DETECTION OF CHRONIC RENAL DISEASE
Past, Present and Future

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> . . . to obtain a more accurate idea of the actual prevalance of the disease . . . in the winter of 1828–9, I instituted a series of experiments, by taking the patients promiscously, as they lay in the wards, and trying the effects of heat upon the urine of each and at the same time employing occasionally other reagents. The whole number I took amounted to 130; out of which no less than eighteen proved to have urine decidely coagulable by heat: and in twelve more traces of albumen were found: giving, therefore, an average of at least one in six, if not one in four of the whole number. (Richard Bright,) Cases and Observations, Illustrative of Renal Disease Accompanied with the Secretion of Albuminous Urine, *Guy's Hospital Reports,* 1, 338, 1836.

The Pisse-Pot-Prophets of medieval Europe used uroscopy to diagnose disease. Four hundred years later, we laugh at them and, perhaps, four hundred years from now, our descendants will laugh at us for our puny efforts aimed at finding chronic renal disease before symptoms appear. One hundred and ten years after Richard Bright's death, the method he developed for finding renal disease in surveys of populations is still the most useful simple test. He boiled the patients' urine in a teaspoon to detect proteinuria. Now the dipstick is used to obtain semiquantitative levels of serum proteins in the urine.

A wide variety of factors causes chronic renal diseases, ranging from genetic to parasitic. Table 1 lists these and an example of each. Members of this conference naturally feel that infections of the kidney with *Escherichia coli* and related organisms constitute the major source of chronic renal disease, but the most common cause the world over is bilharzia (schistosome infestation of the kidney and urinary tract).

TABLE I. COMMON TYPES OF CHRONIC RENAL DISEASES

Genetic (e.g., cystinuria)
Congenital (e.g., polycystic disease)
Nephritis (e.g., chronic diffuse membranous glomerulonephritis)
Vascular (e.g., renal artery fibromuscular stenosis)
Interstitial nephritis (e.g., drug-induced)
Interstitial nephritis with infection (e.g., chronic pyelonephritis)
Infiltrative (e.g., Amyloid)
Granulomatous (e.g., tuberculosis)
"Reactive" or "collagen disease" (e.g., lupus nephritis)
Obstructive uropathy (e.g., bladder neck obstruction)
Parasitic (e.g., bilharzia)

What is the use of finding cases of chronic renal diseases? The real value at the present time would be to provide cases for cooperative studies and therapeutic trials. This problem has been discussed elsewhere[1] and what was written then bears repeating here, especially as the cooperative study of the treatment of lipoid nephrosis in children[41] seems to be going so well. "Reports of the effects of new drugs on the renal pathology of patients need confirmation and these are sometimes hard to come by. For example, the studies by Pollak, *et al.*, on the effects of corticosteroids on the histology and the course of active lupus glomerulonephritis need to be repeated by others. A study was planned at Bethesda, but was not done. Hardwicke, *et al.*, had difficulties in assessing the effects of treatment with one drug in 198 patients with proliferative glomerular changes. What are we then to think of a report, fresh and titillating as it is, in which four patients with hypocomplementemic glomerulonephritis were treated with four different drugs? The reviewer agrees with Hardwicke and his colleagues that, to obtain meaningful data on prognosis and the effects of treatment in renal diseases, we need to set up cooperative studies in centers interested in renal disease wherever they are. Such studies, when properly designed and organized, provide protection for the patient and investigator, adequate numbers of cases for mathematical analyses and clear-cut results which bear, one way or the other, on prognosis."

Long ago in 1949–1950, physicians were disappointed that detecting proteinuria did not allow them to diagnose exactly what was going on in the kidney. They agreed with Addis, who, in 1948, wrote of the hopeless diagnostic problem that was the lot of the physician who found a patient with asymptomatic proteinuria:[2] "Let us consider what happens in the doctor's office, or the outpatient department, when it is

reported that the 'routine' examination shows that the urine has a 'two plus albumin.' In a large proportion of such cases the most searching history and the most exhaustive physical examination fails to reveal any abnormality we can link with the proteinuria. What are we to do, then? Even when we find hypertension, edema, anemia or arteriosclerosis, the relation between these signs and the renal lesion responsible for the appearance of the protein in the urine remains a matter of speculation. It is a question to be decided on grounds of statistical probability, on what pathologists tell us about the frequency of association of various diseases of the kidney, and those external symptoms we observe. It is not determined by anything we can see for ourselves and really know about the patient."

The way out of this impasse was to study the renal histology during life by developing percutaneous renal biopsy.[3] Obviously, renal biopsy is not a useful survey tool, but it is the most valuable laboratory tool available at the present for exact diagnosis of the different kinds of chronic renal disease[4, 5] excluding those like Fanconi's disease, in which genetic disorders of amino acid transport are not associated with renal histologic abnormalities.

