FUNCTIONAL ASPECTS OF THE DIFFERENTIAL DIAGNOSIS OF RENAL DISEASE

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If we read through both the basic papers which William Bright wrote some 136 and 127 years ago, and which laid the foundations of clinical nephrology, we can recognize in the detailed clinical description of the nephrotic syndrome, the effects of severe hypertension and the signs of chronic renal or cardiac insufficiency. These are the end-stages which follow almost all types of chronic renal disease, and these late phenomena cannot be used to differentiate between the various morphological entities which the pathologists later constructed from the original tissue of 'Bright's disease'. Such a differentiation was, of course, to no purpose at the period when therapeutic medicine knew little else than venesection, calomel, diaphoretics, suction-cups and a few other drugs which Bright prescribed with both enthusiasm and conviction for his patients. Even in the century following Bright we had little else in our therapeutic armamentarium than a low-protein, low-salt diet and fluid restriction, so that, again, the differential diagnosis of renal disease was to little avail.

The situation in therapy today is quite different, and attempts at differential diagnosis have thereby taken on considerable practical importance. Since morphology of the kidney itself has been the classical criterion of diagnosis, kidney biopsy can be of great assistance, particularly when combined with histochemistry and electron microscopy of the biopsy material. These latter techniques have taught us a great deal of the early stages of kidney disease, since such cases do not come to the post-mortem table. It must be stressed, however, that biopsy is not without risk, that it requires the services of a pathologist experienced in interpreting such material, that even in the best of hands about one-quarter of all biopsies ends up with no kidney tissue in the needle, that the biopsy piece may contain so few glomeruli that any interpretation at all is risky, and that one has no guarantee at all that the region of kidney punctured by the needle actually contains the disease

process, which might be present only in other portions of the organ. In chronic pyelonephritis, for example, we can find quite normal areas of kidney in close approximation to areas severely altered by the chronic process.

However, morphological criteria are but one consequence of the disease-process—the other consequence consisting of the renal functional changes, which are no less specific than the details of micro-morphology. Our own work, and that of others, has led us to the conclusion that a study of renal function can give us a great deal of information not only concerning the degree of the disease process—hitherto its main application—but also as to the nature of the disease process, with a high degree of reliability. I hope that the material I shall present you, summarising some 25 years of observations on 3,685 patients, will transmit this conviction to you as well.

Methods

The methods used by us in these studies are by no means highly specialized ones—they are within the reach of any local hospital, and in Czechoslovakia they have been introduced into the routine investigational procedure of most medical wards. In addition to history and physical findings, they include: (1) qualitative and quantitative analysis of urine in terms of the content of protein and formed elements in the Addis sediment; (2) an approximation to glomerular filtration rate by means of the endogenous creatinine clearance in one 24-hour urine sample or in several 3- to 4-hour specimens over the course of a single day; (3) measurement of the concentrating ability, which is a very sensitive indicator of tubular function; (4) in selected cases investigation of diluting ability; (5) in cases where asymmetry of the disease-process is suspected, investigation of creatinine concentration or clearance measurements with urine obtained from each ureter separately by catheterization; (6) where indicated, urography, pyelography, aortography or tomography with retroperitoneal air insufflation; (7) if bacterial infection is suspected, the urine is cultured, and if the culture is positive then quantitative estimation of bacterial contamination of the urine is carried out. If there are more than 10,000 organisms per ml. of urine, bacterial infection is highly suspect, and if this count is greater than 100,000 infection is certain.

Functional Classification of Renal Diseases

The simplest method of functional classification

of renal disease is according to the degree to which glomerular and tubular function is altered viz:

- (1) There are disease-states which primarily involve glomerular filtration, leaving tubular function intact.
- (2) There are others in which glomerular and tubular function are altered in a more or less parallel fashion.
- (3) There are further states in which tubular malfunction is the only demonstrable defect for long in the course of the disease, glomerular alteration being a late development (Table 1).

TABLE I
FUNCTIONAL CLASSIFICATION OF CHRONIC
RENAL DISEASE

I. GLOMERULAR FUNCTION RESTRICTED MORE THAN TUBULAR FUNCTION	
A. <i>On Haemodynamic Basis:</i>	
1. Orthostatic proteinuria	
2. Emotional proteinuria	
3. Exertional proteinuria	
4. Heart failure	
5. Essential hypertension (early)	
B. <i>On Organic Basis:</i>	
(a) Without grave changes of basal membrane:	
Vascular nephrosclerosis	
(b) With grave changes of basal membrane:	
1. Diabetic glomerulosclerosis	
2. Amyloidosis	
3. Nephropathia gravidarum	
II. PARALLEL REDUCTION OF GLOMERULAR AND TUBULAR FUNCTION: Glomerulonephritis	
III. TUBULAR FUNCTION RESTRICTED MORE THAN GLOMERULAR FUNCTION:	
1. Chronic pyelonephritis	
2. Polycystic kidney disease	

In individual sub-groups it is of assistance to determine the quality of the glomerular abnormality, the presence of the nephrotic syndrome, hypertension, infection, etc.

