PAPERS AND ORIGINALS

Study of Renal Function in the Differential Diagnosis of Kidney Disease*

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Ever since Richard Bright's (1827) discovery that precipitation in urine heated on a spoon over a candle was diagnostic of kidney disease various tests have been used to assess renal function. For a long time the only aim of these tests was the quantification of the functional residue of the diseased organ, because until relatively recently nothing more effective than a low-protein, salt-free diet could be prescribed for Bright's disease. But now at least some forms of renal parenchymatous disease are amenable to treatment, and their differential diagnosis has become a practical necessity.

Since for the past 50 to 70 years the classification of renal diseases has been based on morphology, it is understandable that attempts to obtain renal tissue for morphological study was the first line of approach in differential diagnosis. However, just as a pathogenic agent affects the morphology of cells and tissues so it affects their function. By learning how to recognize and interpret functional changes patterns of abnormality will be obtained which may be as diagnostic as abnormal patterns in morphology.

Glomerular Lesion

A simple narrowing of the major or minor renal vessels, which reduces the glomerular filtration rate, leads either to no proteinuria or, owing to an enhanced diffusion of protein from prolonged contact of the plasma in the glomerular capillaries with the glomerular filtrate, to only a slight proteinuria which does not usually exceed 2 g/24 hours. However, a lesion of the glomerular basal membrane, encountered in an almost pure form in membranous glomerulonephritis and renal amyloidosis, is always accompanied by a pronounced escape of protein

from the plasma into the glomerular filtrate and into the urine (Fig. 1). The result is a severe proteinuria, exceeding as a rule 4-5 g/24 hours. Larger protein molecules appear in the urine with increasing severity of the lesion and proteinuria becomes "unselective," as shown by Hardwicke (1965) and by Lambert *et al.* (1968) in studies of clearances of macromolecular substances. The resulting protein depletion initiates the nephrotic syndrome, which is a prominent feature of many patients with this type of lesion. These purely membranous lesions as a rule bleed only very little or not at all. Proliferative glomerular lesions, on the other hand, are not necessarily linked with a marked proteinuria, but lead for some reason which is not well understood to a pronounced microscopical and occasionally even macroscopic haematuria (Fig. 1).

FIG. 1—Urine changes in proliferative and membranous glomerular disease (verified by biopsy).

*Based on the Lilly lecture delivered to the Royal College of Physicians of London on 26 February 1971.

The assessment of the glomerular filtration rate, its diurnal variability, and the degree of proteinuria and haematuria (if a subrenal origin can be excluded) therefore defines the nature of the glomerular lesion.

Tubular Function

A variety of methods could be used to study tubular function, and the various saturation procedures have an important place in the investigation of the primary tubulopathies. For practical purposes a study of the concentrating ability, especially when related to the glomerular filtration rate, seems most useful.

It has been established that when the osmotic load per nephron is increased the urine flow rises and its osmolality gradually drops and approaches isotonicity (Fig. 2) (Hervey *et al.*, 1964). Platt (1952) pointed out that when most of the nephrons are obliterated by disease the remaining ones must receive a larger load of urea, and the osmotic diuresis thus produced is responsible for the polyuria and the decrease in concentrating ability seen in chronic renal failure.

FIG. 2—Correlation between urine flow and urinary osmolality in osmotic diuresis (Rapoport *et al.*, 1949). Note that with an increasing urine flow, when the osmotic load per nephron is increased, the urinary osmolality (expressed as the osmotic concentration index U/P) decreases and approaches unity—that is, the osmolality of the plasma P. Reproduced by permission of *American Journal of Physiology*.

This explanation is probably adequate in cases where the maximum osmolality of the urine decreases in proportion to the decrease in the glomerular filtration rate, as in most patients with chronic glomerulonephritis, but it is probably inadequate in those cases of hyposthenuria or isosthenuria in patients with a normal or only slightly reduced glomerular filtration rate often encountered immediately after a bout of renal colic in nephrolithiasis or in convalescents from acute pyelonephritis. Nor is osmotic diuresis an adequate explanation for those instances of isosthenuria when the urinary osmolality is fixed below that of the plasma and the glomerular filtrate (below 300 osm), as is often seen in advanced cases of chronic pyelonephritis, in polycystic kidney disease, and in acute renal failure. This defect can be correlated with the marked tubulointerstitial changes known to be present in these circumstances.

