Current Practice

URINARY TRACT DISEASES

Glomerulonephritis

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In the study of diffuse parenchymatous renal disease facts are being accumulated rapidly. Many ideas have been rendered obsolete but have not yet been replaced. In particular, our ability to describe histological appearances in great detail at a few points in time completely overwhelms our present understanding of their origins and evolution. For the moment, therefore, most diagnosis is still descriptive, first in terms of the clinical features, and then of the histology found.

The Term

Immediately we encounter difficulties of terminology. Glomerulonephritis is a pathological term and strictly should be used to describe anatomical or histological appearances. The less committal term "nephritis" is suitable for clinical situations where glomerulonephritis is suspected. Strictly, also, glomerulonephritis should imply the presence or results of inflammation within the glomeruli. Nevertheless, the term is often broadened in two fashions:

(1) to include all glomerular diseases which are not associated with systemic conditions

(2) clinically, to mean "nephritis" as suggested above, both "acute" and "chronic."

The following gives the simple empirical classification of glomerular disease used by me and by many others:

Proliferative Glomerulonephritis

While the "minimal change" lesion and membranous nephropathy (discussed in the subsequent article) appear to be single conditions with consistent natural histories, proliferative glomerulonephritis presents an almost infinite number of appearances and clinically varies from completely benign to rapidly fatal. Clearly we are not dealing with a single process. The pathologist can distinguish many sub-groups of proliferative glomerulonephritis, and terminology—far less identity—has still to be agreed. The clinician may easily become bewildered. Some of these pathological descriptions, however, are already precise enough to represent processes important to the clinician. Important because they have

reproducible clinical associations and may influence management and prognosis. Other varieties have no such correlations, and it must be said immediately that these affect most patients with long-standing nephritis.

One glomerular reaction is proliferation of its cellular elements. This commonly occurs in association with inflammatory changes and many believe that, even when inflammation is not obviously present, proliferation indicates its presence at low level or in the past.

Proliferative glomerulonephritis consists of

(1) *Proliferation* of endothelial cells (those lining the capillaries); of mesangial cells (those enclosed within the glomerular stalk); of capsular or epithelial cells (those lining Bowman's capsule and covering the outer surface of the glomerular capillaries) to form crescents. Each may be present alone or in combination.

(2) *Exudation*. A variable amount of swelling of the tuft with polymorph infiltration, occasionally with destruction of glomerular architecture (necrosis).

(3) *Scarring* of the glomerular tuft, often with shrinkage, distortion, or obliteration of the glomerular architecture.

Alone or in combination these elements go to make up the spectrum of proliferative glomerulonephritis, sometimes with deposits on or within the basement membrane as well. The varieties which are of clinical importance are as follows:

Acute exudative glomerulonephritis (Figs. 1 and 2)
 Mesangial sclerosis (post-streptococcal glomerulonephritis) (Fig. 3)
 Membranoproliferative (lobular, "mixed") glomerulonephritis (Figs. 4 and 5)
 Glomerulonephritis with extensive epithelial crescents (Fig. 6)
 Focal glomerulonephritis, affecting only parts of some glomeruli.
 Advanced glomerulosclerosis due to glomerulonephritis.
 Other proliferative glomerulonephritis.

The commonest finding in patients with long-standing glomerulonephritis is "other" proliferative glomerulonephritis.

Aetiology

We know nothing whatever about the aetiology of the great majority of chronic forms of glomerulonephritis. Information from animal models of nephritis has been of value, but is of greatest relevance to benign or very rare varieties. What evidence we do possess may be summarized as follows:

(1) Local vascular damage (from various agents, whose nature is unknown) may lead to the activation of both immune and coagulation systems; this leads to antibody and complement deposition, coagulation, fibrin deposition and fibrinolysis, and cellular proliferation.

(2) The kidney may have antigens indistinguishable from those which might appropriately be attacked—for example, those on the cell walls of streptococci or other organisms. The kidney then sustains damage as well as the organisms.

