Cleveland Clinic Quarterly
Volume 38, January 1971

Clinical evaluation of renal function—use of chemical agents

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RENAL function may be evaluated by a variety of clinical tests, some simple and some quite sophisticated. Some of the tests estimate the overall efficiency of the kidneys but may give few clues to specific diagnosis, while other tests may help to establish the diagnosis. Still others may be used to measure differentially the function of each kidney.

Most of the common renal diseases present a similar pattern of renal dysfunction and cannot be distinguished on the basis of simple clinical tests. Yet, the most precise tests for measuring various aspects of renal function are often too time consuming and cumbersome for general office or clinical practice. The ideal renal function test should be safe, accurate, simple to perform, require no laboratory facilities, and should be specific in that the results are affected only by changes in renal function. The tests discussed in this paper do not meet those ideal specifications, yet, when used singly or in combination these tests provide valuable information in regard to the overall adequacy of renal function.

Urinalysis provides critical information about the presence or absence of renal disease and should always be performed by the physician responsible for the patient. A properly collected midstream specimen of urine is most suitable for examination since it avoids contamination by prostatic or vaginal secretions and the risk of causing ascending infection induced by catheterization. The introduction of simple yet sensitive chemical methods for the detection of protein, glucose, and bacteria has made urinalysis a reliable indicator of the presence of latent renal disease. Proteinuria may be recognized by precipitation with sulfosalicylic acid, by boiling urine after the addition of acetic acid, or by the color changes induced in commercially available dip sticks impregnated with tetrabromphenol blue. False-positive results are unusual with the latter method, but may occasionally be obtained in exceptionally alkaline urine in the absence of significant proteinuria. The accurate quantitative measurement of urinary protein may be accomplished by precipitation with Tsuchiya's reagent. Reagent strips impregnated with a buffered mixture of glucose oxidase, peroxidase, and a chromogen system, specifically test for glucose in the urine. These reagent strips are more sensitive than the copper reduction tests (Benedict's solution, reagent tablets), since no substance excreted in the urine other than glucose is known to give a positive result with the glucose test area. In particular, it does not react with other reducing sugars such as lactose, galactose, and fructose, nor re-

ducing metabolites of drugs, for example, salicylates and naladixic acid, as the copper reduction methods do. An occasional cause of inhibition of glucose reactivity is a large urinary concentration of ascorbic acid from therapeutic doses of vitamin C.

There are several chemical methods adaptable to office use which will reportedly detect the presence of significant numbers of bacteria in the urine. I find it simpler to stain a drop of freshly voided urine with Gram's stain. When bacteria are seen on the smear, it can be presumed that the urine contains 100,000 or more organisms per milliliter of urine. When infection is suspected, a culture of a clean voided mid-stream urine specimen should be obtained for identification of the infecting organism and for suitable sensitivity studies.

Reagent tablets are now available for the detection of urine bilirubin, and characteristic odors of certain amino acids may be pathognomonic of certain metabolic disorders.

Qualitative examination of the urinary sediment is of value when accurately performed and interpreted. The urine specimen is centrifuged at 3000 rpm for from 3 to 5 minutes, and an abundant sediment is resuspended in 0.5 ml of supernatant fluid. When the sediment is scanty, the plug may be pipetted from the tip of the centrifuge tube and spread upon the slide. Hematuria must be considered in regard to the many disease processes occurring at any level of the genitourinary tract, whereas the finding of erythrocyte casts confirms the parenchymal origin of the blood cells. Erythrocytes or free hemoglobin in the urine will produce a positive color reaction with benzidine, guaiac, and reagent strips impregnated with orthotoluidin. Clumped leukocytes may be considered pathognomonic of infection, oval fat bodies or fatty casts indicate renal parenchymal disease, while broad casts may be considered indicative of advanced renal failure.

Normally, the specific gravity of the urine ranges from 1.003 or less, to 1.020 or higher. Specific gravity can be measured with an accurate hydrometer or with a drop of urine in a hand refractometer. When a random sample of urine is concentrated to 1.020 or higher, there usually is no need to repeat the specific gravity test or to do a concentration test. The use of urine specific gravity as a test of renal function is considered later in this discussion.

The hydrogen ion concentration (pH) of the urine is best tested in a freshly voided specimen with phenothiazine paper. Normal kidneys can produce urine with a wide pH range from 4.4 to as high as 8, although normally the urine tends to be acid. Persistently alkaline urine occurs in association with infections caused by certain urea-splitting bacteria, but may also follow the ingestion of sodium bicarbonate or other alkalinizing drugs, as well as the ingestion of oral diuretics.