Disease-states with Primary Involvement of the Glomerular Apparatus

Glomerular filtration can be decreased by lesions which restrict the filtration area with infiltration or scar formation, despite a lack of tubular involvement, but also by any state causing vasoconstriction in the kidney. In the first group we find diabetic glomerulosclerosis, renal amyloidosis, toxæmia of pregnancy and primary nephrosclerosis arising on the basis of hypertension of long duration. In the second group we find states in which there is a generalized hæmodynamic reaction to an imbalance between the tissue requirement of oxygen and the ability of the circulatory apparatus to deliver it to the tissues, resulting in vasodilation in muscles and adrenergic vasoconstriction in the splanchnic bed, the

kidneys, and skin. Renal vasoconstriction may result in a decrease in glomerular filtration. Such a decrease of glomerular filtration in an otherwise intact nephron, regardless of how it comes about, has, among others, two consequences of interest: (1) The decreased filtered load of osmotic material to the individual nephron has the opposite effect on final osmolarity of the urine to that of the raised osmotic load in osmotic diuresis. Here, as we know, urine osmolarity decreases asymptotically in the direction of plasma osmolarity. With a decrease in filtered osmotic load urine osmolarity is increased to high values, even in the absence of ADH (Shannon, 1942; de Wardener and del Greco, 1956). (2) When glomerular filtrate is low and the plasma coursing through the glomerulus is in contact with this structure for a longer-than-normal period, there is a greater-than-normal diffusion of protein into the glomerular filtrate (Goværts and Lambert, 1953). At least in some nephrons this diffusion may lead to amounts of protein in the lumen which cannot be reabsorbed in entirety by the tubular cells. The unabsorbed remnant appears then in the urine along with occasional hyaline casts which are the gel-form of this protein, but also with occasional tubular cells and granular casts due to saturation of these cells with protein transport and subsequent disintegration (Addis, 1942).

This is the mechanism of proteinuria which occurs with severe muscular exercise, and during orthostasis in some individuals with circulatory dysregulation in the erect posture (*orthostatic proteinuria*), with so-called '*negative emotional states*' such as fear, anxiety, anticipation—these latter situations being hæmodynamically comparable to preparation for muscular activity (Brod, Fencel, Hejl and Jirka, 1959), and in *congestive failure*. In the first three states mentioned above, there is no protein in the morning urine, which immediately suggests that there is no organic disease in the kidneys themselves. Greater confusion can be caused by the proteinuria of congestive failure, which lasts as long as failure is present: if there is nocturia, the diurnal curve of glomerular filtration shows a rise to normal at night, which is of diagnostic significance (Fig. 1) (Brod and Fejfar, 1950). In severe cases, where glomerular filtration is depressed over the entire 24 hours and the protein and cellular content of the urine is somewhat higher, high urine specific gravity, which shows a normal nephron population even with a glomerular filtration rate as low as 50 to 30 ml./min., can exclude organic renal disease. In these cases, blockage of the adrenergic mechanism by means of dibenamine will be followed by a rise in renal plasma flow and

FIG. 1.—Diurnal rhythm in the rate of glomerular filtration (GFR), tubular reabsorption of water (R) and urine flow (V) in a normal subject and in a patient with heart failure. R is given as % of GFR $\left(\frac{\text{GFR}-V}{\text{GFR}} \times 100\right)$ and varies normally between narrow limits (98.3 to 99.7%). Note that the nocturia in the cardiac patient is due in the first place to an increase of GFR from subnormal values in day-time to low-normal values at night.

glomerular filtration (Brod, Fejfar and Fejfarová, 1954).

A similar situation might be encountered in the initial stages of *essential hypertension*, where the kidneys are morphologically intact and where a decreased glomerular filtration rate is due to vasoconstriction. Glomerular filtration rises when blood pressure is normalised with rauwolfia (Brod and Fencel, 1955), during sleep (Brod and Fencel, 1958), with sedatives (Ratnér, 1959) and pyrogens (Bradley, Chasis, Goldring and Smith, 1945). Suspicion of primary renal disease can remain in this case only if we find proteinuria. In our experience, however, the latter is not frequent or significant and the urinary sediment with proteinuria does not differ from that found in cases of orthostatic proteinuria.

Proteinuria in essential hypertension becomes a more fixed part of the disease-picture when the high blood pressure has lasted some time and has led to arteriolosclerotic changes in the renal vessels with the start of slow, progressive *vascular nephrosclerosis* involving part of the glomerular vascular bed. In this latter situation the diurnal variation in glomerular filtration rate is decreased or disappears entirely. Even in such cases the degree of proteinuria usually does not exceed 1 g./24 hr. with uncomplicated vascular nephrosclerosis. The Addis count shows only a small

FIG. 2.—Frequency of the various types of Addis count in chronic pyelonephritis, chronic glomerulonephritis and vascular nephrosclerosis.

FIG. 3.—Correlation of glomerular filtration and maximum concentrating ability in patients with vascular nephrosclerosis (NSCL), chronic glomerulonephritis (GLN) and chronic pyelonephritis (PN). The diagnosis in all patients has been proved morphologically (biopsy or autopsy). At all stages of the restriction of GFR patients with chronic pyelonephritis concentrate less and patients with vascular nephrosclerosis concentrate better than patients with chronic glomerulonephritis.

rise in formed elements and casts, with values seldom exceeding 200,000 to 300,000 (Fig. 2). With destruction of glomeruli, entire nephrons are then put out of action, thus increasing the osmotic load on the remaining nephrons. An osmotic diuresis results which limits the concentrating ability of the kidney, but the latter impairment is mild in comparison with the degree of limitation of glomerular filtration, as can be seen in Fig 3.

Renal artery stenosis, which is present in a portion of hypertensive patients, regardless of whether it is the causative agent of the hypertension or merely a complicating factor, does not produce a different functional picture from that

FIG. 4.—Incidence of renal artery stenosis in normotensive subjects and in patients with essential hypertension divided according to the absence or presence of clinical signs of organic cardiovascular changes into stages I and II (Hejl, Prát and Dejdar, 1962).

