Spectrum of Tests Available To Evaluate Occupationally Induced Renal Disease

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The traditional tests used to screen workers for renal disease are inadequate to detect early or moderate loss of renal function. More sensitive tests are seldom measured reliably in the occupational setting. Several noninvasive tests of kidney function have proven useful in monitoring the effects of special toxins. This paper will discuss the advantages and disadvantages of various tests of renal function that may be used to detect nephrotoxicity in workers. The discussion includes a brief overview of the tissue types that can be injured by toxic agents and the specific tests that may be used for each. Special research projects are needed to validate the clinical significance of these and other medical tests through careful study in a controlled clinical setting.

Renal disease is a relatively new area of occupational epidemiological research. Although adverse effects on the kidney due to certain drugs, heavy metals, and solvents have been recognized for years, research in this area has traditionally been experimental and clinical, rather than epidemiological. Several considerations have begun to change this. In recent decades, nephrologists and renal toxicologists have identified several noninvasive, sensitive tests of renal function that can be used as markers of injury in epidemiological studies. These tests suggest that for certain industrial substances such as cadmium and some uranium compounds, the kidney may be the most sensitive tissue. Recommendations for monitoring workers exposed to these agents have focused upon the kidney as a critical organ.[1,2]

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Three additional considerations have stimulated interest in the recognition and prevention of occupational nephrotoxicity[3]: (1) the irreversibility of most types of renal disease once substantial loss in renal function has occurred; (2) the large cost to Social Security to finance the treatment of end-stage renal disease, equaling nearly $2 billion in 1982[4]; and (3) the potential utility of identifying those toxic and occupational exposures that contribute to the burden of idiopathic renal disease, because for more than half the patients who develop fulminant renal disease, the etiology is unknown.[3-5]

This paper will discuss various tests of renal function that may be used to detect nephrotoxicity in workers. The scope will be limited to those tests that are potentially useful in cross-sectional epidemiological studies of occupational populations. In practice, a wide gap exists between clinical nephrology, in which invasive and sophisticated tests are routinely used to detect pathology and to measure renal function in hospitalized patients, and the crude tests that are available in the workplace.

The traditional occupational screening program such as preemployment physical examinations or routine periodic medical surveillance, usually measures only blood urea nitrogen (BUN) and serum creatinine (tests that are automatically included in blood chemistry analyses), or the amount of protein and blood measurable by dipstick in the urine. Practical considerations make it infeasible, if not inappropriate, to use any of the more elaborate conventional tests of renal function for routine screening of occupational populations.

However, a number of special screening tests are used frequently in monitoring workers exposed to known nephrotoxins. For example, the urinary excretion of β-2-microglobulin is commonly measured in workers exposed to cadmium. Several other tests show promise as noninvasive measures of both tubular and other types of nephrotoxicity. In reviewing those tests that show potential in studies of occupational renal disease, we will group them in terms of the type of renal injury that

they reflect. We will discuss both the utility of these tests and the limitations or problems that currently exist. Our goal is to provide some guidance on which tests are useful in a given setting.

Kidney Tissue Types Susceptible to Injury by Toxic Agents

Most renal insults can be categorized as to whether they involve primarily the glomerulus, the renal proximal tubules, the distal tubules, the interstitium, or the renal vasculature. Table 1 lists those types of renal pathology that have been associated with a variety of toxic occupational or environmental exposures. In actuality, this classification is simplistic, because many toxic substances affect more than one tissue, depending upon dose, the age of the exposed person, and the chronicity of exposure. For example, lead poisoning in children may lead to increased excretion of glucose, phosphate, and amino acids, characteristic of the acquired Fanconi syndrome. In contrast, chronic occupational lead exposure of adults rarely causes the Fanconi syndrome. Rather, disease becomes manifest as a more chronic interstitial process leading to loss of nephron function.[6-8]

For many types of renal injury, the original pathological process may be unrecognizable at the time that a patient comes for treatment. Often, the process is silent until so many nephrons are lost that the patient becomes symptomatic. Because nephron death can occur from a variety of pathological processes, the end result is nonspecific. The patient comes for treatment with diffuse, "end-stage" renal disease for which the original etiology and pathology may be unrecognizable.[9] However, because the purpose of screening is to identify pathology before the advent of end-stage renal disease, these categories provide a useful framework for discussing which tests of renal function reflect injury to a particular tissue type.