The opposite end of the curve in Fig. 2 is no less interesting. It shows the high urinary osmolality attained when the osmotic load is reduced. This phenomenon, demonstrated for the first time in dogs with diabetes insipidus by Shannon (1942) and confirmed in a different experimental approach by Del Greco

and de Wardener (1955) and by Berliner and Davidson (1956), is possibly responsible for the relatively high urinary osmolality under conditions of renal vasoconstriction (unless the sodium delivery to the renal medulla is reduced), and is possibly responsible also for the high urinary osmolality in conditions in which the glomerular capillaries are gradually obliterated, such as vascular nephrosclerosis. Thus one may conclude that a decrease in concentrating ability more or less parallel with the reduction in the glomerular filtration rate indicates that a corresponding number of nephrons have ceased to function. A disproportionate decrease in the concentrating ability in comparison with the reduction in the glomerular filtration rate suggests that the changes are predominantly tubulointerstitial. A decrease in the glomerular filtration rate with a relatively stable concentrating ability suggests a reduced glomerular filtration rate per nephron.

Irregularity of Distribution of the Renal Lesion

The irregularity of spread of some pathological conditions can be demonstrated, if marked, by renal scintigraphy and by the asymmetrical distribution of radioactivity to the two kidneys in radionephrography, by the large differences in the creatinine concentration on each side, such as is seen in chronic pyelonephritis, or by the unreliable split renal function tests. Radiography adds substantial information not only about the position, size, and shape of the kidneys and the renal hollow space but also about the function of the calices, pelves, and ureters.

Most of these functional studies can be carried out in a small hospital. They are listed, with their normal values, in Table I. We found they can be carried out easily in ambulatory patients in the course of three to four days (Fig. 3).

FIG. 3—Programme of the functional investigation of the kidney.

Classification by Function

Most of these functional abnormalities could form a basis for the classification of renal disease. However, we found the most useful classification of renal lesions to be correlation of the

TABLE 1—List of Obligatory Methods and Normal Limits in Nephrological Examination

Proteinuria	..	..	..	..	0.3 g/24 hr.
Urinary Deposit Qualit.	..	..	..	..	
Addis count { Erythrocytes	..	..	..	..	2 mil./24 hr.
Leucocytes	..	..	..	..	2 mil./24 hr.
Casts	..	..	..	..	0.1 mil./24 hr.
Bacteriology of urine	..	..	..	..	10 ⁶ microbes/ml urine
Glomerular filtration rate (endogenous creatinine clearance)	..	..	..	..	100-150 ml/min
Maximum concentrating ability	..	..	..	..	>1,028 (900 mOsm)
Isotope Nephrography (or other test of symmetry)	..	..	..	..	Symmetrical
Radiology (I.V.P. etc.)	..	..	..	..	
Plasma urea and creatinine, plasma proteins, plasma cholesterol, plasma electrolytes	..	..	..	..	

glomerular filtration rate and concentrating ability, which we suggested 9 years ago (Brod, 1963). (Table II).

TABLE II—Functional Classification of Renal Diseases

(1) Glomerular filtration rate restricted more than concentrating power
On haemodynamic basis:
Orthostatic proteinuria
Emotional proteinuria
Exertional proteinuria
Heart failure
Essential hypertension (stage I, W.H.O.)
On organic basis:
Without grave changes of the capillary wall:
Vascular nephrosclerosis (essential hypertension stage III, W.H.O.)
With grave changes of the capillary wall:
Diabetic glomerulosclerosis
Renal amyloidosis
Toxaemia of pregnancy
(2) Parallel reduction of glomerular filtration rate and concentrating power
Glomerulonephritis
(3) Concentrating power reduced more than glomerular filtration rate
Interstitial nephritis (chronic pyelonephritis, etc.)
Polycystic kidney disease
Shock kidney