(3) The kidney may be attacked by antibody directed specifically against glomerular components—that is, a true "auto-immune" or "auto-aggressive" condition. The best known is that with circulating antibody directed against glomerular basement membrane.

(4) The kidney, receiving one-fifth of the cardiac output and having especially permeable capillaries, sieves out circulating antigen-antibody complexes. Those formed in antigen excess are

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toxic and initiate inflammation. The antigens are non-specific and the kidney is involved as an "innocent bystander."

Clinical Pictures

Glomerulonephritis may present as, or be found in, any of the main clinical syndromes produced by glomerular disease (see Table). Almost all patients with an acute nephritic onset will show some form of proliferative glomerulonephritis in

Clinical Pictures of Glomerulonephritis

	% with Proliferative Glomerulonephritis
Acute nephritic syndrome	100
(a) acute nephritis	80
(b) recurrent haematuria	{ adults 45
Nephrotic syndrome	{ children 10
Symptomless proteinuria or haematuria	50-70
Chronic renal failure	60-70
Acute renal failure	5

FIG. 1.—One of the characteristic lesions of classical acute post-streptococcal glomerulonephritis seen by the electron microscope. On the right is an epithelial cell, with foot processes on the outer aspect of the basement membrane, which runs from top to bottom. These are interrupted by a "hump" (H)—a broad-based, nodular deposit of electron-dense material on the outer surface of the basement membrane. These "humps" are characteristic of the deposition within the glomeruli of soluble, circulating antigen-antibody complexes. On the left, within the capillary lumen, part of a polymorphonuclear leucocyte can be seen (L). E.M. $\times 5,775$ (photograph by Dr. E. Glasgow, patient of Dr. R. H. R. White).

FIG. 2.—Acute post-streptococcal exudative glomerulonephritis: the light-microscopic appearances. The glomerular tuft is swollen, so that Bowman's space is obliterated. The tuft is also hypercellular, both from proliferated endothelial and mesangial cells and from infiltration with polymorphonuclear leucocytes, whose nuclei show smaller and more densely stained than those of the glomerular cells.

FIG. 3.—Mesangial sclerosis (lobular stalk thickening, "post-streptococcal" glomerulonephritis). A glomerulus under low power. The glomerular architecture is well preserved, but there is an accentuation of the centrilobular connective tissue, stained black in this preparation, which gives the glomerulus the appearance of a hand with its fingers radiating from the hilus, seen at bottom left. The peripheral capillary loops, however, are widely patent with normal capillary walls, distinguishing this appearance from membranoproliferative glomerulonephritis. The appearance may be seen in biopsies from healing post-streptococcal glomerulonephritis from about the sixth week onward, or in patients with the nephrotic syndrome and some haematuria, as here. In general, patients with this appearance in their biopsies do well. (P.A.S.M. $\times 137$).

FIG. 4.—Membranoproliferative glomerulonephritis. A low power view of a glomerulus. The tuft is enlarged, and there is proliferation of the endothelial and mesangial cells. The "lobules" of the glomerulus are accentuated. The capillary walls appear thickened, and in some areas there is extensive solidification of the tuft with capillary lumina embedded in areas of proliferation and sclerosis. The capillary wall thickening, unlike that of membranous nephropathy, is irregular in distribution, some loops appearing almost normal. When the "lobular" appearance of the tuft is extreme, this type of glomerulonephritis has been called "lobular." Because both capillary wall thickening and proliferation are both present, it has also been called "mixed membranous and proliferative" glomerulonephritis. The capillary wall lesions, however, are quite distinct from those of membranous nephropathy (see Fig. 5), and those proliferative glomerulonephritis which show nonspecific capillary wall sclerosis from scarring and shrinkage. The patient had a nephrotic syndrome complicated by hypertension and reduced renal function, and had macroscopic haematuria throughout the course of the disease. (H. and E. $\times 146$).

their kidneys. Though an important proportion of the other groups show proliferative glomerulonephritis, many patients presenting with these syndromes may have other conditions.