TABLE 1
Classification of Toxic Response by Primary Area of Renal Involvement

Target Tissue	Pathological Lesion (Toxic Agent)
Glomerulus	Immune complex glomerulonephritis (GN) (inorganic mercury, gold, penicillamine) Proliferative GN (silica) Focal sclerosing GN (heroin) Goodpasture's syndrome (?? solvents)
Renal tubule	
Proximal	Acute tubular necrosis (acute high doses of inorganic mercury, uranium, carbon tetrachloride, chloroform, aminoglycosides, cephalosporins) Fanconi syndrome (acute lead poisoning in children) Fanconi syndrome with tubular proteinuria (chronic cadmium intoxication)
Distal	Defects in concentration of acidification (amphotericin B, methoxyflurane, lithium, also a secondary effect in any chronic renal disease)
Interstitium	Acute interstitial nephritis (antibiotics, thiazides, nonsteroidal anti-inflammatory drugs) Chronic interstitial nephritis (lead, analgesics)
Vasculature	Hypersensitivity reaction (busulfam, penicillin)
Other	Nephrocalcinosis (ethylene glycol) Tubular necrosis secondary to hemolysis (arsine) Kidney stones (cadmium)

TABLE 2
Tests Commonly Used to Detect Glomerular Dysfunction

Markers of glomerular filtration
BUN
Serum creatinine
Creatinine clearance
Markers of abnormal glomerular permeability
Dipstick measurements of urine protein
Albumin/creatinine ratio on a spot urine
Fractionation of urine proteins
Quantitative 24-hr measurement of urine proteins
Examination of urine sediment for red cell casts

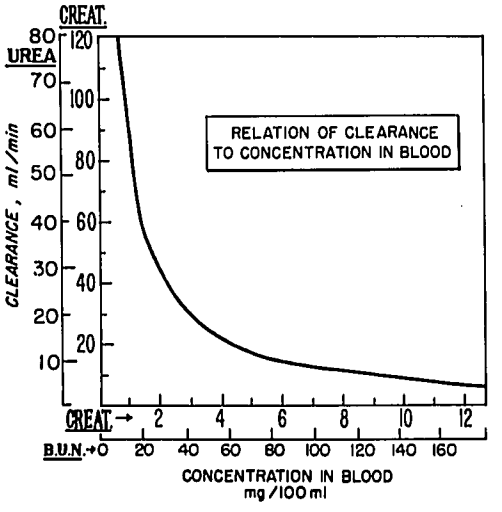

Fig. 1. Relation of urea and creatinine clearance to blood concentrations (reproduced with permission from Ref. 10). Assumes a constant urea nitrogen excretion of 11.5 g/day (8 mg/min) and a creatinine excretion of 1.2 g/day (0.84 mg/min).

Markers of Glomerular Dysfunction

Table 2 shows several tests commonly used to detect impaired glomerular function. These are listed in order of increasing use, which in most cases corresponds to the increasing difficulty of obtaining the test. As mentioned earlier, BUN and serum creatinine are the most commonly measured markers of glomerular filtration. However, these measures are inferior to creatinine clearance for detecting significant reduction in glomerular filtration for two reasons. The first, illustrated in Fig. 1, is that the blood concentration of either urea or creatinine increases quite slowly, in absolute terms, in the initial phases of glomerular disease.[10] Creatinine clearance must decrease greatly, in absolute terms, to

produce a small absolute increase in serum creatinine. For example, if a person's creatinine clearance decreases from 120 to 60 mL/min, serum creatinine will increase only from 0.7 to 1.4 mg/100 mL. A 50% loss in the glomerular filtration rate (GFR), represented here by creatinine clearance, will result in a doubling of serum creatinine. For a person who begins with a low initial value, however, serum creatinine may still fall within the normal population range.

The problem with serum creatinine is not actually one of test insensitivity, as is commonly thought, but rather is a consequence of the wide interindividual variability.[10] Serial measurements of serum creatinine in the same person would reduce at least this source of variability, allowing each person to serve as his or her own control. This type of longitudinal analysis, although still subject to analytic variability, would provide a better marker of decrease in glomerular function than does a single value compared with normal subjects in the population.