Filtration Rate Reduced more than Concentrating Ability

A condition in which the glomerular filtration rate is reduced more than the concentrating ability can be due to vasoconstriction in the kidney, or to narrowing of the major or small renal vessels, or to an organic obliteration of the glomerular capillaries. All these will reduce the glomerular load of osmotically active urinary solutes, and unless the sodium delivery to the loop of Henle is restricted to the extent of abolishing the medullary sodium gradient they will lead to a high urinary osmolality in face of a reduced glomerular filtration rate. The difference between conditions based on vasoconstriction and those due to an organic disease is in the temporary nature of the first and the permanency of the second. The difference between conditions due to interference with the glomerular blood supply and disease of the glomerular capillary tuft is in the amount and nature of the protein in the urine and in the urinary deposit.

HAEMODYNAMIC CAUSES

Benign cyclic proteinuria (orthostatic, exertional, or emotional) is due to adjustment to a circulatory emergency, with preferential blood supply to the muscles, myocardium, and brain and vasoconstriction in the kidneys, splanchnic area, and skin (subject in the case of the skin to thermoregulatory requirements). The accompanying reduction in the glomerular filtration rate is not so pronounced as the sympathetically mediated renal vasoconstriction which induces it, and the filtration fraction rises. This change in renal function is necessarily temporary and lasts only so long as the stimulus that initiated it exists. It is absent at night while at rest.

Renal vasoconstriction would pass unnoticed but for the enhanced protein diffusion into the glomerular filtrate made possible, if our present views are correct, by the longer contact of the glomerular filtrate with the plasma flowing more slowly through the glomerular capillaries. Chance discovery of a transient proteinuria may cause alarm, especially when accompanied by hyaline or granular casts and tubular cells in the urinary deposit. Hyaline casts, however, merely signify that the Tamm-Horsfall mucoprotein, which is permanently excreted in small amounts by the tubular cells in the urine, has been converted from sol to gel by the albumin in the tubular urine, and formed casts (McQueen, 1966). Granular casts originate in tubular cells loaded with reabsorbed protein and degenerated by it (Addis, 1948). Protein losses under these circumstances are always slight, usually not exceeding 2 g/24 hours, and the proteinuria is selective. A wrong diagnosis can easily be avoided by making it a rule always to examine a morning specimen of urine.

Some diagnostic difficulties could be encountered in patients with heart failure. In these cases the reduced renal blood flow and glomerular filtration rate leading to proteinuria may persist during the whole day. At night, however, the cardiac output may be sufficient for the reduced body requirements, and the renal blood flow and glomerular filtration rate increase despite the cardiac output remaining unchanged (Fig. 4). An erroneous assessment of the significance of the proteinuria can therefore be avoided if the day and night glomerular filtration rates are estimated separately—or preferably every three to four hours over the 24 hours. A rise at night to normal (Fig. 5) proves that the cause of the daytime reduction is not organic. As in benign cyclic proteinuria the urinary protein losses do not usually exceed 2 g/24 hours, and similarly small numbers of casts and cells may be found in the urinary deposit (Fig. 6).

FIG. 4—Changes in cardiac output and renal haemodynamics and function during the nocturnal rise of urine flow (nocturia) in a subject with chronic heart failure. (Brod and Fejfar, 1950). Note that the increase in urine flow and electrolyte (chloride) excretion ($U_{Cl} \cdot v$) runs parallel with the increase in the renal blood flow, this being due to a shift of the cardiac output to the kidneys (increase in the renal fraction of the cardiac output). The increase in the urine flow is partly due to a rise of the glomerular filtration rate, but mainly to the simultaneous drop of the tubular reabsorption of water (decrease in the inulin concentration index— $U/P \text{ inul.}$). The drop in the filtration fraction is suggestive of a decrease in pressure in the glomerular capillaries, possibly due to a release in the tone of the efferent arteriole. Reproduced by permission of *Quarterly Journal of Medicine*.

ORGANIC CAUSES

Similar conditions are encountered in the early stages of essential hypertension before any organic narrowing of the afferent arterioles develops. The decrease in blood flow is still reversible under the influence of pyrogens (Smith *et al.*, 1943) or at night (Brod and Fencil, 1958), and in these cases also the slightly reduced glomerular filtration rate which may be present during the day is probably the reason for traces of protein in the urine. The urinary deposit is trivial and the concentrating ability high.