The value of renal biopsy is controversial in the diagnosis of chronic interstitial nephritis with infection (chronic pyelonephritis). Some investigators claim that because infection involves the kidney in a patchy manner, a biopsy will not be representative. That is true. However, the renal tissue removed from these patients, if analyzed properly, indicates the presence of histologic change and the diagnosis, but one cannot know very much about the extent of the involvement, its activity, the number of scars and so on. Experiences agree in general with that of J. D. Williams. He wrote that:[6] "Renal biopsy may yield a pathogenic organism in cases of chronic pyelonephritis where repeated urine cultures have proved negative. More frequently, bacteria appear in the urine after biopsy, presumably released into the urinary tract as a result of the trauma of biopsy which causes breakdown of fibrous tissue or inflammatory barriers. The frequency with which helpful bacteriological information has been obtained as a consequence of renal biopsy has been a striking feature of those patients studied at Guy's. In a number of instances pathogenic organisms have been recovered from the first or second urine sample passed after biopsy, and in a few, organisms have been grown from the biopsy material. Of 16 patients whose urine contained both protein and pus cells, in only three had pathogenic organisms been isolated from the urine prior to biopsy. In

one of these three patients a positive culture was obtained only after repeated samples had been examined. Similar organisms were obtained from the biopsy material itself. In seven of this group of 16 patients, histological evidence of chronic pyelonephritis was found."

Simple Methods of Diagnosing Chronic Renal Disease Now and in the Future

No single simple method now exists, and probably never will, with which one can diagnose all cases of chronic renal diseases. The kidney is unique in possessing nephrons, but it is also made up of blood vessels, ground substance and connective tissue, nerve fibers, cells and fat and is heir to all the diseases of these tissue elements. To thoroughly survey all renal diseases in the population would require a flexible multidirectional search for evidence, as perhaps has been done by the Interdepartmental Committee for Nutrition in National Defence when conducting nutrition surveys[7] all over the world. A critical look at the present methods that might be of value in a multidirectional search for undiagnosed chronic renal disease is in order as is an attempt to extrapolate into the future. The traditional approach to the patient whose kidneys are diseased is the clinical one and its component parts are listed in Table 2.

TABLE 2. METHODS OF DETECTING CHRONIC RENAL DISEASE

A. History (e.g., family history of diabetes)
B. Physical Examination (e.g., finding hypertension)
C. Urine examination
    1. Fixed and reproducible proteinuria
    2. Increase or decrease in casts
    3. Fixed and reproducible bacteriuria
    4. Enzymuria
    5. Urinary metapathy
    6. Urinary parasites
D. Blood examination
    1. Immunologic responsiveness
    2. Circulating enzyme abnormality
    3. Metapathy
E. Radiology: magnification contrast radiology
F. Isotopic examination: gamma camera flow distortion
G. Ultrasound examination: pattern distortion
H. Tests of function
    1. Test excretions
    2. Radioisotopes
I. Vital statistics

History. As most of the patients one would like to detect are asymptomatic, history taking is of little value unless directed to specific ends. One such would be genetic, for example, detecting deafness in an inbred population (e.g., in Utah) with familial nephritis (Albright's disease).

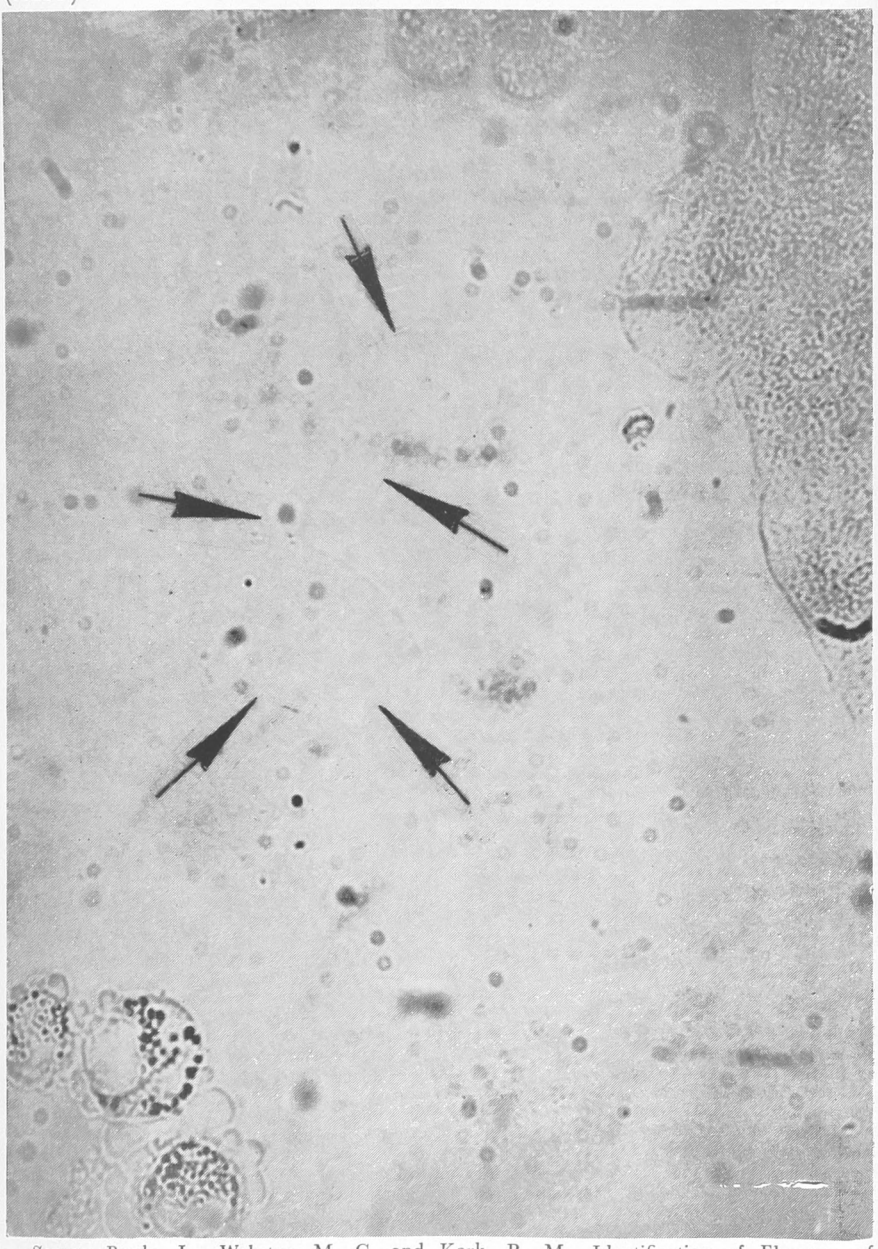
Physical examination. In many cases of chronic renal disease the kidney may be smaller than usual, but one cannot feel this. Physical examination is not of value for early case-finding except for special situations, for example in measuring blood pressure in populations, or listening for abdominal bruits in young women suspected of having fibromuscular disease of the renal arteries, or in looking for readily recognized abnormalities of a congenital nature that might be clues to specific renal diseases.