The second problem with using these serum markers to reflect GFR is that, for BUN at least, blood levels can be dramatically affected by dietary protein. The effect of diet can be most clearly seen in a patient with renal failure (Fig. 2), in whom the BUN can be seen to rise sharply following protein intake, reabsorption of blood from the intestine, or the use of catabolic steroids.[10]

While the limitations of using these surrogate measures to detect reduced glomerular function are obvious, finding alternatives is more difficult. The ideal situation would allow a 24-hour urine collection for the determination of creatinine clearance, or better yet, determination of iothalamate clearance, the reference technique for measuring GFR. This might be feasible in a hospital situation, but is clearly unattainable in the usual occupational setting. In some circumstances, a timed urine sample can be collected during the 8-hour work day. However, measurements of creatinine clearance obtained under these conditions are probably not comparable to population normal values measured in hospitalized subjects over a 24-hour period, because measurements of creatinine clearance in a working population may well be influenced by physical exertion and body posture.

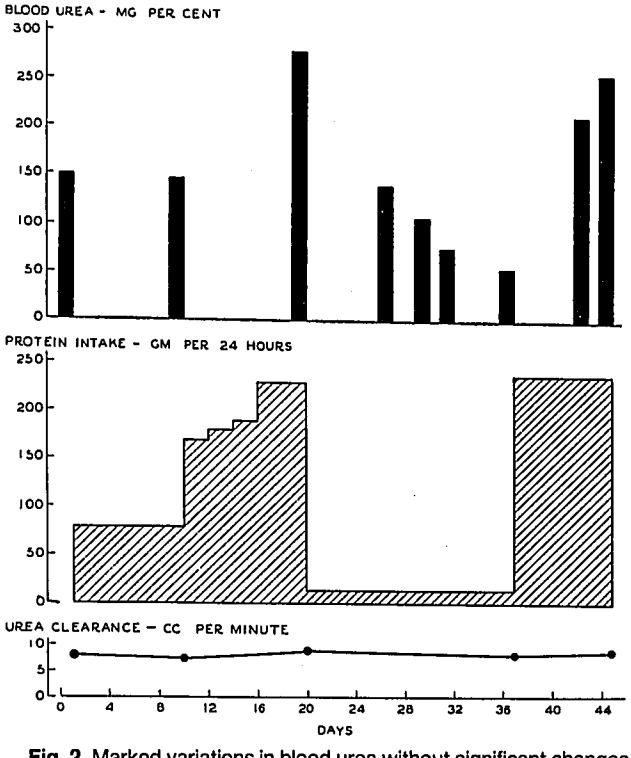

Fig. 2. Marked variations in blood urea without significant changes in urea clearance, produced by alterations of protein consumption in patient with renal disease (reproduced with permission from Ref. 10).

Techniques have been developed to shorten the collection period required in measuring glomerular filtration to observation periods as short as two hours. One such method measures the two-hour renal clearance of radiolabeled ethylenediaminetetraacetic acid (51-Cr-EDTA). However, a two-hour collection period provides less reliable estimates of GFR than does a 12- or 24-hour measurement. Furthermore, these methods also require close clinical monitoring, and a setting in which such medical testing is clearly justifiable. Given these constraints, researchers who require a reliable measurement of GFR in special high-risk populations should obtain such measurements in a controlled setting, such as in a clinical research unit, or the metabolic ward of a hospital.

Another common signal of glomerular disease is the presence of increased protein in the urine. In choosing a test that is most appropriate to measure protein excretion in a working population, the following three decisions must be made.

Probable Source of Proteinuria

The first decision is to anticipate whether proteinuria is due to glomerular or renal tubular disease. Injury to the glomerulus characteristically increases glomerular permeability and allows large, high-molecular-weight (mol wt) proteins the size of albumin (mol wt 69,000) or larger to appear in the urine. By contrast, injury to the renal proximal tubules prevents reabsorption of small, so-called low molecular weight proteins, which then appear in increased concentrations in the urine.[11,12]

Sampling Schedule

The second decision in measuring proteinuria is whether a spot urine sample will suffice, or whether 24-hour collection is necessary. Single voided urine samples are susceptible to fluctuations in urine concentration due to position, fluid intake, etc. On the other hand, reliable 24-hour urine collections are notoriously difficult to collect even in the hospital setting. They are particularly difficult in a working population where the collection is unsupervised during two thirds of the study