The development of renal vascular changes in nephrosclerosis interferes gradually with the delivery of the glomerular filtrate to the individual nephrons and the average daily glomerular filtration rate gradually gets less, but the concentrating ability, for reasons explained above, may remain surprisingly good

FIG. 5—Diurnal rhythm of the glomerular filtration rate in a normal subject and in a patient with chronic heart failure. Note that in the cardiac subject the glomerular filtration rate is low during daytime and rises at night to the same level to which the glomerular filtration rate falls in a normal subject.

FIG. 6—Urine changes in 18 subjects with heart failure.

(Fig. 7). In long-established renal disease, however, when pronounced interstitial fibrosis may have developed, the concentrating ability may be markedly reduced. Its finding does not therefore exclude a diagnosis of vascular nephrosclerosis.

Except in cases of malignant hypertension, when necrotic changes in the glomerular capillaries with severe cellular reaction may cause marked proteinuria and an increase in erythrocytes and leucocytes in the urinary deposit, proteinuria is usually absent or slight in an uncomplicated case of vascular nephrosclerosis, and the urinary deposit is small (Fig. 8). The clinical findings in vascular nephrosclerosis are summarized in Table III.

Renovascular hypertension (renal artery stenosis) and the Conn syndrome must be differentiated from essential hypertension. It is now certain that renal artery stenosis can also exist in hypertensives without signs of malignancy or causing a rapid progression of the disease. Two points are of value in differentiating renal artery stenosis from essential hypertension. Investigating 350 unselected patients with hypertension diagnosed as essential, Hejl *et al.* (1964) found that in subjects below the age of 50 a severe stenosis was encountered only in stages II and III (W.H.O. classification) (Fig. 9). This means that stenosis need not be looked for in a large number of hyper-

FIG. 7—Correlation between glomerular filtration rate and maximum concentrating ability in patients with a glomerular (vascular nephrosclerosis, renal amyloidosis, diabetic glomerulosclerosis), and tubulointerstitial (chronic pyelonephritis) disease. All diagnoses were verified by renal biopsy or necropsy.

TABLE III—Vascular Nephrosclerosis

Proteinuria	..	..	..	±	Asymmetry	..	..	0
Addis count	..	..	..	Trivial	Radiology	..	..	0
Bacteriuria	..	..	..	0	Nephrotic syndrome	..	..	0
Conc./G.F.R.	..	..	..	→	Hypertension	..	..	100%

FIG. 8—Urine changes in 23 subjects with vascular nephrosclerosis verified by renal biopsy in all cases.

tensives. Rapid sequence intravenous pyelography (Maxwell, *et al.*, 1964) and isotope nephrography (Hornych *et al.*, 1962) (Fig. 10) show an asymmetry of the renal lesion or abnormal nephrograms in up to 95% of cases. These must be subjected to a thorough study by split renal function tests, Rapoport or Stamey tests, and aortography.

Except for the asymmetry, the clinical findings, for understandable reasons, are similar to those in vascular nephrosclerosis (Table IV). The Conn syndrome can be differentiated from essential hypertension by the early loss of renal concentrating ability due to potassium depletion and by the reversed K^+/Na^+ ratio in the urine (Table V). A Conn tumour should be looked for in hypertensives with such findings by

investigating plasma renin activity, aldosterone secretion or excretion, retroperitoneum, etc.

FIG. 9—Distribution of renovascular hypertension according to the grade of hypertension (W.H.O. classification) and to age (after Hejl *et al.*, 1964). a = <30 years. b = 30-49 years. c = 50-59 years. d = 60+ years.