Crystalluria may be entirely asymptomatic or may be associated with the formation of urinary tract calculi, giving rise to clinical manifestations associated with urinary tract obstruction. The demonstration of a particular

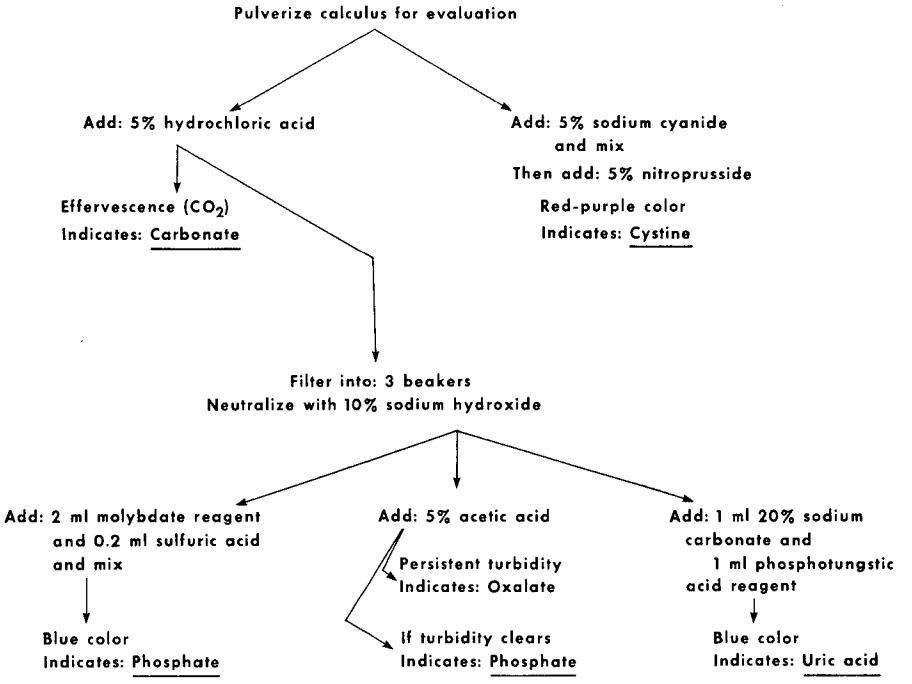

Fig. 1. Chemical tests for identification of crystalline sediment. (Based on Annino, J. S.: Clinical Chemistry, 3d edition, Boston: Little, Brown and Company, 1964, p. 388–390.)

crystal in a patient with urinary lithiasis may serve as a guide to the diagnosis of an underlying disease process producing excretion of excessive amounts of a normal urine constituent, such as calcium in hyperparathyroidism, or increased uric acid and urate excretion with gout. Although crystals have a discrete structure with a specific or characteristic form and are readily recognized by routine examination of the urine sediment under ordinary light microscopy, differentiation among crystals may require more detailed examination. Simple chemical procedures will help in the rapid identification of many inorganic or crystalline urine components. A sample flow sheet for several tests is outlined in *Figure 1*.

Blood constituents, such as the blood urea nitrogen (BUN) value, are commonly relied upon as an indicator of renal function. Unfortunately, the BUN is neither specific nor sensitive and does not increase beyond the normal range until glomerular filtration rate has declined by as much as 60 percent. In addition, the BUN is determined not only from the net effect of glomerular filtration and tubular resorption of urea nitrogen, but also from the rate of urea nitrogen production. Therefore, a number of extrarenal factors, such as dietary protein intake, state of hydration, and hepatic function help to determine the level of the BUN. More specific than the BUN is the serum creatinine concentration, which is largely independent of diet, being influ-

enced mainly by muscle mass, and remains relatively constant at any specific rate of glomerular filtration. The major limitation in the use of serum creatinine concentration, as with the BUN, is the fact that it provides no indication of renal impairment until the renal clearance has been substantially reduced.

Clearance methods provide a quantitative expression of the rate at which the kidneys excrete various substances relative to their concentrations in the plasma. The clearance of any substance by the kidney can be determined when the plasma concentration is measured along with the rate of urinary excretion of that substance in milligrams per minute. The determination of effective renal plasma flow and glomerular filtration rate by the use of para-aminohippuric acid (PAH), and inulin, respectively, are still the standard methods despite the time-consuming features and the hazards of catheterization of the bladder.

In an attempt to simplify these methods, the clearances of a number of radioactive substances have been tested and compared with the reference standards, PAH, and inulin. Simultaneous determinations have shown good correlation between the clearances of ^{57}Co-labeled vitamin B-12, iothalemate sodium ^{125}I and inulin, while the clearances of substances such as orthoiodohippurate ^{131}I or ^{125}I have demonstrated good correlation with clearance of the reference standard PAH. Radioactive clearances may be performed by blood counting or by surface counting, both methods measuring the rate of clearance of isotope from the circulation.

In general clinical practice, the two most readily available indexes of glomerular filtration rate are the urea clearance and the creatinine clearance. The endogenous creatinine clearance provides the most practical method for estimating the glomerular filtration rate and has definite advantages over the more popular urea clearance test, since the former does not vary with the rate of urine flow, as discussed earlier, and is not affected so much by extrarenal factors. Creatinine concentrations are easily determined in urine and serum by the picric acid method of Folin and Wu, or by a newer method using dinitrobenzoic acid. Both methods are easily adapted to the Auto-Analyzer. The rate of creatinine excretion remains relatively constant over short periods, and correlates well with simultaneously determined inulin clearance over a wide range of renal function.