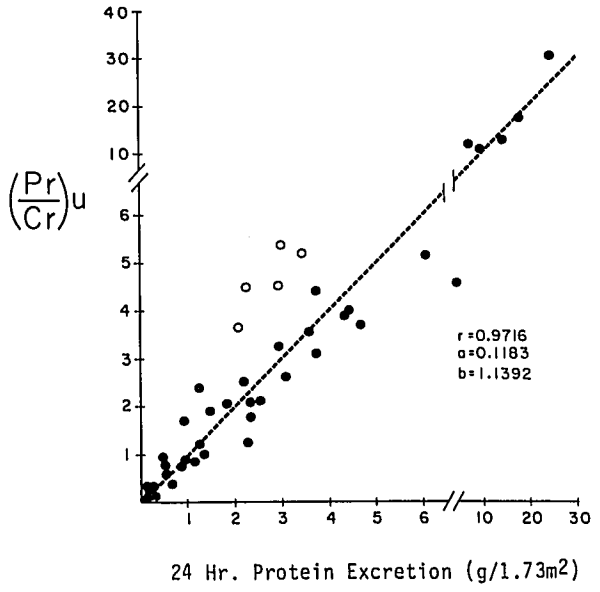

Fig. 3. Relation of total protein/creatinine index [(Pr/Cr)u] in single voided urine samples to 24-hour protein excretion (reproduced with permission from Ref. 13). Protein/creatinine index was computed using urine protein and creatinine concentrations expressed as milligrams per deciliter. The letters r, a, and b indicate the correlation coefficient, intercept, and slope as computed by the least squares method. The five open circles denote values for patients who had a protein/creatinine ratio of more than 3.5 and a protein excretion rate of less than 3.5 g/24 hours/1.73 m^2.

period. Two recent studies have attempted to deal with this dilemma by showing that the ratio of total urine protein to creatinine in a spot urine sample corresponds closely to the values measured from a 24-hour urine collection.[13,14] Figure 3 shows the concordance between the two measures.[13] In fact, the authors of the article contend that the protein/creatinine ratio is potentially more accurate than the 24-hour urine results because it eliminates error due to incomplete collection.

Degree of Quantitation

The third decision regarding measurement of proteinuria in occupational studies is the degree of quantitation needed. Table 3 shows the analytic techniques used to measure protein in urine. By far the most commonly used screening tests for urine protein are the dipstick methods containing bromphenol blue. Both Albustix and the Ames dipstick use this colorimetric method, in which the yellow indicator turns green-blue upon contact with protein.[15] These tests can reliably detect albuminuria exceeding 500 mg/day, but are insensitive to globulins and may miss lower levels of proteinuria in dilute urine.[10] The lower detection limit for free albumin of these tests is 20 to 30 mg/100 mL. Excretion of total protein in excess of 150 mg/24 hours is considered abnormal by population standards.[10]

A much better semiquantitative test for protein is the precipitation of protein by heat and tricholoracetic acid. This test has a lower detection limit of 5 to 10 mg/100 mL and is more sensitive to globulins.[15] The false-positive results due to radiopaque dyes are unlikely to pose a problem in the occupational setting, and those due to tolbutamide exposure can easily be identified by questionnaire.

TABLE 3
Tests Commonly Used to Measure Protein in Urine

Semiquantitative
Dipstick using bromphenol blue colorimetric method (Albustix, Ames)
Precipitation using heat and acetic acid
Quantitative
Sulfosalicylic acid turbidity method
Radioimmune assay for albumin

In general, however, any epidemiological study intended to detect early or subclinical increases in protein excretion in an occupational population should use an analytical test that yields quantitative results. Otherwise, the imprecision and insensitivity of the laboratory results will limit the interpretability of the findings. A study based on qualitative measurements would only be convincing if it documented gross proteinuria among the exposed. A negative result would not be convincing. Several good quantitative assays for total or for specific proteins in urine are available, including the sulfosalicylic acid turbidity method. Radioimmune assays for albumin are also available that can quantify very low concentrations of albumin. At present, the radioimmune assay is available only in research centers, and it is unclear whether this level of sensitivity is necessary.