Examination of the urine. As history taking and physical examination are not fruitful methods for rapidly finding chronic renal disease in a population, the laboratory must be used to seek old and new fruitful ways of case-finding. Examining the urine will be most useful for this effort in the future as in the present. The detection of bacteriuria will not be discussed except to say that very shortly, as a result of Kass' ideas, physicians will demand that some accurate quantitative methods of measuring bacteriuria be done by clinical laboratories each time a standard urinalysis is done. Eventually, this will be done by a dip-stick, either microbiologic or chemical. In fact, Kass will demonstrate at this meeting the Swedish model of his "dip-slide" for quantitative urine cultures.[8] This is now available from the manufacturers.[42]

Proteinuria. Richard Bright's test for proteinuria can be applied to random or to timed urine samples. Presently, clinicians seek quantitative results of total urine protein excreted per unit time, expressed in grams or milligrams per 24 hours, or in milligrams per minute. Indeed, quantitative results per unit time is the scientific way of expressing excretion of all urinary dejecta measured, including cells and casts, and should soon replace the semiquantitative units so widely employed.

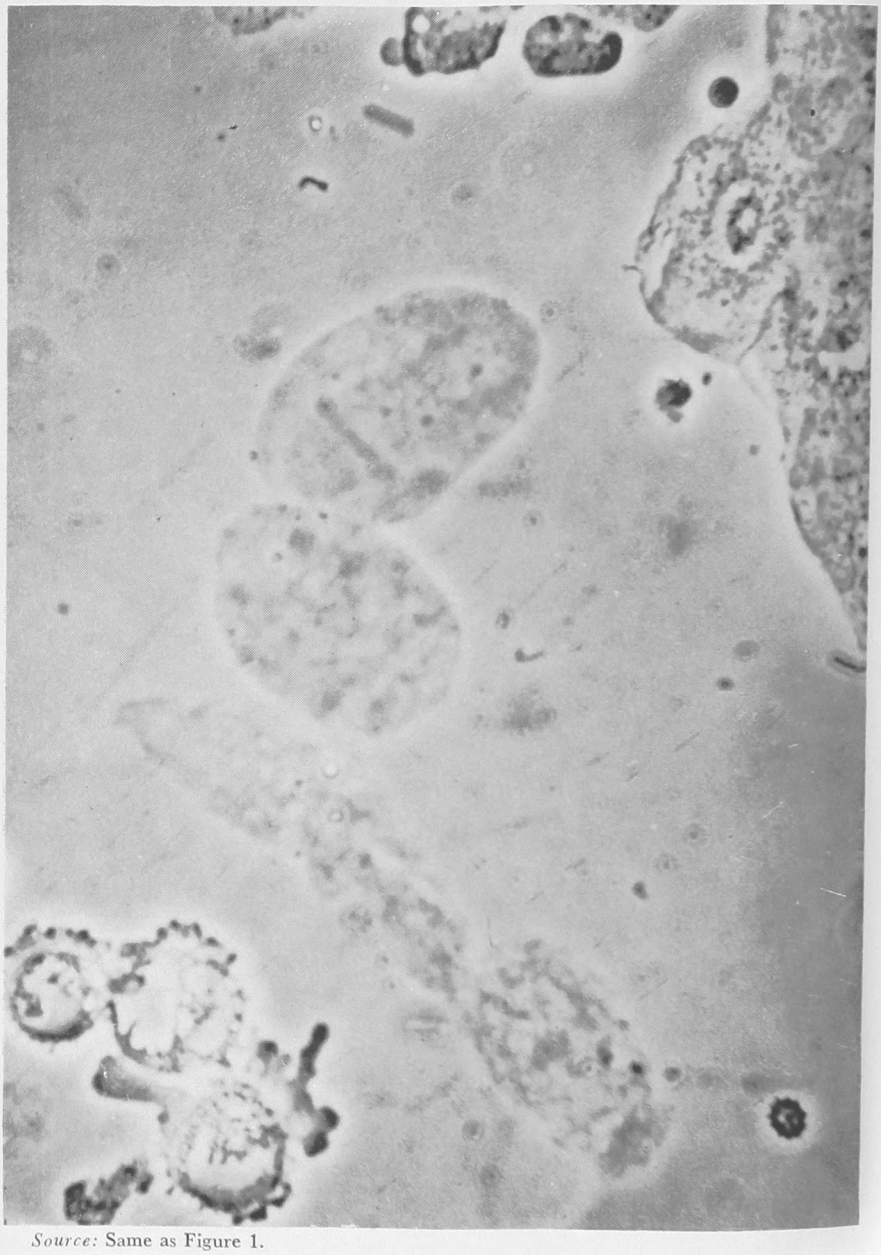
Urinary proteins are derived from the serum and from the mucoproteins secreted by the kidneys and urinary tract. Renal mucoproteins are the Tamm-Horsfall mucoproteins, which are the matrix of all casts.[9] The amount of urinary proteins excreted in health is about 30 mg/24 hours,[10] but insurance firms accept 100 mg/100 ml of a random sample as "normal" and most physicians use an arbitrary upper limit of 150 or even 250 mg/24 hours as "normal." This is probably too high, but reliable ranges for normal by sex and age for any large population are