TABLE IV—Renovascular Hypertension

Proteinuria	..	..	..	0-±	Split renal function	Asymmetry
Addis count	..	..	..	Trivial	Howard or Stamey test	..
Bacteriuria	..	..	..	0	Aortography	..
Conc./G.F.R.	..	..	..	↑	Nephrotic Syndrome	..
Asymmetry	..	..	..	+	Hypertension	..
Radiology	..	..	..	+		+

Diabetic Glomerulonephrosis and Renal Amyloidosis.—The remaining organic conditions which initially affect the glomerular function are diabetic glomerulosclerosis, renal amyloidosis, and toxæmia of pregnancy. A feature common to all three are changes in the glomerular capillary wall, caused in the first two conditions by a deposit of mucoproteins and mucopolysaccharides into the basal membrane and in the third by swelling of the endothelial cells without any pronounced proliferation of the cells of the glomerular tuft. This leads therefore to a marked proteinuria, to body protein depletion, and to a nephrotic syndrome. As in the membranous lesions, there are few erythrocytes and leucocytes in the urine and the casts may be numerous. The concentrating ability in most cases is surprisingly good compared with the glomerular filtration rate unless cylinders of amyloid form round the papillary ducts and interfere with osmosis. Clinically apparent diabetic glomerulosclerosis hardly ever occurs in diabetics of less than 8 to 10 years' standing and typical diabetic retinopathy was absent in only 5% of our patients (Table VI). Renal amyloidosis is, of course, most unusual without an initiating cause, and, unlike all other parenchymatous renal diseases, it is accompanied by hypertension in only 17% of instances, mostly when the disease has progressed finally to renal failure (Table VII).

Toxæmia of Pregnancy.—The differentiation of toxæmia of pregnancy from essential hypertension and glomerulonephritis should present no particular difficulties if the functional renal criteria are carefully considered (Table VIII). Essential hypertension never leads to a marked proteinuria nor to a nephrotic syndrome, and casts in the urinary deposit are exceptional. Haematuria is a prominent feature in glomerulonephritis of the proliferative type and the concentrating ability may be more reduced than in the nephropathy of pregnancy. Pure mem-

TABLE V—Conn Syndrome

Proteinuria	..	..	..	0-±	Nephrotic syndrome	..	0
Addis count	..	..	..	Trivial	Hypertension	..	+
Bacteriuria	..	..	..	0	Urinary K ⁺ /Na ⁺	..	↑
Conc./G.F.R.	..	..	..	↓	Plasma K ⁺	..	↓
Asymmetry	..	..	..	0	Plasma HCO ₃	..	↑
Radiology	..	..	..	0			

TABLE VI—Diabetic Glomerulosclerosis

Proteinuria	..	..	..	+++	Asymmetry	..	0
Addis count	{ Erythrocytes	..	..	±	Radiology	..	0
	{ Leucocytes	..	..	(+)	Nephrotic syndrome	..	+
	{ Casts	..	..	+++	Hypertension	..	70%
Bacteriuria	..	..	..	0	Diabetes mellitus	..	>8 years
Conc./G.F.R.	..	..	..	↑	Diabetic retinopathy	..	95%

TABLE VII—Renal Amyloidosis

Proteinuria	..	..	..	+++	Conc./G.F.R.	..	↑
Addis count	{ Erythrocytes	..	..	±	Asymmetry	..	0
	{ Leucocytes	..	..	(0)	Radiology	..	0
	{ Casts	..	..	+++	Nephrotic syndrome	..	80-90%
Bacteriuria	..	..	..	0	Hypertension	..	17%

TABLE VIII—Differential Diagnosis of Toxæmia of Pregnancy

	Toxæmia of Pregnancy	Essential Hypertension	Glomerulonephritis
Proteinuria	..	++	0-±
Addis count	{ Erythrocytes	..	0
	{ Leucocytes	..	0
	{ Casts	..	0
Bacteriuria	..	0	0
Conc./G.F.R.	..	↑	0
Asymmetry	..	0	0
Radiology	..	0	0
Hypertension	..	+	- or +
Nephrotic syndrome	..	+	+

branous glomerulonephritis may present a difficulty in differential diagnosis unless it is one of the 36% of cases that have erythrocytes in the urine and unless the immunoglobulins in the blood are studied—which, in my experience, are raised.