Tests of Proximal Tubular Dysfunction

Recently, the area that has received the most attention in the study of occupational renal disease includes various tests of proximal tubular dysfunction. As shown in Table 4, there are two general categories of these tests. One group measures increased urinary excretion of those substances that are normally reabsorbed from the urinary filtrate by the proximal tubules. The second group measures cell components normally not excreted in the urine.[12] Urinary excretion of amino acids and small proteins is often used as a marker of impaired tubular reabsorption. Normal urine contains only trace amounts of proteins with molecular weights less than 40,000 daltons. These small substances, which pass freely through the glomerulus, are normally reabsorbed and (possibly) catabolized by the tubular cells.[11,16,17] Following tubular injury, the concentration of amino acids and small proteins in urine may be greatly increased, due to decreased tubular reabsorption. Substances that have been measured as markers of this process include the amino acids, β-2-microglobulin, and retinol-binding protein.

Aminoaciduria accompanies the acquired Fanconi syndrome in childhood lead poisoning, in workers exposed to cadmium and to a lesser extent mercury and uranium, and in persons who habitually inhale toluene-based glues.[18-21] Although quantitative measurement of urinary amino acids is a well-established clinical test, it

TABLE 4
Tests of Proximal Tubular Injury

Tests of impaired protein reabsorption
Low-molecular-weight proteinuria
Aminoaciduria
β-2-microglobulinuria, retinol-binding proteinuria
Markers of cell injury
Enzymuria
Alkaline phosphatase, γ-glutamyltransferase
Lactic dehydrogenase, N-acetylglucosaminidase

is usually too expensive to employ in screening a large number of subjects in an epidemiological study. Also, aminoaciduria is usually only detectable during acute tubular injury and is not manifest in persons with chronic or interstitial renal disease.[6]

Radioimmune assay for small proteins such as β-2-microglobulin has been more commonly used. A kit for β-2-microglobulin measurement is commercially available and easy to use. One problem with β-2-microglobulin is that it is unstable in acid urine. Although various methods have been proposed for either alkalinizing the collection bottle, or administering alkali to the worker prior to collection, these complicate the process of obtaining a valid measurement. Retinol binding protein, the major α-1-microglobulin, has been proposed as a protein of similar size, since it does not hydrolyze in the usual range of pH of urine.[22] Its use remains even more experimental than that of β-2-microglobulin.

Enzymes released into the urine from the kidney itself comprise a second category of markers of renal tubular injury.[12,23,24] These enzymes include alkaline phosphatase and γ-glutamyltransferase (GGT) present in the brush border of the proximal tubular cells, aspartate aminotransferase and lactic dehydrogenase (isoenzyme) in the cytosol, and N-acetyl glucosaminidase (NAG) in the lysosomes. Some of these, such as GGT, have a higher activity in renal than in other tissue, and show a two- to fourfold higher activity in urine than in serum, suggesting that the enzyme leaks from the kidney into the urine.[12] N-acetyl glucosaminidase is known to increase during renal transplant rejection in patients with hypertension and in patients with drug-induced renal injury.[25,26] Enzymuria has received less attention as a signal of proximal (or distal) tubular injury than has low-molecular-weight proteinuria, and its utility in occupational studies remains unestablished.

Fractionating Proteins in Urine

The techniques for fractionating urine proteins, regardless of size, have improved so that it is possible to resolve at least 250 separate proteins in urine. One widely available technique, which has less resolution, uses one-dimensional electrophoresis. Figure 4 shows polyacrylamide gel separation of urine proteins in three workers exposed to lead, mercury, and cadmium compared with an unexposed subject.[27] The proteins are separated by molecular mass, with mass decreasing from right to left. The pattern of proteinuria clearly shows

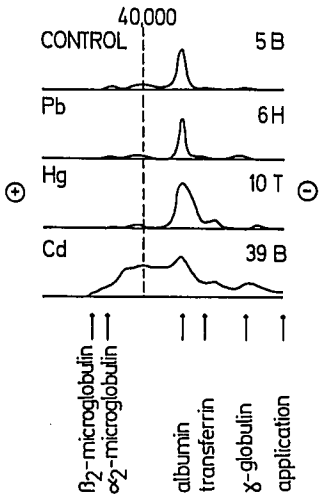

Fig. 4. Densitometric profiles of urine proteins of control worker compared with those of workers exposed to lead (Pb), mercury (Hg), or cadmium (Cd) (reproduced with permission from Ref. 27). The circled + and − indicate the anode and cathode orientation on the sodium dodecylsulfate polyacrylamide (SDS) gel. Individual worker's samples are labeled 5B, 6H, 10T and 39B.

the increased concentration of low-molecular-weight proteins in the cadmium worker, and also the less-well-recognized increase in high-molecular-weight proteins (transferrin and γ-globulin), presumably due to increased glomerular permeability.