FIGURE I. BRIGHT FIELD VIEW OF HYALINE CASTS (ARROWS). VAGINAL EPITHELIAL CELLS ARE ALONG UPPER RIGHT AND TOP BORDERS OF FIELD. NOTE THREE SMALL RENAL EPITHELIAL CELLS IN LOWER LEFT CORNER (×400).



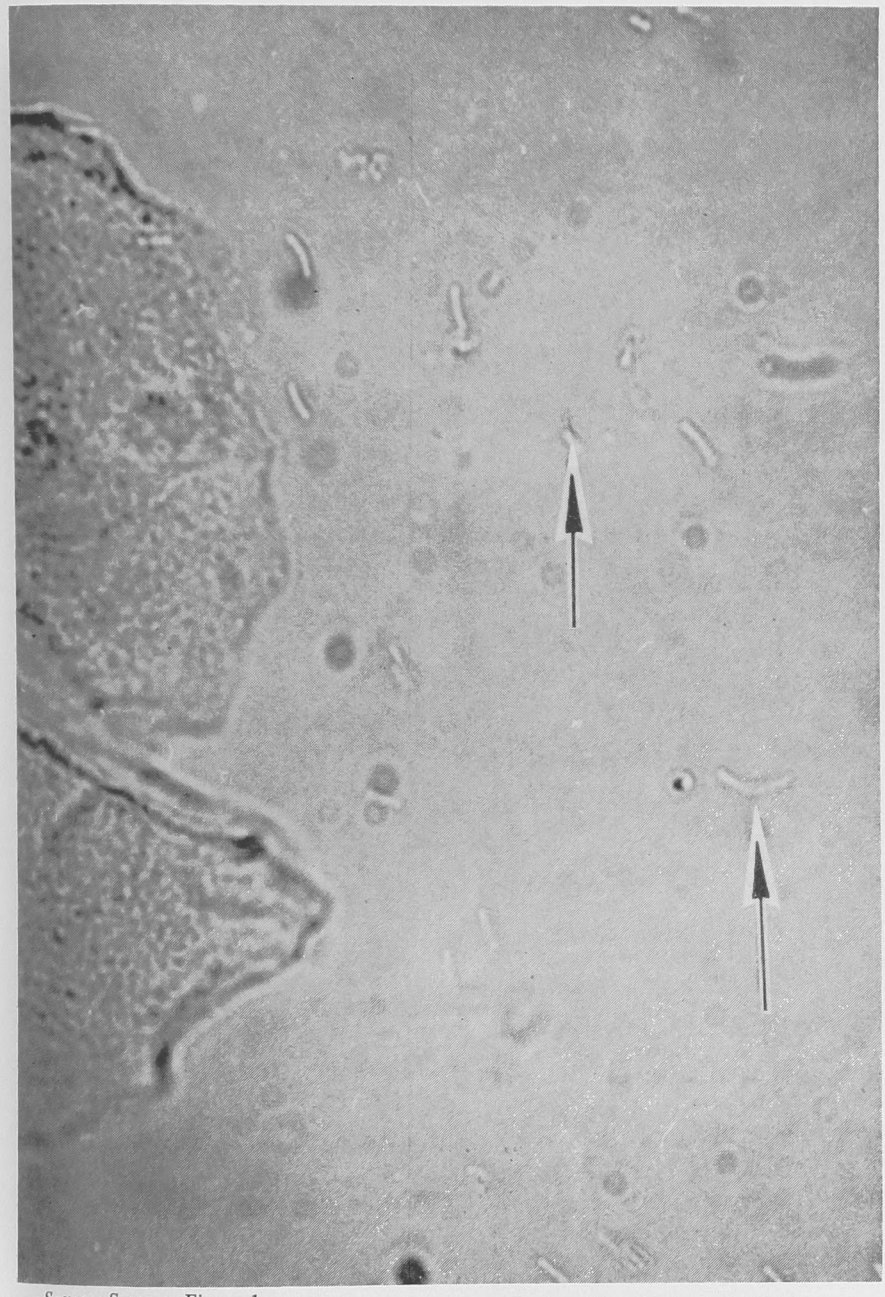
Source: Brody, L., Webster, M. C. and Kark, R. M., Identification of Elements of Urinary Sediment with Phase-Contrast Microscopy, Journal of the American Medical Association, 206, 1777–1781, November 18, 1968.

FIGURE 2. PHASE CONTRAST VIEW OF FIELD IN FIGURE 1. HYALINE CASTS, VAGINAL AND RENAL EPITHELIAL CELLS ARE CLEARLY VISIBLE. ALSO NOTE THREE RED BLOOD CELLS, NOW VISIBLE, TO THE RIGHT OF HYALINE CASTS.