FIG. 5.—Prevalence of renal artery stenosis according to age (Hejl, Prát and Dejdar, 1962).

just described. As can be seen in Fig. 4 (Hejl, Prát and Dejdar, 1962) this finding is rare (3%) in the early phases of hypertension, whereas in patients with organic complications renal artery stenosis was found in 38.5% of cases, and in

juvenile hypertensives in this stage of the disease actually in 46%. This would suggest that renal artery stenosis is a secondary phenomenon due to acceleration of the atherosclerotic process in hypertension. However, the age distribution of patients with renal artery stenosis (Fig. 5), with a clear double-peaked curve, allows the possibility that stenosis in young patients can be a separate disease entity and be associated with the later development of hypertension. Our present research programme with aortographic investigation of all hypertensives found in a large, unselected population, should give the answer to this question. The preliminary data do show that suspicion of stenosis is aroused in cases of severe hypertension with signs of organic cardiovascular involvement, particularly if there is apparent asymmetry of the kidneys in the plain abdominal X-ray.

Small changes in the basement membrane of the glomerular capillaries, the slight degree of escape of protein into the glomerular filtrate and final urine, the insignificant changes in the urinary sediment and the lack of signs of protein depletion differentiate the renal correlate of hypertension (primary vascular nephrosclerosis) from the other three disease processes which involve the filtration area of the glomerulus: diabetic glomerulosclerosis, renal amyloidosis and nephropathy of pregnancy. In these diseases, there is a deposition of mucoproteins and mucopolysaccharides, manifestations of a generalized metabolic disturbance, in the basement membrane of the glomerular capillaries. In amyloidosis this infiltration can also be in the basement membrane of the tubules. This deposition in the glomerular-capillary walls leads to an enormous rise in glomerular permeability to protein, with intense proteinuria, saturation of the tubular cells with reabsorbed protein and the appearance of such packed cells as well as of their product—granular casts in the urinary deposit, and finally the appearance of the nephrotic syndrome. There is a progressive decrease in the glomerular filtration area, with final disappearance of filtration.

Diabetic glomerulosclerosis, or Kimmelstiel-Wilson disease, is found in some 22.9% (Horn and Smetana, 1942) to 63.7% (Laipply, Eitzinger and Dutra, 1944) of diabetics, depending on whether one uses as the histological criterion of the diagnosis the presence of characteristic hyaline balls or diffuse thickening of the basement membrane, the latter being an earlier stage of the lesion (Fig. 6a, b).

Diabetic glomerulosclerosis is one of the most difficult of clinical diagnoses, since we only recognize it pre-mortem in 6.3% of diabetics. The causes of the different percentages noted by the pathologist and the clinician are two

FIG. 6.—Microscopical picture of diabetic glomerulosclerosis. (a) Early—with predominant thickening of the capillary walls; (b) late—with typical formation of nodules (courtesy of Dr. Rossmann).

number: in some of our diabetics we make the wrong diagnosis of glomerulosclerosis from proteinuria and oedema which are actually due to congestive failure. On the other hand, in the initial stages the presence of morphological changes need not be accompanied by pathological changes in the urine (Brun, Gormsen, Hilden, Iversen and Raaschou, 1953). We are therefore faced with the prospect that diagnosis at an early stage, which by correction of the metabolic disturbance might perhaps still be amenable to therapy, will be only possible by repeated biopsy during the course of diabetes, and will probably require electron microscopy to detect changes

which are difficult to see under ordinary microscopy. By the time the disease presents itself clinically—which is rare in a diabetic of less than ten years duration—there is usually a rapid progression to uræmic death or cardiac failure or both which, according to our own experience, supervene within four to five years of the first clinical recognition of this disease. The functional diagnosis (Table 2) is based upon: (1) Proteinuria in 100% of cases, with more than 10 g./24 hr. in 56.4%, and numerous tubular cells, counted along with the leucocytes in the Addis count, and casts. Due to the defect in fat metabolism also present, the casts and epithelial

TABLE 2
THE LEADING DIAGNOSTIC FEATURES OF DIABETIC GLOMERULOSCLEROSIS AND RENAL AMYLOIDOSIS. CHRONIC PYELONEPHRITIS HAS BEEN PRESENTED FOR COMPARISON

	Diabetic glomerulosclerosis	Amyloidosis	Chronic pyelonephritis
Past history	Diabetes (over 10 years 88.9%)	Chron. infection 79.3% Rheum. arthritis 20.7%	Pain 64.7% Frequency 44.4%
Proteinuria > 5g./24 hr. ..	69.5%	89.5%	11.0%
Addis count: Erythrocytes +++	17.3%	3.6%	16.0%
Leucocytes +			o
Erythrocytes +++	30.4%	25.0%	
Leucocytes +++	30.4%	35.7%	76.0%
Erythrocytes +	21.7%	35.7%	8.0%
Leucocytes +	43.5%	40.7%	31.0%
Casts 0.1 – 1 mil. ..	47.8%	37.0%	11.0%
> 1 mil. ..	26.3%	77.2%	o
Hypoproteinæmia	88.8%	77.2%	o
Hypoalbuminæmia	65.2%	86.5%	o
Nephrotic oedema	87.0%	92.6%	Rare
ESR > 50 mm.	69.5%	24.2%	59.7%
Hypertension	95.0%	o	o
Diabetic retinopathy	o	80.0%	o
Congo red test positive ..

FIG. 7.—Correlation of glomerular filtration and maximum concentrating ability in patients with diabetic glomerulosclerosis, renal amyloidosis and chronic pyelonephritis. The diagnosis in all patients has been proved histologically. There is no great difference in the relationship in the first two diseases. The regression line for chronic pyelonephritis is far below those for the other two diseases.

cells are filled with refractile droplets of fat. 'Leucocytes' in the Addis count usually exceed 50 million/24 hr. only when there is urinary tract infection also present. Erythrocytes are not prominently represented in the sediment. The severe proteinuria results in the nephrotic syndrome, present in 65.2% of clinically diagnosed cases, and present in all patients with a daily loss of protein greater than 5 g. Progressive decrease in glomerular filtration rate, also contributed to by congestive failure and atherosclerotic closure of the smaller renal vessels, is in contradistinction to the normal concentrating ability. The latter may decrease late in the course of the disease due to osmotic diuresis from reduction of the nephron population, just as in primary vascular nephrosclerosis (Fig. 7). In three patients in whom the exceptional finding of hyposthenuria was present, there was also urinary tract infection.