The techniques of electrophoresis have been refined still further to allow two-dimensional mapping. Figure 5 shows a complex map of urinary proteins.[12] The proteins have been separated horizontally on the basis of charge (acidic to the left), and vertically on the basis of mass (with increasing molecular weight to the top). Each spot can be identified using a computerized library containing the molecular mass and charge of all potential standard proteins. The concentration of each can be measured semiquantitatively using densitometry. Although this method is still a research tool and requires future clinical validation, it allows more detailed fractionation of urine proteins than is possible by other means.

For example, in Fig. 6, the urine of a worker exposed to thorium shows an unusual stratum containing a number of low-molecular-weight proteins in increased concentration.[12] A similar approach could be used to recognize what nephrologists call nonselectivity, the excretion of larger than usual proteins such as albumin, transferrin, and various macroglobulins into the urine of a patient with glomerular injury. The technique is also useful in recognizing sentinel proteins such as the Bence Jones protein in persons with multiple myeloma.

Tests of Distal Tubular Dysfunction

Relatively fewer measures are available in field settings to detect distal tubular dysfunction (Table 5). The most commonly used are various techniques that assess renal concentrating ability after a period of fluid dep-

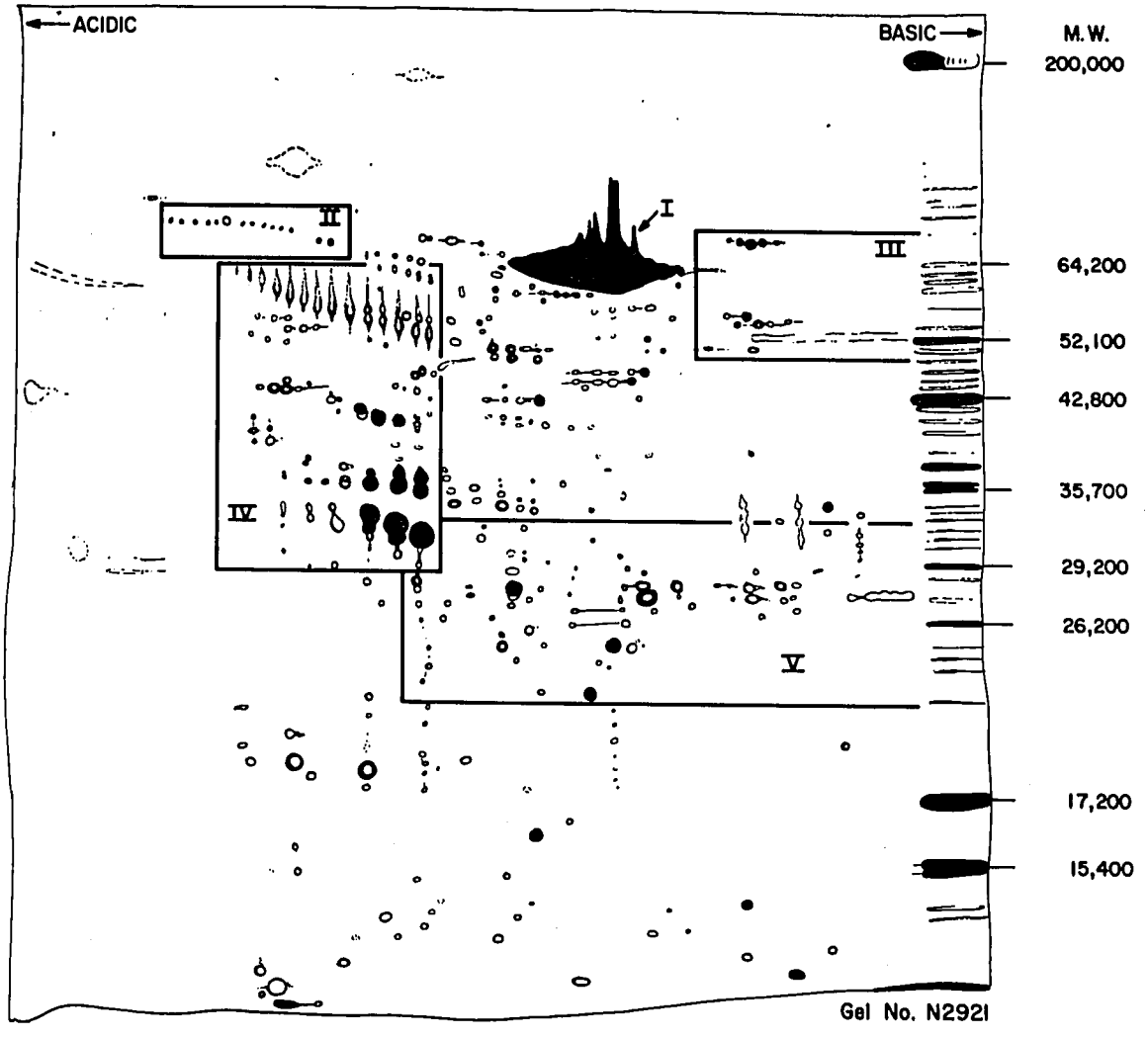

Fig. 5. Human urinary proteins (reproduced with permission from Ref. 12). Proteins in higher concentrations are shown in black for orientation purposes. Rat heart molecular mass standards are shown along right edge.