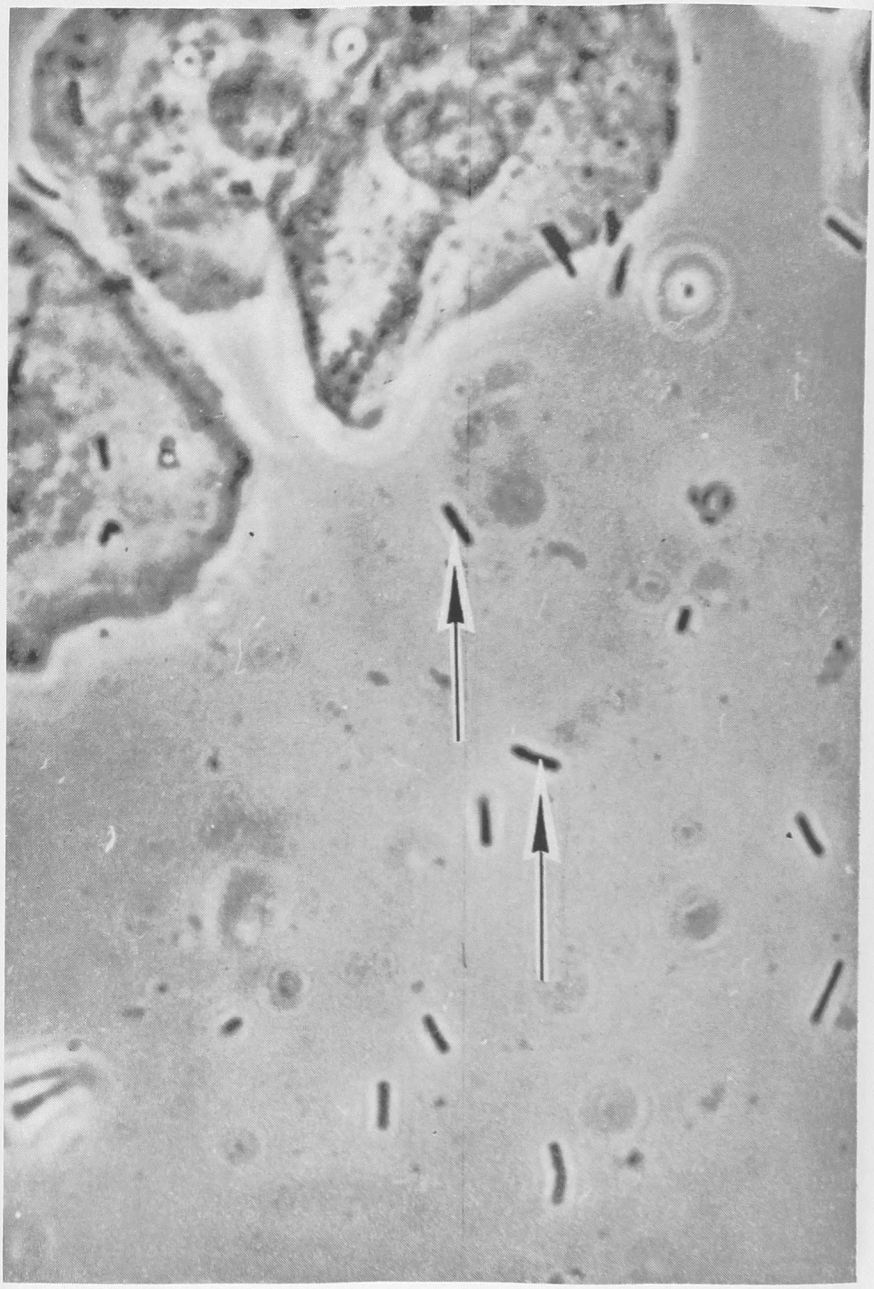
Source: Same as Figure 1.

FIGURE 3. BRIGHT FIELD VIEW OF BACTERIA (ARROWS) AND EPITHELIAL CELLS (×400).



Source: Same as Figure 1.

FIGURE 4. PHASE CONTRAST VIEWS OF SAME SEDIMENT, DIFFERENT FIELD FROM FIGURE 3. HERE BACTERIA (ARROWS) ARE BLACK AND EASY TO DISTINGUISH FROM OTHER DEJECTA IN SEDIMENT (×400).



Source: Same as Figure 1.

few, by modern quantitative methods. *Transient* proteinuria has many causes, from exercise to fever, and in renal disease one finds fixed and reproducible proteinuria.

Gravity affects proteinuria. When healthy individuals or the sick lie flat in bed, their protein excretion per minute is decreased. Thus, orthostatic proteinuria is not a disease entity, but a physiologic reaction. The 14 per cent of adolescents and young adults diagnosed as having "benign orthostatic albuminuria"[11] probably have a "touch of lipoid nephrosis,"[12] which nearly always recovers spontaneously and completely. On the other hand, in the older age group, complete and spontaneous recovery from fixed and reproducible "orthostatic" or "asymptomatic" proteinuria is less common. It has been found that only ten to 15 per cent of patients over age 40 have spontaneous remissions of asymptomatic proteinuria,[13] and in these older patients, as in the young, the most common abnormality responsible for these remissions is lipoid nephrosis. On the other hand, the vast majority of middle-aged patients and older patients with asymptomatic proteinuria have one form or another of potentially serious chronic renal disease.