Aside from the kidneys, there are specific diabetic lesions in the retinal vessels, which were present in 95% of our cases. The reverse is not true, however. Iversen and Ohlsen (1951) reported that only seven of 16 diabetics with retinopathy showed simultaneous signs of a renal lesion.

We found hypertension less frequently than would be expected from the earlier reports. Normal pressures were found in two of 23 patients and five showed the 'windkessel' type of hypertension. Definite diastolic hypertension was present in 69.5% of cases, but there was no correlation between the degree of the latter and the degree of

FIG. 8.—Correlation between systolic blood pressure and the rate of glomerular filtration in patients with diabetic glomerulosclerosis. Although there is a slight tendency to higher pressures in patients with severely restricted GFR, the correlation is very low. The same is true for diastolic pressure.

alteration in the rate of glomerular filtration (Fig. 8).

It is clear, then, that the diagnostic signs of diabetic glomerulosclerosis are diabetes of long duration and retinopathy, without which the renal lesion does not appear, the finding of marked proteinuria with only insignificant haematuria, but with many fat-containing epithelial cells and granular casts, marked decrease in glomerular filtration with relatively little change in concentrating ability, and the presence of the nephrotic syndrome. As we shall see, these criteria are quite the reverse of what is found in chronic pyelonephritis, which is another frequent complication in diabetes and may, of course, also complicate diabetic glomerulosclerosis. Signs of pathology in the basement membrane of the glomerular capillaries (proteinuria, nephrotic syndrome) differentiate diabetic glomerulosclerosis from hypertensive disease *per se* and from vascular nephrosclerosis, both of which may complicate the course of diabetes mellitus (Table 3).

On the other hand, it is very difficult to differentiate on functional grounds renal amyloidosis from diabetic glomerulosclerosis, if the former is a complication of a purulent or wasting disease which has also occurred in the course of diabetes: the absence of retinopathy and the presence of a normal blood pressure are of assistance.

The causes of amyloidosis in our series of cases are shown in Table 4. The first clinical signs of amyloidosis appeared from three months

TABLE 3
DIFFERENTIAL DIAGNOSIS OF DIABETIC GLOMERULO-
SCLEROSIS, RENAL AMYLOIDOSIS AND VASCULAR NEPHRO-
SCLEROSIS

	Diabetic glomerulo- sclerosis	Amyloi- dosis	Vascular nephro- sclerosis
Diabetes mellitus ..	> 10 yrs.	—	—
Diabetic retinopathy ..	+++	—	—
Proteinuria ..	+++	+++	o - ±
Addis count:			
Erythrocytes ..	+	+	o - ±
Leucocytes ..	++	++	o - ±
Casts ..	+++	+++	o - ±
Conc. power/GFR ..	↑	↑	↑
Asymmetry ..	o	o	o
X-ray of kidneys ..	o	o	o
Nephrotic syndrome ..	++	++	—
Blood pressure ..	↑	—	↑

TABLE 4
CAUSES OF AMYLOIDOSIS AND SIGNS OF SIMULTANEOUS
INVOLVEMENT OF OTHER ORGANS AMONG THE PATIENTS
OF THE INSTITUTE FOR CARDIOVASCULAR RESEARCH

CAUSES OF AMYLOIDOSIS:				
Tuberculosis of bones ..	..	..	8	(27.6%)
Tuberculosis of lungs ..	..	..	6	(20.7%)
Bronchiectasis ..	..	..	4	(13.8%)
Rheumatoid arthritis ..	..	..	6	(20.7%)
Chronic osteomyelitis ..	..	..	3	(10.3%)
Ulcerative colitis ..	..	..	1	(3.45%)
Lymphogranulomatosis ..	..	..	1	(3.45%)
Total ..	..	..	29	(100.0%)
SIMULTANEOUS CLINICAL INVOLVEMENT OF OTHER ORGANS:				
Liver ..	..	..	..	9 (31.0%)
G.I. tract ..	..	..	..	4 (13.8%)
Spleen ..	..	..	..	4 (13.8%)

to 32 years after the start of the initial pathology, with an average of 11.3 years, and there was no clustering of cases in this wide range of time. There were signs of extra-renal amyloidosis in 34.4% and the Bennhold (Congo Red) test was positive in 80%, and at the lower margin of significance in 12%.

Proteinuria (Table 2) is usually massive from the very start: 86.3% excreted more than 5 g. in 24 hr. and showed the presence of the nephrotic syndrome. As in diabetic glomerulosclerosis, there are many epithelial cells in the 'leucocyte' fraction of the Addis count and many casts, with only mild red-cell excretion.

Fig. 7 shows the regression curve of the rate of glomerular filtration and concentrating ability in our cases, and this was not markedly different from that found in nephrosclerosis and glomerulo-sclerosis. The somewhat greater scatter of values

in some cases with markedly decreased con-
centrating ability, with only moderate decrease in
glomerular filtration, is probably due to the
presence of amyloid in the basement membrane
of the tubules and collecting ducts.

Hypertension proved to be rare despite the
marked degree of renal pathology (Fig. 9).
Only five patients had a raised pressure, and three
of these had very low rates of glomerular filtration.
It is difficult to say whether the absence of
hypertension is due to the presence of the provo-
cative disease or focus or to some other cause.