One of the few constant features of proliferative glomerulonephritis is haematuria at some time in the disease. This may be macroscopic and is usually present constantly over periods of weeks or months. In general, those forms of nephritis which are progressive also show appreciable proteinuria.

FIG. 5.—Membranoproliferative glomerulonephritis. A high power view of three glomerular capillary loops, in a silver stained preparation. Mesangial cells (centre) are proliferated and surrounded by dense fibrillar matrix, which extends out round the inside of the capillaries on the left, giving an appearance of "duplication" of the basement membrane. In fact, the true basement membrane is the thin black line on the outside of the capillaries. In addition, there are deposits (arrow) which do not take the silver stain and which separate the basement membrane from the cell cytoplasm and the mesangial sclerosis. These deposits are thus on the inside of the basement membrane (subendothelial deposits), and contain both immunoglobulins and C3 component of complement, imparting a beaded or "lumpy bumpy" appearance to the specimen stained for these substances using specific immunofluorescent techniques. Of patients with this glomerular appearance, 60–80% show also persistently low plasma concentrations of the C3 component of complement, and this appearance is sometimes referred to as "hypocomplementaemic (persistent) nephritis." (P.A.S.M. $\times 1,000$).

FIG. 6.—Proliferative glomerulonephritis with extensive epithelial crescents. The glomerular tuft, which is itself the site of active proliferation, is surrounded by an enveloping crescent of proliferated epithelial cells lining Bowman's capsule. Healing of this lesion, even if it should take place can occur only with complete sclerosis of the glomerulus. The patient had a rapidly progressive glomerulonephritis, and despite treatment with corticosteroids, cyclophosphamide, heparin, and peritoneal dialysis he died. (H and E. $\times 175$).

The acute nephritic syndromes are characterized by sudden onset, haematuria (often macroscopic), and by variable hypertension and oedema. There are five main varieties.

(1) Classical Acute Nephritis

This is no longer a common condition, whether because of prompt treatment of antecedent infections, or a change in the principal causative organism (the streptococcus) is unknown. Antibiotic treatment is the more likely. The preceding infection is usually a β -haemolytic streptococcus of only a few specific types (for example, 12, rarely 2 and 49), but has been proved on occasions to be a pneumococcus or a virus. In Britain, the site of infection is usually the throat, but in less developed countries is more frequently cutaneous. During the latent period of one to three weeks following the infection antibody to the organism is formed—but in rather small amounts, so that there is still an excess of antigen. Soluble antibody-antigen complexes are formed when an excess of antigen is present; these pass to the kidney and are trapped there, probably forming the extracapillary "humps" which may be seen during the first six weeks of the disease (Fig. 1). The plasma concentration of all components of complement falls (Fig. 7), returning to normal after about six weeks. The

FIG. 7.—The complement activity of the plasma, measured by the plasma concentration of the C3 component of complement, B1C globulin, in 27 patients with uncomplicated acute nephritis (●) and one patient with persistent hypocomplementaemia (▲). The C3 concentration was low initially in all patients studied at this time, and returned to normal within, at most, eight weeks in all the uncomplicated patients. Biopsy in eight of these patients showed in every case appearances similar to those shown in Figs. 1–3. In the other patient (▲) there were several atypical features during the acute attack—in particular, heavy proteinuria and no hypertension at onset. Histologically this patient's biopsy specimen looked like a healing poststreptococcal glomerulonephritis (Fig. 3), with normal capillary walls, but the plasma C3 concentration remained persistently low, even though protein disappeared from the urine, only microscopic proteinuria persisting. Fourteen months later she had a severe exacerbation with uraemia, and a nephrotic syndrome. Another renal biopsy showed the typical picture of a lobular membranoproliferative glomerulonephritis (Fig. 4) so frequently found in patients with persistent hypocomplementaemia. The value of making C3 measurements is obvious, particularly in the first two weeks of an apparent acute nephritis, and after eight weeks have elapsed if the patient is giving cause for concern.

kidney shows an acute exudative and proliferative glomerulonephritis (Figs. 1 and 2). It has also been suggested that the kidney may share antigenic sites with streptococcal membrane, and that the type 12 streptococcus particularly gives rise to soluble antigens.