Proteinuria is usually detected by one of three methods: (a) by boiling the urine; (b) by measuring the precipitate produced when it is treated with sulfosalicylic acid and (c) by use of dip-stick. Rennie and Keene have shown dip-sticks to be reliable in detecting greater than 10 mg protein/100 ml urine and of distinguishing accurately by color depth among various concentrations of protein in urine.

In chronic renal disease, the urinary proteins[14] may be measured or studied after manipulation or separation by electrophoresis, immunoelectrophoresis, immunodiffusion, paper and column chromatography, thin layer chromatography and ultracentrifugation. These techniques may also be useful in the diagnosis of myelomatosis or renal tubular diseases, such as cadmium poisoning. Prior to study, the urine proteins may have to be concentrated by dialysis or by pressure.

Protein clearances[15,16] allow one to plot "slopes of selectivity" based on the molecular size of the serum protein and the varying sizes of the "molecular sieves" or "pores" in the glomerular capillary walls or in tubular cell walls, through which the serum proteins are lost from the blood into the urine. Steep slopes are typical of highly selective renal membranes that allow passage only of serum proteins of small molecular weight. Steep slopes of selectivity are stated to be diagnostic of lipoid nephrosis.[17] Another method of finding out the nature of the renal membrane pore size and of separating normal from abnormal renal

membranes, is to inject intravenously mixtures of radioactive polyvinylpyrrolidone (PVP) of known molecular weight and then to recover and analyze what comes out in the urine. The PVP test might be a very sensitive method for detecting early chronic renal disease. The PVP test and the protein clearance method require refinement—technically and statistically—before they can be of use.

As yet, no serum proteins in the urine are known to be specific for acute or chronic renal infection and no patterns of protein excretion suggestive of infection. In 1958, when "asymptomatic" proteinuria was found in adults and biopsies were done,[13] cases of "chronic pyelonephritis" with and without positive cultures were found.[18] But since then it has been found that the histologic criteria for chronic pyelonephritis are not unique for infection. For example, what pathologists diagnosed in 1958 as "chronic pyelonephritis" they might diagnose in 1969 as "microcystic disease," "interstitial nephritis associated with potassium deficiency" and "interstitial nephritis, the result of drug reaction." In other words, when one talks about "chronic pyelonephritis" he is thinking about a syndrome. It has been called "the chronic renal medullary syndrome" and it includes cases of—among others—chronic interstitial nephritis with infection (which is the new name for chronic pyelonephritis) and other forms of chronic interstitial nephritis such as ischemia, diabetes mellitus, microcystic disease, potassium deficiency, gout, sickle-cell disease, lead poisoning, analgesic "abuse" and drug-induced nephropathy. Simple ways will eventually be found to separate the causes of infective and noninfective chronic renal medullary syndromes. Studying serum proteins or protein clearances may be one way.

Urinary Sediment

Red cells and white cells in the urine. Red cells and white cells come from anywhere in the urinary tract or contaminate the urine from the vagina. Some claim that "Sternheimer-positive" or "glitter" cells arise within the kidney and indicate renal infection.[19] The evidence presented thus far does not substantiate the claims. Excess of white cells or white cell clumps in the urine indicates inflammation somewhere in the urinary tract, and methods more precise than examining the voided or bladder urine are needed to pinpoint the origin of white cells. The same may be said for red cells in the voided or bladder urine.

Increase or decrease in casts. All casts in the urine come from the kidneys. Each day epithelial cell casts, granular casts and hyaline casts are

shed by the healthy kidney. Any decrease or increase in their excretion rate is abnormal. However, the presence of white cell casts or red cell casts is always to be considered abnormal. The replacement of conventional bright-light microscopy with phase microscopy[20] for examining casts is a real forward step in rapid and accurate detection of renal disease (see Figures 1 and 2).

Detection of patients with chronic renal medullary syndrome by quantitative renal exfoliative cytology. Patients with chronic disease of the medulla may well constitute the largest group with asymptomatic and undetected chronic renal disease. Many go through life without knowledge of their renal pathology, which may be found, incidentally, during postmortem examination. Over the years, it has been observed that these patients tend to secrete a singular urine that is pale, in some patients is of a somewhat low specific gravity (± 1.016), contains variable numbers of white blood cells, but shows a decrease in the numbers of small epithelial cells and casts. Moreover, very few hyaline or granular casts and usually no red cell or white cell casts are found in casual examination. In looking further for evidence of renal inflammation, one might have to carefully scan the sediment from 20 or so fresh, early morning urine samples before finding a white cell cast. This clinches the diagnosis of chronic inflammation of the kidney. This sort of search for casts is tedious and time-consuming diagnostic work. What is needed is a rapid screening device to find patients with interstitial nephritis long before they are unexpectedly overwhelmed by renal failure. A method is being investigated to collect and display all casts secreted into urine per unit time. This is done on a specially designed Millipore membrane that allows most of the cells, crystals and debris to pass through it. The retained casts are stained with Brodie-Prescott stain[21] and Ponceau red stain. Thereafter, one can rapidly scan under a dissecting microscope and count and calculate the different kinds of casts excreted per minute. White cell casts stain black, hyaline casts are pink, mixed cell casts are black and red, and so forth. This method is much more discriminating, and more accurate than an Addis count and, in addition, one has a permanent slide for reference.[43]

Phase microscopy for bacteriuria. Kunin has shown that examination of fresh or properly preserved urine for bacteria is useful diagnostically, but notes that crystals and fragments of tissue make recognition of bacteria difficult at times.[22] Phase microscopy[20] makes recognition easy in all urines (Figures 3 and 4).