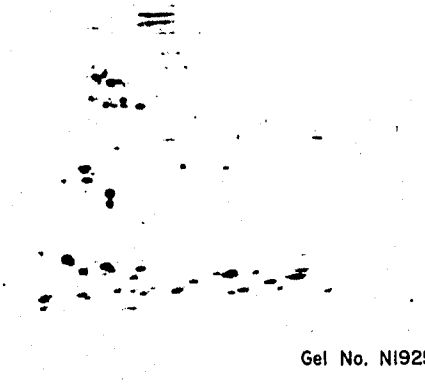

Fig. 6. Urinary proteins in a thorium worker (reproduced with permission from Ref. 12). The predominance of low-molecular-mass proteins in the lower strata suggests tubular damage.

TABLE 5
Markers of Distal Tubular Injury

Measurements of renal concentrating ability
Specific gravity on a spot urine
Specific gravity following water deprivation
Urine osmolality following water deprivation
Urine osmolality following exogenous vasopressin
Measures of urine acidification
Urine pH

rivation. Renal concentrating ability is clearly a general measure of the integration of many physiological functions involving the medulla, the distal tubule, and the collecting system that affect urine concentration. This nonspecificity poses less of a problem than two other factors. First, in field studies it is impossible to ensure that subjects abstain from water during the deprivation period. In some industrial settings such as in hot environments, fluid deprivation would even be contraindicated. Nor can one administer exogenous vasopressin, an alternative stimulus to water conservation. A second source of imprecision in these studies is the use of specific gravity, rather than urine osmolality, as the measure of concentration. Figure 7 shows that specific gravity corresponds rather closely with urine osmolality when the urine is dilute, but diverges increasingly as

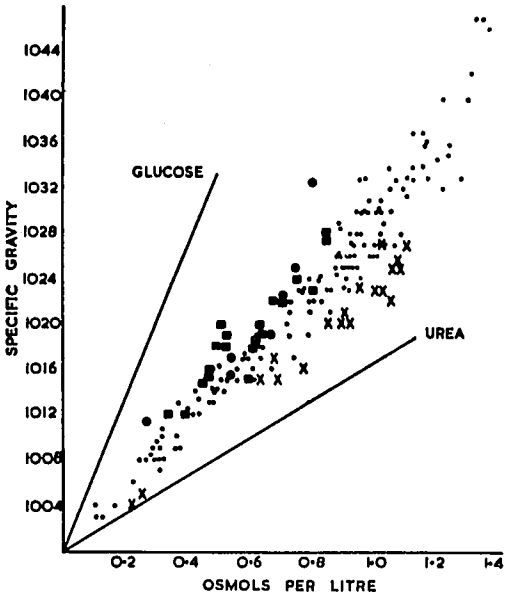

Fig. 7. Relation between osmolality and specific gravity of urine (reproduced with permission from Ref. 10). Different urines are shown as follows: no sugar or protein (·); 3+ sugar (●); 3+ protein (■); after 25 g of urea by mouth (x). The lines show the relation of specific gravity to osmolality for pure glucose and urea solutions.