In severe renal insufficiency the ratio of creatinine clearance to inulin clearance tends to exceed 1, reflecting tubular secretion of creatinine. Although the creatinine clearance may be from 10 to 30 percent higher at low glomerular filtration rates, the absolute differences are small; i.e., a clearance of creatinine of 13 ml per minute equals a clearance of inulin of 10 ml per minute. The endogenous creatinine clearance is particularly useful as a prognostic guide, since its ease of determination and accuracy of results over a wide range of renal function allow serial determinations to follow the course and progression of established renal disease.

Renal clearance of phenolsulfonphthalein (PSP test) provides an extremely simple clinical test for the approximation of renal plasma flow. PSP is remarkably nontoxic, is not metabolized, and is largely excreted by the kidneys. Alkalinization of collected urine specimens with sodium hydroxide brings out the crimson color that may then be compared in a colorimeter with reference standards. The rate of excretion is proportional to the plasma concentration, thus the excretion rate is greatest immediately after injection when the plasma level is highest. Normal adults may clear from 35 to 50 percent of PSP in 15 minutes after injection, and from 60 to 85 percent of the injected dose in two hours. In early renal impairment the 15-minute excretion may be decreased, whereas, when time for repeated recirculation is allowed, the two-hour excretion may be normal. Therefore, the 15-minute specimen is by far the more valuable and is the only specimen needed to provide an approximation of renal plasma flow.

There are numerous opportunities for misinterpreting PSP clearance. Errors are unfortunately common in the timing of urine collections, and it is important that the patient be well hydrated before the test, so that he voluntarily may empty the bladder completely precisely 15 minutes after the intravenous injection of 6 mg of PSP. PSP excretion may be impaired when performed within 8 to 12 hours after an intravenous urogram, because of competition for the same tubular excretory mechanism. Probenecid may also decrease PSP excretion by the same mechanism. Drugs such as nitrofurantoin, pyridium, and the sulfobromophthalein (BSP) interfere with the colorimetric determination of PSP.

Tubular function is measurable by no one clinical test because of the complex, interrelated function of the proximal and distal tubules. A number of studies may be applied to measure various aspects of tubular function. We can measure resorptive or secretory tubular maximums for substances such as glucose, PAH, or Diodrast. The extremes of concentrating or diluting ability of the kidneys may be estimated from standardized concentration and dilution tests, free-water clearances, or maximal and minimal osmolality determinations. The ability of the kidneys to acidify urine may be determined from urinary pH measurements after the ingestion of a standard dose of ammonium chloride. Although precise, these methods are tedious and may require elaborate laboratory facilities and are, therefore, not suited for clinical practice.

Impairment in the ability to concentrate the urine to a normal degree is an early feature of most generalized renal diseases. Measurement of the specific gravity of the urine after a period of dehydration provides an extremely simple, yet reasonably accurate assessment of tubular function. The test loses its sensitivity when glomerular filtration rate is decreased to 20 percent of normal, since urinary osmolality (or specific gravity) becomes relatively fixed at a value similar to that of plasma. No special diet is necessary as long as adequate protein and salt intake are insured. A specific gravity

of more than 1.023 obtained on any random specimen of urine or after overnight dehydration indicates normal tubular function. Twenty-four hours of dehydration or even longer periods may be required to attain a maximum specific gravity. To avoid prolonged fluid deprivation, five units of pitressin tannate in oil may be administered intramuscularly and will achieve comparable urinary concentration in a period of from 10 to 12 hours.

Misleading results will be obtained in patients with unrecognized proteinuria or glycosuria and, in fact, heavy glycosuria may induce solute diuresis which invalidates the concentration test. Erroneous readings may also result from imprecise calibration of the hydrometer, or failure to correct the readings for temperature changes, or during the diuresis of edema fluid, or critical electrolyte depletion associated with the administration of potent diuretics.

Other nonrenal influences on urinary concentrating ability include diets persistently low in protein or salt, or an habitually high fluid intake as practiced by some patients. It is common to have the specific gravity inadvertently determined on urine specimens after an excretory pyelogram or other angiographic procedures. Also to be kept in mind is the lack of production of antidiuretic hormone by the pituitary, or the rare patient with nephrogenic diabetes insipidus. When these limitations are kept in mind, the urinary concentration test provides an accurate assessment of the adequacy of renal tubular function.

Comment

From the foregoing discussion, it is seen that a great variety of laboratory procedures have been devised to measure precisely or to estimate various aspects of renal function. For evaluation of the overall efficiency of renal function, this list can be drastically shortened to include five simple clinical tests as follows: (1) urinalysis, (2) serum creatinine concentration, (3) endogenous creatinine clearance, (4) phenolsulfonphthalein clearance (PSP test), and (5) urinary concentration test.

A carefully performed urinalysis will provide invaluable information in regard to the presence of renal disease, whereas the serum creatinine concentration, the endogenous creatinine clearance, phenolsulfonphthalein excretion, and the urinary concentration test provide adequate clinical assessment of renal excretory function and tubular function. Specific diagnosis will depend upon the careful application of more specific studies and may require additional studies such as intravenous urography, retrograde pyelography, selective renal angiography, or percutaneous renal biopsy.