidence of such reduction occurs. It is likewise possible that a portion of the renal function may be lost before any appreciable diminution of the urea clearance value is obtained. In one instance, an apparently normal kidney had to be removed as a result of an accident, and five days after nephrectomy, urea clearance tests showed 62 per cent function. In other patients, higher values have been obtained from the kidney remaining after nephrectomy, but these were mostly patients in whom a functionless kidney had existed for some time, and in whom hypertrophy of the remaining kidney might well have occurred.

Three hundred cases of renal disease have been selected for study. Detailed investigation has been carried out and some of the patients have been seen on repeated occasions. These cases have been grouped

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according to the classification of Addis.[6] Exact classification is a matter of opinion in some instances, especially since postmortem examinations have been possible in only a few.

Fifty-four of these cases fall into the group of hemorrhagic Bright's disease in varying stages. It has not been our privilege to observe any severe cases of the initial type. In three rather mild and subsiding cases, clearance values ranged from 40 to 60 per cent of normal without any evidence of nitrogen retention. Opportunities to recheck these patients at later times have been rather rare, but in two cases, definite increase in function was found some months after the initial test although in neither case had there been a return to the normal standard. Van Slyke[7] has reported cases of acute hemorrhagic Bright's disease with uremia in which the urea clearances were below the critical 20 per cent level. These levels markedly increased following the patients' recovery, and Van Slyke feels that the results vary with the healing process.

Sixteen of our patients were in the chronic active stage of the disease and the clearance values were definitely reduced, ranging from 60 to 20 per cent. Hypertension and urinary evidences of chronic hemorrhagic Bright's disease were manifested in these patients. Several were rechecked after a period of months and little change was noted, although the general tendency was downward. Unfortunately, most of our patients with the hemorrhagic type of Bright's disease were in the terminal stage on admission to the hospital and the urea clearance values were in the level below the critical 20 per cent. Uniformly, these patients had clinical evidence of uremia with characteristic blood chemistry findings.

Eighteen cases of degenerative Bright's disease are included in this series. Even with massive edema and heavy proteinurea, these patients had urea clearance values which frequently were close to normal. Inasmuch as postmortem examination in such cases shows tubular degeneration as the outstanding pathological feature with relatively good glomeruli, the clearance value theoretically should be good. At the first observation, the levels ranged from 40 to 80 per cent of normal. In one case, a blood urea of 66 milligrams per cent accompanied a 40 per cent clearance level. In two patients who have been followed for some months, however, marked decrease in the clearance values has accompanied clinical evidence of a downward progress. One patient had a clearance of 95 per cent when he was first seen and this decreased to 76 per cent in six months. In another case, the level progressively decreased from 60 per cent to 16 per cent in a period of nine months and the patient died with definite manifestations of uremia. Postmortem examination confirmed the diagnosis. From our study of these interest-

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ing cases, it would seem that the course, in adults at least, is progressively downward and usually terminates in renal failure if the common intercurrent infections are escaped.

In 228 patients in this series—76 per cent of the entire group—the lesion evidently was of vascular origin. Such a diagnosis is made chiefly from a family history of vascular disease, absence of antecedent renal history or infection which usually is associated with renal disease, such as scarlet fever, the history of insidious onset or the accidental discovery of hypertension coupled with evidence of vascular disease in the eyegrounds and the absence of the findings in early stages of urinary disease. It is possible that a certain number of these were advanced cases of the hemorrhagic type in which the onset had been insidious, and in which the clinical findings could not be definitely separated from those of primary vascular disease.

Senile arteriosclerosis involving larger arteries appears to reduce renal function only by degrees as the circulation through the kidney is impaired. Such patients have a mild reduction in clearance values, but it is evident that they do not have a progressive renal lesion and that there is little disturbance of glomerular activity.

Younger individuals who have hypertension without urinary signs frequently exhibit normal clearance values. However, when albumin and occasional casts are present in the urine, some reduction may have occurred, although some patients seem to carry on over long periods without any demonstrable kidney defects. Reduced urea clearance is particularly true in those patients who have a persistent elevation of the diastolic pressure, although this is not absolutely constant. With the onset of well-marked vascular changes in the fundus and increased signs of urinary disturbance, urea clearance values become lower in harmony with the deterioration of health generally. Several such cases have been seen when the terminal stage had been reached in which the clearance values were around 10 per cent and marked nitrogen retention was present. The rate at which the process progresses appears to vary considerably. One patient of 40 years has a marked family history of vascular disease and his blood pressure has been at least 200 mm. systolic, 120 mm. diastolic for the ten years we have observed him and still his clearance is 65 per cent. However, in several others, there appears to be a very rapid process with marked hypertension, marked vascular changes in the eye, urinary findings suggestive of the hemorrhagic type of Bright's disease, and rapid reduction of clearance values suggesting the development of a progressively rapid renal deterioration which corresponds to the malignant hypertension of Volhard and Fahr.[8] Thus in one patient whose blood pressure was 260 mm.

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systolic, 140 mm. diastolic, the urea clearance value was reduced from 55 to 14 per cent in six months. Clinically, this patient had a rapidly progressive downhill course, ending in uremia and the urea clearance test corresponded with this very closely.

In reviewing these cases, it has been possible to form some ideas regarding the comparative value of the urea clearance test and the phenolsulphonphthalein test. When all patients with renal disease are considered, it appears that the phenolsulphonphthalein test gives higher values in the more efficient kidney and shows little reduction in results until the urea clearance values reach an average of 60 per cent; then the phenolsulphonphthalein values fall more abruptly and tend to become equal to clearance values at about 30 per cent. From this stage, the phenolsulphonphthalein values are consistently below the clearance results, and below clearance values of 10 per cent, the phenolsulphonphthalein test shows practically no excretion. According to Van Slyke, the phenolsulphonphthalein test improves before the urea clearance when the patient is recovering from acute hemorrhagic Bright's disease. This may be a useful finding in the prognosis in some cases. In our experience, the phenolsulphonphthalein test values in the degenerative type tend to be higher than the clearance values by a greater margin than in other forms of renal disease. It would appear that, although the two tests tend to approximate each other, the urea clearance test seems to reflect the actual state of the kidney more accurately. The urea clearance test also is not affected by bladder retention which will alter the results of the dye test unless a catheter is used.

SUMMARY

1. The simultaneous comparison of urinary and blood urea levels offers a method of checking the glomerular function.

2. The results obtained should not be considered as mathematically exact, but rather as an expression of the two main factors in the urea excretion, namely, the blood urea content and the urinary volume.

3. Considerable variation in the results of the urea clearance test in normal individuals and in the same individual at different times has been noticed.

4. Reduction in renal function is evidenced by lessened urea clearance values. Values below 20 per cent are apt to be accompanied by evidences of renal failure and if they are below 10 per cent, death usually occurs in a short time unless these levels are due to transient renal conditions which may be corrected.

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5. For medical purposes at least, the urea clearance test would appear to be more accurate than the phenolsulphonphthalein test, and it constitutes the best single test of renal function which has been devised.

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