the urine becomes more concentrated.[10] Although technically simple, measurement of specific gravity is imprecise compared with measurement of urine osmolality using the freezing point method. The practical implication of this imprecision is that a study may be unable to detect small decrements in renal concentrating ability in a study using field methods, when in fact a real decrement exists. The use of a refractometer to measure the refractive index of a solution provides a somewhat better indication of the concentration of dissolved solutes than does specific gravity. This technique is simple, rapid, and easier to use in the field than is that of the freezing point depression.[15]

A final means of examination not yet discussed involves microscopic examination of the urine sediment. Visible changes in the urine sediment occur in a variety of pathological states involving lesions from the glomerulus to the urethra. Neither qualitative nor quantitative microscopy has been used extensively in epidemiological studies of renal disease, even though examination of the urine sediment is considered an indispensable part of the clinical examination of the kidney. At least one epidemiological study has attempted to use quantitative microscopy to count the number of cells and casts in the urine of workers participating in an occupational epidemiological study.[28] Quantification poses certain practical problems because the investigators must (1) standardize the amount of urine studied, (2) standardize either the centrifugation time or use uncentrifuged urine, (3) examine fresh, clean, voided urine samples to avoid degradation of casts in alkaline urine, and (4) have all samples read by a single examiner who is skilled in both microscopy and in the use of a hemocytometer or counting chamber. It remains to be seen whether these logistical difficulties will ever allow quantitative microscopy to become a valuable component of field studies.

Other Factors in Renal Testing

Several other general areas that do not deal with a specific type of renal dysfunction should be discussed. The first was mentioned previously in discussing urinary protein excretion. It concerns the choice of appropriate units for expressing excretion of substances in the urine. Because the volume of a spot urine sample varies greatly in response to hydration, caffeine intake, and other factors, a variety of units have been proposed to adjust or standardize for urine concentration and lean body mass. These include creatinine excretion (mentioned above), time (excretion per 24 hours), specific gravity (standardizing to a specific gravity of 1.024), and body surface area (standardizing to 1.73 m^3). Few studies have systematically examined the usefulness of these different standardization techniques, although several have shown that adjustment for either creatinine or for specific gravity reduces the variation of measurements made on a single individual over a period of time.[29,30]

Another area of controversy involves the appropriate techniques for preserving urine samples to prevent degradation of the substances of interest. In field studies, hours or days may be required to transport the samples to the laboratory. Some measurements, such as specific gravity, must be made promptly before solutes precipitate. In practice, the method of preserving samples must be tailored to the substances to be measured and may be complicated if the preferred technique of preserving urine for one analysis interferes with other desired tests.

Conclusion

This paper has reviewed the advantages and disadvantages of a number of tests of renal function which could be used in occupational epidemiological studies. The review is not intended to be all-inclusive. Certainly, other tests could be added, and the utility of any particular measure will be modified as research provides additional experience. Given the present state of the art, the choice of test for a given setting rests upon considerations of feasibility and on the type of pathology expected from the agent under study. The purpose of using these noninvasive tests is twofold: (1) For the worker, the goal is to detect renal injury at an early stage when the damage is potentially reversible. (2) For the public health practitioner, the objective is early recognition of adverse renal effects so that exposures can be reduced.

In interpreting the meaning of these tests, it is important to distinguish between epidemiological and clinical objectives. Tests used epidemiologically to determine whether there are measurable and/or statistically significant differences between an exposed group of workers and a comparable occupational referent group are not in themselves diagnostic for individual workers.

Differences between groups can occur without any worker being clearly diseased. Establishing a diagnosis for an individual worker requires additional clinical follow-up. For clinical purposes then, the screening tests are primarily useful as a first step to identify those workers for whom more complete diagnostic evaluation is indicated.

In addition, none of the screening tests discussed has been evaluated in a systematic manner that allows us to measure sensitivity, specificity, and predictive power in screening for any particular renal abnormality. Nor has the long-term clinical importance of abnormalities such as β-2-microglobulinuria, been defined. To resolve some of these questions, it will be necessary to examine selected high-risk populations in a controlled clinical setting such as a metabolic research unit or other facility allowing in-patient examination. Any such study group should have prolonged and relatively intense exposure. Prospective studies will be needed to determine decline in renal function over a period of time.

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