The clinical picture is well known, with malaise, heaviness or pain in the loin, haematuria (usually macroscopic), and sometimes periorbital oedema. Small amounts of urine are passed, which is concentrated but low in sodium and contains red cells, leucocytes, a small amount of protein and casts. On examination there is often hypertension, the circulation may be overloaded and the lungs are congested clinically and on x-ray examination. A few patients (who may be missed initially) present with hypertension and relatively minor or even absent urinary findings.

The clinical course is in virtually all cases benign, but during the acute attack heart failure, uraemia, and extreme hypertension with convulsions may occur. Their appearance bears no relation whatever to ultimate prognosis. Venesection is especially valuable but a large dose of intravenous frusemide or ethacrynic acid may be equally effective. The blood pressure may be lowered by methyl dopa, or intravenous hydralazine in emergency; fits are best treated with diazepam, since its removal is not dependent on the kidney and it is more pleasant for both doctor and patient than paraldehyde. Until the diuresis appears fluids must be limited according to output and calculated needs, and a high carbohydrate, low-salt, low-protein diet fed. Since most patients are from 5 to 15 years of age this usually means unlimited sweets with Hycal or Caloreen, and the substitution of Edosol for milk in the rare infant with the condition. It is logical to give a ten-day course of antibiotic to eliminate the causative organism after a throat swab has been taken and Antistreptolysin O (A.S.O.) titre has been performed.

The outlook for almost all young patients with acute nephritis is good, but with advancing age more patients are found to be suffering from other types of acute nephritic syndrome carrying a much poorer prognosis. Most patients' urinary sediment remains abnormal for three to six months, and it may take two years for haematuria to disappear. There is no benefit from keeping the patient in bed after the acute stage is over, and may be psychologically and physically harmful.

With careful investigation of the initial attack, it now appears that those forms of acute nephritis which go on to progressive disease are usually atypical from the start—for example, the onset was not particularly definite; heavy proteinuria was present from the outset and became the dominant feature; hypertension was not present; or the serum complement remained low for longer than six or eight weeks. In all such patients, and in those with extreme or persistent oliguria or anuria, early renal biopsy will be necessary; this will be a small minority. Membranoproliferative glomerulonephritis (Figs. 4 and 5) is particularly important.

A more frequent need for biopsy information arises in the patient whose urine is not clear several months after the attack: if renal function is good, proteinuria slight, the serum complement normal and the initial attack typical then biopsy should prove unnecessary, but parental anxiety or social factors may dictate otherwise. Renal biopsy at this stage, from six weeks to six months following the attack, may show the "post-streptococcal" pattern of mild mesangial sclerosis (Fig. 3). Whether this has long-term significance, leading eventually to chronic renal failure, is unknown but now seems improbable.

(2) Recurrent Haematuria

In this condition, repeated attacks of macroscopic haematuria appear immediately after exercise or minor, usually viral, upper respiratory tract infections. Hypertension is usually absent, and the patient may be quite well during the attack. A minority feel ill, have fever, loin pain, and sometimes a blotchy erythematous rash. The bleeding may be profuse enough to lead to clot colic during the attack, or even anaemia if attacks are frequent. The patients are predominantly male, and usually children or young adults.

The condition, though alarming, is usually benign. Other causes of haematuria must be excluded, and the finding of red cell casts is particularly valuable in indicating a renal origin for the blood. Biopsy is not necessary unless there is hypertension, persistent heavy proteinuria, persistent low serum complement, reduced or falling renal function, or a family history of nephritis or deafness. If biopsy is performed in a straightforward case, the appearance is frequently entirely normal, or glomeruli may show endothelial and mesangial

proliferation, but the appearances found in the occasional patient with persistently low serum complement are described below. Though corticosteroid therapy will abolish attacks in most straightforward cases, this is usually unnecessary; the principal problem is reassurance. The prognosis in the familial case is, in contrast, usually poor, and response to any treatment is doubtful. This is true both of the Alport variety (haematuria and deafness) which affects males, and usually of familial haematuria without deafness.