Parallel Reduction of Filtration Rate and Concentrating Ability

GLOMERULONEPHRITIS

Under this heading are listed the various forms of glomerulonephritis, whether primary or secondary to a systemic disease—for example, disseminated lupus erythematosus. The pathogenicity of the two basic types, proliferative and membranous, may possibly be different—the first being a response to the fixation of the non-specific antigen-antibody complexes in the form of lumps on the wall of the renal capillaries, and the second being due to a fixation of antibodies along the basement membrane of the capillaries, the obvious implication being that the basement membrane itself is the antigen. As I have explained, the two lesions can be distinguished by examining the urine and its deposit and by the fact that the nephrotic syndrome is very often present in the membranous type and absent in the proliferative. Both lesions can sclerose and ultimately cause chronic renal failure (usually heralded by the advent of hypertension), but progression to this is as a rule very slow (Fig. 11).

In addition to these two basic lesions at least three other histological patterns have been shown by biopsy to exist in clinical glomerulonephritis. They are: (1) the membranoproliferative type, which cannot be viewed as a simple combination of the two basic lesions but rather as a consequence of a pronounced proliferation of the mesangial cells and an exaggerated

TABLE IX—Differential Diagnostic Criteria of Various Biopsy Types of Glomerulonephritis

	Proteinuria	Haematuria	Leucocyturia	Casts	Hypertension	Nephrotic syndrome	Progression
Minimal residues ..	±	±	±	—	±	—	None
Proliferative ..	+→++	+→++++	±	±	±	—	?
Membranous ..	++++	→+	±	++	±	+++	?
Membrano-proliferative ..	+→++++	+→++++	±	+→++++	+→+	+++	Slow
Lobular ..	++++	+→++++	+	+→++++	++	+++	Slow
Extra-capillary ..	++++	+→++++	+	+→++++	+++	+++	Fast

FIG. 10—Isotope nephrogram and renal scintigram in renal artery stenosis (courtesy of Professor Hundeshagen).

formation of the mesangial matrix; (2) the lobular type, which is possibly a further developmental stage of the membranoproliferative; and (3) the extracapillary type with a pronounced proliferation not only of the mesangial cells but also of the capsular epithelium.

In these three types proteinuria exceeding 5 g/24 hours is present in 56.2% of cases in type 1, in 65.3% of type 2, and in 95.5% of type 3; a marked microscopical haematuria is present in 32.3% of cases in type 1, in 51% of type 2, and in 80.8% of type 3; and a marked cylinduria in 32.5% of type 1, in 44.8% of type 2, and in 75% of type 3. In 20.4% of the lobular type of

FIG. 11—Prognosis of the various biopsy types of glomerulonephritis.

cases and in 29.8% of the extracapillary type leucocytes in the urinary deposit are increased along with the erythrocytes (it is, of course, necessary to exclude infection of the urinary tract) (Fig. 12).

Because of the severe loss of protein the nephrotic syndrome is often present in all three types, and hypertension is a frequent finding in the lobular and extracapillary types, even before the glomerular filtration rate has been greatly reduced. The disease progresses slowly in some 50% of the patients with the membranoproliferative or lobular type, and fast in 10% with the lobular and in 61% with the extracapillary type (Fig. 11).

Another type which must be added to the list is represented by the minimal residual lesions in the form of small scars and thickenings of the mesangium and synechiae of the glomerular loops and the capsule which are often found after an acute glomerulonephritis. There is only a slight residual proteinuria in these cases, and a few erythrocytes, leucocytes, and casts in

FIG. 12—Urine changes in subjects with various biopsy types of glomerulonephritis.

the deposit (Fig. 12). The nephrotic syndrome and hypertension are rarely present, and the lesion does not progress (Fig. 11).

The differential diagnostic criteria by which the various types of lesion may be distinguished are summarized in Table IX. From the data in Fig. 11 it is obvious that this differentiation is not only of academic interest but also of great practical significance. It separates with a probability of 82% those cases which will not progress within five years from those which will (Brod and Rossmann, 1969). No therapeutic inferences can as yet be drawn from the differentiation of the various types of glomerulonephritis, but since the pathogenicity of some is possibly different, and since some patients with glomerulonephritis respond to some therapeutic agents, such as corticoids, antimetabolites, or heparin, and others do not, it is obvious that only by perfecting differential diagnosis can further progress in treatment be hoped for.

Concentrating Ability Reduced more than Filtration Rate

The different kinds of interstitial nephritis (with chronic pyelonephritis as its most important representative), polycystic kidney disease, and shock kidney will be discussed under this heading.