The lack of hypertension can to some degree
be used in the differential diagnosis of renal
diseases with massive proteinuria and the neph-
rotic syndrome, and in the case of glomeruloneph-
ritis further assistance is given by the history, the
predominance of erythrocytes in the Addis count
and the presence of erythrocyte—and blood—
casts (Table 3). In the case of disseminated
lupus erythematosus there are in addition signs
of systemic involvement. When the nephrotic
syndrome is present along with thrombophlebitis
of the lower extremities or constrictive pericarditis,
or the appropriate histories thereof, one must also
consider the rare possibility of thrombosis of the
renal vein.

The importance of early diagnosis of renal
amyloidosis can be seen from evidence that
radical treatment of the evocative pathological
process leading to amyloidosis in the early stages
of the latter can occasionally prevent the further
progress of renal degeneration.

The last of the diseases in this group—
toxæmia of pregnancy—also involves a de-
position of mucopolysaccharides in the basement
membrane of the glomerular capillaries. This
again leads to proteinuria and an increase in
tubular cells present in the 'leucocyte' fraction
of the Addis count, along with hyaline and
granular casts and a moderate decrease in glo-
merular filtration rate. For the same reasons as
in renal amyloidosis, tubular concentrating ability
remains fairly well preserved in the face of
restriction of the rate of glomerular filtration.
Diagnostic difficulties arise in differentiating
between nephropathia gravidarum and glomerulo-
nephritis or the renal affection in hypertension
(Table 5). As opposed to the hypertensive kidney,
nephropathia gravidarum is associated with a
greater degree of proteinuria, more elements in the
urinary sediment, a lower filtration fraction,
œdema and hypoproteinæmia. Glomerulonephri-
tis, on the other hand, is differentiated by many
more red cells and erythrocytic casts in the
urinary sediment, by a far greater restriction of
the concentrating ability, and by the history, if it
is known that the renal disease started before

FIG. 9.—Correlation between diastolic pressure and the rate of glomerular filtration in patients with renal amyloidosis. It may be noted that with one exception the only registered elevations of blood pressure were found in patients with a severely restricted GFR.

TABLE 5
DIFFERENTIAL DIAGNOSIS OF TOXÆMIA OF PREGNANCY

	Toxæmia of pregnancy	Essential hypertension	Glomerulo-nephritis
Proteinuria ..	++	o - ±	++
Addis count:			
Erythrocytes ..	±	o - ±	+++
Leucocytes ..	++	o - ±	++
Ery/Leuco ..	↓	—	↑
Casts ..	++	—	++
Conc. power/GFR	↑	↑	=
Filtration fraction	↓	↑	↓
Asymmetry ..	—	—	—
X-rays of kidneys	—	—	—
Blood pressure ..	↑	↑	o - ↑
Nephrotic syndrome ..	+	—	+

pregnancy. Pyelonephritis is a common renal complication of pregnancy, but the functional diagnosis is quite clear in terms of differentiation from nephropathia gravidarum.

Renal Disease, Involving Glomerular and Tubular Function in Parallel

Our second group of renal diseases is represented in the first instance by glomerulonephritis. The name itself tells us that the disease process involves the glomeruli, and experimental work over the past 15 years has shown that immunotoxic reactions, thought to lie at the basis of this disease, can produce a similar picture in animals and that the antigen-antibody reaction occurs in the basement membrane of the glomerular capillaries. However, the work of Schwentker and Comptoir (1939) and the more recent observation of Antoine (1961) have shown that other renal

FIG. 10.—Development of the signs of acute glomerulonephritis in the course of the first six months. Ordinate indicates the percentage incidence of the individual sign. Note the more or less parallel retreat of œdema, hypertension and raised NPN (an indirect indicator of glomerular obstruction) and the persistence of proteinuria, granular casts and reduced concentrating ability (Brod, 1949).

structures, in particular the tubules, can also serve as the antigen-container for this immunological reaction. The decrease in concentrating ability early in the course of acute glomerulonephritis could be attributed to the osmotic effect of a decreased nephron population. Against this argument is the fact that reduced concentrating ability remains for months after signs of the acute stage of the disease, such as a low glomerular filtration, have been completely normalized (Fig. 10).

Despite a large amount of experimental data, the pathological basis of glomerulonephritis remains unclear. The working hypothesis most in agreement with known clinical facts is that the disease arises as a result of an allergic reaction involving the walls of capillaries and the smooth musculature of the arterioles, both in and outside the kidneys. In the latter organ these alterations tend to block glomerular circulation and produce an inflammatory exudation into Bowman's capsule, with a resulting fall in glomerular filtration, oliguria (rarely anuria), proteinuria and excretion of erythrocytes, leucocytes and erythrocytic and granular casts into the urine. The initial decrease in concentrating ability has already been mentioned. Extrarenally, spasm of the smooth muscle of the arteriolar wall leads to a rise in blood pressure, increased capillary permeability and a shift of fluid into the interstitial space, and the resulting mobilisation of the 'dehydration reaction' leading to salt retention and œdema

FIG. 11.—Grouping of leading signs and their development in a group of 66 patients with acute glomerulonephritis in the course of the first six months. The whole group has been split into subgroups according to the presence (+) or absence (–) of the individual signs, indicated on the left side of the graph. The figures in circles indicate the number of patients in each subgroup. Note that at the start over 80% of the patients exhibited all the four leading signs (hypertension, oedema, reduced GFR and changes in the urine). After one month these were still present in only one-third of the patients and after two months they subsided in all but two patients. However, only a small fraction of the patients moved into the subgroup ‘healed’; in the majority signs of renal involvement persisted. After the acute phase there follows obviously a phase in which residual changes are present in the kidneys. The patient may be quite symptom-free at this stage of the disease.