Parasites, eosinophils, monocytes and other cells in the urine. Various histocytes, monocytes, eosinophils and cells containing viral inclusion bodies are present in some urines. They may have diagnostic meaning in the future. Parasites such as *Giardia lamblia* and eggs of schistosomes may be seen in the urine.

Abnormalities in the blood in chronic renal disease. The late Arnold P. Meiklejohn coined the word "metapathy" to encompass and describe biochemical and metabolic pathologic lesions as opposed to structural pathologic lesions. For example, ketonemia is a metapathic lesion that indicates diabetes mellitus or other metabolic derangement. As yet no metapathic findings are *central* to chronic renal failure, abnormal levels of blood urea nitrogen (BUN) and creatinine, which are applicable for surveys. A dip-stick is available for measuring BUN levels that is useful for surveys.

Both the blood urea nitrogen and the creatinine levels are raised in chronic renal disease and their measurement has become a routine procedure in all hospital admissions and in most office examinations. Unfortunately, when abnormal, they are found to be insensitive tests of renal failure and, if abnormal, usually reflect severe histologic or functional derangements.[27]

Other metapathic lesions in the blood, such as high levels of renal enzymes, may pinpoint early chronic renal disease, but no such tests or battery of tests are available yet.

Immunologic detection of chronic infectious renal disease. When type-specific sera become generally available for the 14 or so *E. coli* types that are clearly pathogenic and for other common gram-negative bacteria, another step forward will have been made. Eventually, one will be able to measure changing titers of these and other renal pathogens like *B. proteus* in the blood when cultural evidence of their presence cannot be found in urine or blood.[24,25] A few immunologic tests are of value in the diagnosis of lupus nephritis and other collagen diseases involving the kidney.

Radiology. For the nephrologist radiology takes the place of physical examination in the diagnosis of renal disease. The scout film, the excretory urogram, the renal tomogram, the timed nephrogram, cinevesicoureteroscopy and selective renal arteriography are of immense value to the clinician, but too cumbersome for routine surveys, save in special circumstances when one is searching for congenital lesions or renal artery stenosis in a population group. Radiologists are beginning

to use magnification radiology and this may have great promise for future diagnostic studies of the kidney. These will be able to pick up readily scars, infarcts and patterns of vascular distortion not easily found today.

Isotope studies and ultrasound disturbances. Methods for detecting disturbances of renal blood flow by using radioactive noble gases and radioactive mercury scans are under study, but are not yet clinically useful. Scans by the gamma camera may become more useful than these two methods for finding distortion in kidneys and in their blood flow, but equipment is expensive and methods are not yet refined enough for general use.

The characteristics of the upstroke of the radioactive Hippuran renogram are useful in the diagnosis of renal artery stenosis. Analysis of both upstroke and excretory phase of the curve is under study with computers in a number of centers. Refinement of instruments, techniques and methods of analysis may make this test of great value in screening patients for renal disease, but cost will probably be prohibitive.

Pattern distortion of ultrasound waves is useful in detecting structural changes and excess fluid in solid organs. The instruments and methods are not yet sufficiently refined to apply routinely to the kidney.

Tests of renal function. The well-known inulin and para-amino hippurate clearance tests and their clinical counterparts, the creatinine clearance and the phenolsulfonphthalein excretion tests are not sensitive enough to detect and discriminate between early cases of chronic renal failure.[26] When one grades by blind systematic review of sections of renal tissue taken by biopsy in a semiquantitative manner from 0 to 4 plus units,[27] it has been shown that tests of renal function, including concentration tests, do not show up as abnormal until considerable damage (3+ to 4+) has developed in the kidneys.[23] Unfortunately, no physiologic "function tests" at this time look even remotely useful for routine detection of early chronic renal failure. Of course, specific tests like the ammonium chloride test for diagnosis of renal tubular acidosis can be used in surveys, but do not have a general application.

Vital statistics. Knowing that certain renal diseases have a high incidence in certain populations (e.g., microcystic lesions in Finland; lead nephropathy in Queensland, Australia) can be of value in organizing detection programs. But until recently, few approved criteria for diagnosis of renal disease were available to the clinician. International committees have been working for a short time and their development of a

TABLE 3. RENAL TISSUE AND TISSUE BREAKDOWN SUBSTANCES IN URINE THAT PROVIDE CLUES TO DIAGNOSIS OF CHRONIC RENAL DISEASE

1. Enzymes (e.g., cathepsin E, glucosyl transferase and medullary L.D.H. isoenzymes)
2. Renal proteins (e.g., basement membrane, metallothionine)
3. Histuria (e.g., Renal, medullary and cortical)
4. Substances adsorbed to casts (e.g., IgA)
5. Reaction products (e.g., Kinins)

uniform nomenclature and criteria for diagnosis of renal disease will speed planning of detection programs.

Renal tissue and renal tissue breakdown or reaction products in the urine. As the urine flows out of the damaged kidney it must contain, besides epithelial cells and serum proteins, a variety of substances, the result of renal parenchymal damage. These substances include bacteria, their antigens and toxins, and products of the reaction between bacteria and renal tissue. In addition, it contains minute fragments of renal tissue, specific renal proteins, renal enzymes, renal hormones and kininogens released by immunologic or chemical damage. During passage down the urinary conduit, all these clues to renal damage are diluted by cells, secretions and other dejecta shed by ureter, bladder and urethra. Looking in the voided urinary specimen for these renal clues to parenchymal damage is like "looking for a diamond in a sewer."[44] Turck, *et al.,* collected renal urine for study from the renal pelves of patients with chronic bacteriuria, by passage of ureteric catheters into the renal pelvis following bladder washout.[28] Obviously this method is not suitable for routine detection of chronic renal disease. However, their studies of uncontaminated renal metapathic products in renal urine will provide a background experience from which methods can be developed to detect and quantitate the same contaminated renal tissue products in voided or bladder urine. Some of the substances under study in different laboratories are recorded in Table 3.