INTERSTITIAL NEPHRITIS

The discrepancy between the decrease in concentrating ability and the reduction in the glomerular filtration rate can be seen in the downward shift of the line correlating maximum concentrating ability and glomerular filtration rate in cases of chronic pyelonephritis compared with that in purely glomerular disease such as renal amyloidosis, diabetic glomerulosclerosis, or vascular nephrosclerosis (Fig. 7) (Brod, 1956). This is due, no doubt, to the functional damage of the tubular cells (Fig. 13). The relatively unrestricted glomerular filtration rate accords with the finding of normal glomeruli even in a severely damaged

FIG. 13—Electronmicroscopical picture of the interstitium and tubular wall in chronic pyelonephritis (courtesy of Professor Mohr). Note the invasion of *Escherichia coli* (dark oval or red-shafted structures) into the tubular epithelium.

portion of the kidney. However, the glomeruli may be strikingly intact even in advanced cases with the filtration rate reduced below 20 ml/min. Since the clearances of endogenous creatinine and inulin are usually identical in these cases, this can hardly

be due to a leak of the clearance substance through the damaged tubular wall, and the explanation must be sought in haemodynamic factors—perhaps in the compression of the intrarenal vessels by the interstitial infiltrate and scars. This is possibly also the reason for the slight proteinuria found in 90% of patients with pyelonephritis. In the remaining 10% glomerulitic changes, due to spread of the inflammatory process across the Bowman capsule or perhaps to allergic phenomena, are responsible for a more pronounced proteinuria, which indicates a bad prognosis.

However, another reason for the proteinuria must be considered. Traeger *et al.* (1964) showed that in most cases of pyelonephritis proteins of tubular origin appear in the urine together with plasma proteins, and Hall *et al.* (1967) found a tubular pattern of the urinary proteins in cases of Balkan nephropathy with predominantly interstitial changes. The urinary deposit consists mainly of leucocytes in numbers corresponding to the degree of bacteruria. In most patients with chronic pyelonephritis the leucocyte count is usually less than 50 million in 24 hours when infection is kept under control. Erythrocytes may predominate, however, in cases secondary to nephrolithiasis or tumour of the urinary tract (Fig. 14). Casts rarely exceed one million in 24 hours and may be entirely absent. The finding of a leucocyte cast, however, is diagnostic. In florid infections the infecting agent may be found in the urine. They are of five kinds in chronic pyelonephritis: *Escherichia coli*, *Aerobacter aerogenes*, *Proteus*, *Pseudomonas aeruginosa*, and *Streptococcus faecalis*, and they number at least 10⁵/ml urine.

FIG. 14—Urine changes in 27 subjects with chronic pyelonephritis (verified by biopsy).

More often than in other diseases, the maximum urinary osmolality in patients with a far advanced chronic pyelonephritis is fixed at values below those of the glomerular filtrate (300 mOsm, specific gravity 1012) (Fig. 7).

The irregular spread of infection through the renal interstitium may be detected by renal scintigraphy, by differences in creatinine concentration in the urine from the two sides, by isotope nephrography or by serial intravenous pyelograms. These will show, in addition, irregularities in renal contour, uneven thickness of the renal parenchyma, dilatation and distortion of the renal calices and fornices, flattening of the papillae, loss of ureteric tone, and reduced motility of the calices and pelvis (Dejdar, 1959) (Fig. 15). The diagnostic criteria in chronic pyelonephritis are summarized in Table X.

TABLE X—Chronic Pyelonephritis

Proteinuria	..	..	±—+	Conc./G.F.R.	..	..	..	↓
Addis count	Erythrocytes	..	±—+	Asymmetry	..	..	..	+
	Leucocytes	..	±—+	Radiology	..	..	..	+
Bacteriuria	Casts	..	0—+	Nephrotic syndrome	..	..	..	0
	..	..	0 or +	Hypertension	..	..	..	60%

POLYCYSTIC KIDNEY DISEASE

This disease, especially when the kidneys are infected, has practically the same functional pattern as chronic pyelonephritis. In the absence of infection and bleeding the urine, of course, is sterile and there are no leucocytes or erythrocytes in the deposit. The presence of a mass in each flank or the findings on intra-venous pyelography clinch the differential diagnosis from chronic pyelonephritis (Table XI).