formation. This assumed independent course of vascular changes in the kidneys and outside of them is supported by data from a series of 66 patients treated during the war in British Military Hospitals in North Africa and Italy (Fig. 11) (Brod, 1949). As can be seen, some patients with acute glomerulonephritis had combined renal and extrarenal manifestations, while others showed only renal damage with or without glomerular blockade. There was a continuous gradation between these two groups, suggesting that they all had the same disease. At the other end of the scale the signs of the renal lesion were pushed into the background, leaving at the end only hypertension and oedema. Like the previous figure also, the present one demonstrates that the full-blown picture of the acute disease tends to subside within one to two

months in the great majority of patients. The signs of obstruction of the glomerular circulation decreased, glomerular filtration rose again to normal values and hypertension and oedema receded, though not all necessarily at the same rate, which again lends support to the idea that the changes are independent expressions of the disease-process. However, signs of a lesion of the glomerular membrane, such as proteinuria, microscopic hæmaturia, and erythrocytic casts and leucocytes in the urinary sediment remained in some cases, along with signs of a decreased area for glomerular filtration—a decrease in the diurnal variation in glomerular filtration. The further course of the disease can show three types of development. The signs of the disease can decrease over the following weeks or months,

FIG. 12.—Diagrammatic representation of the development of glomerulonephritis.

or the patient remains unchanged for years, or glomerular filtration can progressively decrease at a greater or lesser rate, either continuously, or in jumps, this being possibly related to intercurrent infection (Fig. 12).

The nephrotic syndrome or hypertension can complicate the further course of the disease, be it otherwise stationary or progressive. Hypertension occurs mainly in patients with disease of longer duration, and where glomerular filtration has decreased to below 50 to 60 ml./min. (Fig. 13). This hypertension may take on a malignant character and be the predominant clinical sign, while the functional state of the kidney remains as before, that is with red cells predominating in the Addis count, with marked proteinuria, casts in the urine, and a more or less parallel decrease in the rate of glomerular filtration and concentrating ability.

Recognition of the fully developed picture of acute glomerulonephritis is not difficult (Table 6). As opposed to oedema from right-sided congestive failure the venous pressure is normal and the rate of glomerular filtration does not increase at night;

the decreased concentrating ability is in contrast with the highly concentrated urine of the cardiac patient, while with the exception of cases with renal infarction, hæmaturia in congestive failure is insignificant. Acute tubular insufficiency is usually preceded by shock or intoxication, and neither hypertension nor oedema belong to the initial signs. If a small sample of urine can be collected in acute tubular insufficiency, the presence of red cells is without diagnostic significance, but their absence rules out glomerulonephritis, just as in the case of a urine specific gravity below 1.012. With simple febrile proteinuria the rate of glomerular filtration is normal (provided that the basic disease has not resulted in dehydration or myocardial damage), the concentrating ability is normal and the urinary sediment may contain only an increased amount of hyaline casts.

Malignant hypertension which occurs in chronic cases of severe essential hypertension might also be accompanied by a marked increase in proteinuria and the number of elements in the urine, and one finds left ventricular hypertrophy, which is not present early in acute glomerulonephritis. There

FIG. 13.—Incidence of hypertension (B.P. over 145/95 mm. Hg) in patients with chronic glomerulonephritis and chronic pyelonephritis in relation to the grade of reduction of GFR and to the duration of the disease.

is also a high filtration fraction* (if known), while the frequent absence of erythrocytes or casts in the urine also tends to exclude glomerulonephritis.

*Ratio of the rate of glomerular filtration/renal plasma flow (PAH clearance).

Differential diagnosis may be difficult in the latent stage of chronic glomerulonephritis with only residual changes in the urine, particularly if there is no history of an acute initial disease (Table 7). As opposed to benign forms of proteinuria, protein is present in the morning urine, the Addis count is high and there are functional signs of renal impairment. A history of œdema and oliguria is evidence against chronic pyelonephritis, whereas a history of back pain, nephrolithiasis or some other urological disease such as repeated cystitis speak in favour of the latter diagnosis. Proteinuria greater than 5 g./24 hr., a large number of casts in the sediment (over 1 to 2 million in 24 hr.) as well as a marked increase in both red and white cells in the sediment are all evidence for glomerulonephritis, rather than pyelonephritis, in addition to a concentrating ability which is decreased in proportion to the degree of decrease in the rate of glomerular filtration. Symmetrical renal involvement, as determined by separate collection of urine from each ureter, is not characteristic of pyelonephritis. X-ray investigation of the urinary passages can also be used to test for symmetry, and a normal picture here is not the rule in pyelonephritis. We can exclude primary vascular nephrosclerosis accompanying hypertensive disease by the fact that in a disease of a short duration and without grave kidney involvement there is often no rise in blood pressure (Fig. 13). Nephrosclerosis is not accompanied by marked proteinuria or a high Addis count, the concentrating ability is only moderately affected and usually far less than one might expect from the degree of depression of glomerular filtration. The filtration fraction is raised in nephrosclerosis, but decreased in glomerulonephritis. Of the other disease-states associated with the nephrotic syndrome, amyloid can be excluded on the basis of the history, the lack of red cells in the urinary sediment, a satis-

TABLE 6
DIFFERENTIAL DIAGNOSIS OF ACUTE GLOMERULONEPHRITIS

	Acute glomerulonephritis	Heart failure	Acute tubular insufficiency	Febrile proteinuria	Malignant hypertension
History	Infection	Dyspnoea	Shock; intoxication	Fever	Hypertension
œdema	+	+	—	—	—
Anuria	++	+	+	—	—
Venous pressure	—	+	—	—	—
Nocturnal rise in GFR	—	+	—	—	+
Conc. power	↓	+	↓	↑	↑
Addis count: Erythrocytes	+++	○	○	○	±
Leucocytes	+++	○	+	○	±
Casts	+++	+	+	○	±
Filtration fraction	↓	↑	?	—	↑