Enzymes. Schwartz and Mattenheimer and their colleagues have been studying the renal arteriovenous differences and urinary excretion of enzymes liberated into the circulation from heart, liver, kidney and other organs.[29] They found that the clearance of circulating organ enzymes across the kidney depends on the molecular size of the enzyme. Small enzymes, such as amylase from salivary glands or pancreas, can pass across normal renal membranes into the urine, but large enzymes (greater than 110,000 molecular weight) are held back. If large en-

zymes, such as lactic dehydrogenase (L.D.H.), appear in the urine then they must arise from the kidneys and not from other organs, unless the renal glomerular membrane has been damaged, which will allow large molecular weight serum proteins into the urine. Some renal enzymes like glucosyl transferase, which takes part in the synthesis of glomerular basement membrane,[30] and renal medullary L.D.H. isoenzymes[31, 32] may eventually pinpoint the locus of damage in the nephron or kidney. At present, interference by inhibitors and release of enzymes from the lower urinary tract interferes with interpretation and all that one can say when large molecular enzymes are in the urine in excess is that they indicate abnormalities in the kidney. Moreover, their presence in urine does not allow one to predict whether the renal disease is trivial or serious.

Cochrane has reported measuring cathepsin E in the urine of rabbits following induction of experimental nephritis.[33] Cathepsin E appears as a result of interaction between leukocytes and complement in the damaged renal environment. Its source is perhaps the leukocytic lysosomes. Lysosomal enzymes, such as acid phosphatase and beta-glucuronidase, are found in voided urine. But if present in excess the cells from which they came cannot be identified, and until one can pinpoint their origin results of studies will be nonspecific.

Renal proteins. Tamm-Horsfall mucoprotein, glomerular basement membrane and metallothionine appear to be unique renal proteins. Tamm-Horsfall protein is a normal constituent of the urine, but thus far no quantitative studies are available that give data for levels of urinary excretion in health and disease.

Recently, McPhaul reported finding glomerular basement membrane in urine and serum from healthy subjects and in those with nephritis.[34] Large amounts of urine have to be extracted for study. More sensitive methods are needed to make the technique useful for general application. If this is done and if McPhaul's observations are confirmed, a most useful and sensitive index may be appearing on the scene for detecting those forms of chronic renal disease that involve the glomerular basement membrane. Metallothionine[35] is an unusual renal protein in that it contains relatively abundant amounts of zinc and cadmium and these elements constitute markers for future detection in urine. It may have functional activity in relation to transport of sodium in the tubule and a possible relation to hypertension.

Histuria. Antoine and Neven have tackled the problem of renal "macromolecules" in urine by raising antibodies to kidneys and using

antihuman kidney sera in immunoanalysis of renal tissue antigens in urine.[36] They looked for and found evidence of "histuria" (i.e., presence of renal tissue macromolecules) in a variety of renal disorders. This is a powerful diagnostic tool presently under study. Antibodies raised from cortex, separately from medulla, hopefully would allow one to extend the potential diagnostic usefulness of the method.

Substances adsorbed to casts. Various proteins are adsorbed to casts in their passage down the tubules. Berger has demonstrated IgA in renal casts in renal biopsies from patients with Henoch-Schonlein purpura. Studies on IgA in casts in voided urine are underway at Presbyterian-St. Luke's Hospital in Chicago.

Reaction products in urine. Reaction products between endotoxin and kidney tissue, and among antibodies, glomerular basement membrane and complement need to be recognized and described. One group of reaction products appearing in the urine are kinins. Rocha e Silva has described the finding of what he calls *kinin hormones* in the urine in relation to renal hypertension, the result presumably of renal release of angiotensin.[38] Other polypeptides[39] are apparently released from renal tissues in experimental hypertension, and these may perhaps be detected in urine. Certainly fragments of fibrinogens, as well as fibrinogen, appear to stimulate crescent formation in damaged glomeruli developing during the course of experimental glomerulonephritis. Some of these circulating fibrinogen breakdown products might also appear in urine and be detected there if they are small enough to pass into Bowman's space.

CONCLUSION

The kidneys are highly integrated organs with tremendous reserve powers. In animals four-fifths or more of healthy kidneys have been removed without development of symptoms of uremia. Everyone is aware of patients fully employed in work and thoroughly involved in pleasure despite contracted diseased kidneys and astronomic levels of blood urea nitrogen or serum creatinine. Small wonder, then, that usual tests of renal function do not accurately reflect minor degrees of renal tissue damage. It is imperative that new simple methods be found to detect early renal damage. Regarding new methods, however, a most pertinent statement was made by William Bosworth Castle about new investigations and their effect on health. What he wrote in 1939 is true not only for early detection of renal disease but also is valid for detec-

tion of bacteriuria, hypertension and chronic pulmonary disease now and in the future. He said: "No matter how important are new discoveries and methods, they cannot be considered to have reached fulfillment until generally applied to the sick."[10]

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