TABLE XI—Polycystic Kidney Disease

Proteinuria	..	..	0—+	Conc./G.F.R.	..	..	..	↓
Addis count	Erythrocytes	0—	(+++)	Asymmetry	..	..	..	+
	Leucocytes	0—	(+++)	Radiology	..	..	..	+
Bacteriuria	Casts	..	0	Nephrotic syndrome	..	..	..	0
	..	..	0 or +	Hypertension	..	..	..	95%

SHOCK KIDNEY

The oliguria in the acute stage of shock kidney distinguishes this condition from all the others. The low urinary osmolality helps to distinguish it from acute glomerulonephritis, though the presence in the latter of haematuria, oedema, and hypertension makes the distinction easy. The defect in the concentrating power disappears only very slowly during convalescence.

Conclusion

Table XII summarizes the functional patterns on chronic renal disease. It is obvious that they provide as good a basis for classifying kidney diseases as do histological changes. However, just as the histological picture may become difficult to interpret owing to a combination of various lesions, especially in advanced disease, so may the functional pattern lose its clarity in

TABLE XII—Summary of Functional Patterns in Chronic Renal Disease

Diagnosis	Prot.	Addis count			Bacteriuria	Conc./G.F.R.	Asymmetry	Radiology	Nephrotic Syndrome	Hypertension
		Ery.	Leuc	Casts						
Heart failure	..	0—±	0	0	0	↑	0	0	0	
Vasc. nephroscl.	..	±	0	0	0	↑	0	0	0	100%
Renovasc. hypert.	..	±	0	0	0	↑	+	+	0	100%
Conn Syndr.	..	±	0	0	0	↓	0	0	0	100%?
Diab. Glomeruloscl.	..	+++	±→+	±→+	0	↑	0	0	60—70%	60—70%
Ren. amyloidosis	..	+++	±	±	0	↑	0	0	80—90%	17%
Toxaemia of pregnancy	..	+++	0	0→±	0	↑	0	0	+	+
Glomerulo-nephritis	..									
Minimal	..	±	+	0	0	=	0	0	0	0
Prolif.	..	↑→+++	+++	±	0	=	0	0	±	±—+
Membr.	..	+++	+	++	0	=	0	0	++	0→±
Membrano Prolif.	..	↑↑↑↑↑	+++	±	0	=	0	0	++	±—+
Extracapil.	..	+++	+++	++	0	=	0	0	+++	+++
Pyelonephritis	..	±→+	±→+	±—+++	+	↓	+	+	0	60%
Polycyst. kidneys	..	0→±	0→+++	0→+++	0..+	↓	+	+	0	90%
Shock kidney	..	±→+	0→++	0→++	0	↓	0	0	0	0

FIG. 15—Summary of radiological findings in chronic pyelonephritis (Dejdar, 1959). P = Chronic pyelonephritis. G = Chronic glomerulonephritis. Reproduced by permission of Fortschritte auf dem Gebiete der Strahlenkunde.

advanced cases. Despite this reservation, the independent diagnoses of clinician and pathologist were identical in well over 90% of our patients (Fig. 16). But to achieve the best possible accuracy in diagnosis all of the methods I have discussed must be applied in every case. Omitting some will immediately reduce the rate of diagnostic accuracy (Fig. 17). It is to be hoped that new techniques in future will further increase the precision of differential diagnosis.

Thomas Addis (1948) insisted that the urine of the renal patient is “full of evidence of the sort of disease that involves

FIG. 16—Agreement of the functional and morphological diagnosis of renal disease.

still-functioning nephrons,” and that we must try to learn to interpret this evidence properly. May I suggest the substitution “pattern of renal function” for the word urine and express the hope that by learning how to exploit this evidence fully we shall make a further important step in the clinical approach to the problems of renal disease?

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FIG. 17—Rate of accuracy of the diagnosis of chronic pyelonephritis established at necropsy was compared with the clinical diagnosis in vivo. The diagnostic success rate decreased when the scope of the functional methods was reduced.

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