TABLE 7
DIFFERENTIAL DIAGNOSIS OF CHRONIC GLOMERULONEPHRITIS

	Chronic glomerulonephritis	Amyloidosis	Diabetic glomerulosclerosis	Pyelonephritis	Vascular nephrosclerosis
Proteinuria	++	+++	+++	+	±
Addis count: Erythrocytes	++	±	+	±	○ - ±
Leucocytes	+	++	++	++	○ - ±
Ery./Leuco.	↑	↓	↓	↓	—
Casts	+	+++	+++	○ - ±	○ - ±
Conc. power/GFR ..	=	↑	↑	↑	↑
Filtration fraction ..	↓	—	—	—	—
Asymmetry	—	—	—	—	—
X-rays of kidneys ..	—	—	—	—	—
Blood pressure	↑	—	↑	↑	↑
Nephrotic syndrome ..	○ - +	+	+	—	—

factory concentrating ability and absence of hypertension provided that the patient is not in renal failure. The first three of these criteria also exclude diabetic glomerulosclerosis, quite apart from the fact that for the latter diagnosis we must also observe diabetes and retinopathy.

Differentiation between glomerulonephritis and nephropathia gravidarum has already been discussed. The very difficult differentiation from renal venous thrombosis may be assisted by a history of thrombosis of the lower extremities, the presence of visible collateral vascular channels on the abdominal wall, and the combination of a satisfactory concentrating ability with only slight hæmaturia.

These differential diagnostic criteria remain valid even in the presence of renal failure. Fig. 14 shows that even at this stage these criteria are not merely of academic interest, since using them we can determine the prognosis, which is very different in glomerulonephritis as compared with pyelonephritis (Prát, Fencel and Jirka, 1961).

Renal Diseases, Affecting Primarily Tubular Function

Group 3 contains those renal diseases which affect primarily tubular function, and which is represented by chronic pyelonephritis and polycystic disease. The correctness of this classification in the case of pyelonephritis can be seen already by observing a histological section (Fig. 15), where it can be observed that the normal contour of the tubule is lost in an interstitial inflammatory infiltrate, spreading irregularly through the kidney, whereas glomeruli are involved, in the form of a glomerulitis, only very late in the course of the disease. Lambert (1943) has established the primary involvement of the tubules in polycystic disease by means of a plastic reconstruction which revealed that the cysts originated from the tubular lumen. In addition, these inadequate

FIG. 14.—Progress of GFR in patients with chronic pyelonephritis (PN) and chronic glomerulonephritis (GN) who were first seen with a GFR reduced below 35 ml./min. Note that the rate of descent of GFR is faster in patients with glomerulonephritis than pyelonephritis and that in the course of seven years all the patients with glomerulonephritis were dead, while 80% of the pyelonephritics survived. The ages of both groups were comparable (Prát, Fencel and Jirka, 1961).

FIG. 15.—Microscopical picture of chronic pyelonephritis. Note the heavy round-cellular infiltration of the left half of the kidney and the normal appearance of the right half. In the inflamed zone the outlines of the tubules have practically disappeared, while the structure of glomeruli is well preserved.

FIG. 16.—Quantitative bacteriology of the urine in chronic glomerulonephritis and chronic pyelonephritis. Note the high incidence of severely infected urines in chronic pyelonephritis (Prát and Horák, in press).

organs are also very susceptible to infection and chronic pyelonephritis.

Chronic pyelonephritis arises on the basis of an interstitial infection and in 60% of cases the causative agent can be isolated from the urine in quantities which exclude the possibility of chance contamination of the samples, i.e. usually more than 10,000 and as a rule up to 100,000 organisms/ml. (Fig. 16). With late involvement of the glomeruli proteinuria need not be, but usually is, present, but seldom reaches values greater than 1 to 2 g./24 hr. (Fig. 17). It is perhaps a consequence of an abnormal circulation in the glomeruli due to pressure from the inflammatory exudate. In favour of this is the fact that treatment of the infection at this stage may result in a rise in glomerular filtration. In addition to protein and micro-organisms in the urine we can also find there a direct reflection of the interstitial inflammation in the form of leucocytes, which are more numerous in the Addis count than red cells in 75% of cases (Fig. 2). Casts, so typical in histological section, arising in nephrons which have been blocked by the inflammatory process, are few or absent.

There is a characteristic decrease in concentrating ability present from the early stages of the disease, in sharp contrast to the lack of involvement of glomerular filtration, as can be seen in Fig. 3. As opposed to glomerulonephritis and vascular nephrosclerosis, there is a decrease in the specific gravity of the urine in the final stages of the disease to values below those of the glomerular

FIG. 17.—Severity of proteinuria in chronic pyelonephritis (PN) and chronic glomerulonephritis (GLOM).

filtrate. This tubular involvement from the early stages of the disease is one of the causes of the continuing tendency to extracellular dehydration in these patients, which acts in the opposite direction from the tendency to œdema formation in congestive failure. Since protein-loss is small and since there is a tendency to lose salt rather than retain it, the nephrotic syndrome is never seen in chronic pyelonephritis.

The irregularity of the spread of the disease process in the kidney explains the asymmetry of the two kidneys found in 90% of cases by analysis of creatinine concentration separately in the urine collected by catheter from each ureter (Prát and Kočvara, 1957) (Fig. 18), as well as by X-ray studies of the size and shape of the kidneys and the rate at which injected contrast material appears in the renal pelvis (Dejdar, 1959). The latter technique has also demonstrated abnormal shapes of the calyces, papilla and pelvis, and abnormal motility of the ureter in serial films (Figs. 19 and 20).

There are, therefore, a large number of signs which assist in the diagnosis of this most frequent of renal diseases, provided that we consider this diagnosis not only in clear urological cases, but also in all cases of asymptomatic proteinuria, hypertension with proteinuria and even in patients with vague, general complaints, e.g. minimal temperatures. Urinary examination will then give rise to the initial suspicion of pyelonephritis, and the above detailed tests can establish the presence of the disease (Table 8).

The presence of the nephrotic syndrome excludes the diagnosis of chronic pyelonephritis. Even without œdema, the presence of heavy

FIG. 18.—Ratio of the concentration indices of endogenous creatinine of the left and right kidney in subjects with normal kidneys (left upper group), in patients with chronic glomerulonephritis and vascular nephrosclerosis (right upper group) and in patients with chronic pyelonephritis. The three lines indicate the $\pm 10\%$ limit, within which are situated almost all the data of subjects with normal kidneys and with the symmetrical bilateral diseases. In the right subgroup of pyelonephritis a unilateral disease was suspected on other grounds, whereas no such suspicion existed in cases in the left subgroup (Prát and Kočvara, 1957).

FIG. 19.—X-ray picture of chronic pyelonephritis. Note the unequal size of the two kidneys, the blunting of the calyces, the flattening of the papilla and the uneven thickness of the parenchyma overlying the renal pelvis (Dejdar, 1959).

FIG. 20.—Summary of the X-ray findings in chronic pyelonephritis. Patients with chronic glomerulonephritis were used for comparison (Dejdar, 1959).

proteinuria and casts in the urinary sediment rather indicate glomerulonephritis, diabetic glomerulosclerosis, amyloidosis or nephropathia gravidarum. The last-named three syndromes in addition show a higher concentrating ability than

corresponds to the decrease in the rate of glomerular filtration. Primary vascular nephrosclerosis is an after-effect of hypertension, and can thus be excluded in 40% of cases of pyelonephritis who run the course of their disease with normal pressures. In the presence of hypertension, the pyelonephritic case will show a predominance of leucocytes in the urinary sediment, bacteriuria, a greater restriction of concentrating ability in relation to the level of glomerular filtration, asymmetry and pathological X-ray findings.

Polycystic disease shows a similar accentuation of loss of concentrating ability in relation to glomerular filtration as in pyelonephritis, but the urine is not infected and does not contain leucocytes if the polycystic organ has not become secondarily infected (Table 8). The most important differential diagnostic criteria are the findings on palpation and X-ray.

Table 9 summarizes the differential diagnostic criteria of the individual disease states, as presented above. The validity of these criteria is documented in Fig. 21, which shows the high degree of correlation between the functional diagnosis and the histological findings. Moreover, the functional diagnosis is at the same time a quantitative one, and gives more information than can be obtained from a small biopsy sample.

Conclusion

Modern renal physiology—from its very beginnings in London with Bowman and Cushny—has put clinical nephrology on a scientific basis which was lacking when Bright first set his observations down on paper. It is to be hoped that it will continue to provide more effective measures to control and eradicate kidney disease, with which until recently the physician was forced to play more the role of the observer than of the therapist.

TABLE 8
DIFFERENTIAL DIAGNOSIS OF CHRONIC PYELONEPHRITIS AND POLYCYSTIC KIDNEY DISEASE

	Chronic pyelo-nephritis	Polycystic kidneys	Vascular nephro-sclerosis
Proteinuria ..	± - +	○ - ±	○ - ±
Addis count:			
Erythrocytes ..	±	○ - ±	○ - ±
Leucocytes ..	↑	○ - ±	○ - ±
Ery./Leuco. ..	↓	—	—
Casts ..	—	—	—
Conc. power/GFR	↓	↓	↑
Asymmetry ..	+	+	—
X-rays ..	+	+	—
Blood pressure ..	○ - +	↑	↑
Nephrotic syndrome	—	—	—

FIG. 21.—Degree of agreement between the clinical and morphological diagnosis of the most important renal diseases.

TABLE 9
SURVEY OF THE DIFFERENTIAL DIAGNOSIS OF RENAL DISEASE ON CLINICAL AND FUNCTIONAL BASIS

	Past history	Hyper-tension	Nephrotic syndrome	Proteinuria	Addis count					Relationship of conc. power to GFR	Low fixation of sp. grav.	Asymmetry of renal function	X-rays abnormal
					E	L	+	++	+++				
Heart failure	Heart disease	—	—	0 - +	—	—	—	—	—	↑	—	—	—
Essent. hypert.	—	100%	—	0 - ±	—	—	—	—	—	↑	—	—	—
Vascular nephrosclerosis	Hypertension	100%	—	0 - +	—	—	—	—	—	↑	—	—	—
Diabetic glomerulosclerosis	Diabetes over 10 years	65%	65.2%	++	+	+	+	+	+	↑	—	—	—
Renal amyloidosis	Chronic suppur.; rheum. arthr.	17%	86.5%	++	—	—	—	—	—	↑	—	—	—
Acute glomerulosclerosis	Infection	85%	+	++	++	++	++	++	++	=	—	—	—
Chronic glomerulosclerosis	Ac. glom. 70%	60%	+	++	++	++	++	++	++	=	—	—	—
Chronic pyelonephritis	Pain, urin. sympt. 65%	60%	—	+	—	—	—	—	—	↓	+	++	+
Polycystic kidneys	Family history	96%	—	±	—	—	—	—	—	↓	+	++	+
Acute renal failure	Shock, intox.	—	—	+	(+)	—	—	—	—	↓	+	—	—
Toxaemia of pregnancy	5th-9th month of pregnancy	73.5%	+	++	—	—	—	—	—	↑	—	—	—

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