(3) "Mixed" Acute Nephritis and Nephrotic Syndrome: "Hypocomplementaemic" Nephritis

Many patients present with features of both an acute nephritis and proteinuria heavy enough to lead to a nephrotic syndrome. These patients almost invariably have some form of glomerulonephritis in their renal biopsy specimen. Renal biopsy is usually called for in this group, and a variety of appearances may be seen, though some form of proliferative glomerulonephritis is usual. A particular feature may be the persistently low level of the serum complement (Fig. 7) and there is a characteristic form of glomerulonephritis which is associated with this finding (Figs. 4 and 5). In addition to the endothelial and mesangial proliferation the capillary walls are thickened with a deposit on the inner surface, or within the capillary wall. This type of glomerulonephritis has been called both "membranoproliferative" and "lobular." As mentioned above, these patients may initially appear to have acute nephritis; more rarely recurrent haematuria is the presenting symptom but the majority have persistent proteinuria or a nephrotic syndrome with hypertension and haematuria.

Treatment of this group is unsatisfactory. Immunosuppressant drugs seem logical in view of the persistently low serum complement, but apparently the latter is not directly related to complement fixation in the kidney since a low complement persists after bilateral nephrectomy. No treatment has been shown to affect the prognosis of this group of patients, which is slowly downhill to uraemia in early adult life; corticosteroids in high dose may even be dangerous in the early acute hypertensive phase.

(4) Rapidly Progressive Glomerulonephritis

A characteristic, unfortunate but rare group of patients are those with glomerulonephritis and extensive proliferation of epithelial cells lining Bowman's capsule (Fig. 6). This may present as an acute nephritis with anuria or as a nephrotic syndrome rapidly declining into uraemia over a few weeks. This pattern may also be seen in several systemic vascular diseases, particularly polyarteritis nodosa and Goodpasture's syndrome. Many of these patients show circulating antiglomerular basement membrane antibody and lymphocytes committed against the kidney; the result is a rapidly destructive lesion which usually leads to death or regular dialysis treatment. A prominent feature of crescent formation is the presence of fibrin, and these patients have been treated with various immunosuppressant and anticoagulant regimens. Controlled information of their value is lacking, but treatment is worth while since the condition virtually always destroys the kidney; the circulating antibody and cells may also attack a kidney transplanted into the patient.

(5) Acute Nephritis as Part of Systemic Disease

The systemic condition associated most commonly with acute nephritis is Henoch-Schönlein purpura. This affects mainly children of school age, and fortunately the prognosis of the nephritis is usually good, even when quite severe histological changes are present, probably because they usually affect the kidney patchily. The histological picture

seen in renal biopsies varies from the mildest proliferation (the common pattern) to very severe rapidly progressive nephritis with crescents. Corticosteroids do not appear to affect the prognosis of the more severe forms—associated with reduced renal function, hypertension, heavy proteinuria, and a nephrotic syndrome—but cyclophosphamide may. As usual, controlled information is lacking and in this varied group will be difficult to obtain. *Polyarteritis nodosa* and *Goodpasture's syndrome* are discussed above. *Subacute bacterial endocarditis* may be complicated by proliferative glomerulonephritis, which is frequently focal (segmental) within the glomerulus. This is probably immune in origin, not embolic.

Persistent Proteinuria and the Nephrotic Syndrome

These may be taken together since the presence or absence of oedema is a shifting distinction (see following article). Any variety of proliferative glomerulonephritis mentioned above may be found in these patients: acute exudative, mesangial scarring, "focal," membranoproliferative or lobular, or with extensive crescent formation. The prognosis will vary accordingly, so that even if no satisfactory treatment is available renal biopsy is worthwhile in any patient with persistent proteinuria who has haematuria, hypertension, reduced renal function, persistently low serum complement, or non-selective pattern of differential protein clearances (see following article). However, when all patients have been allocated to these defined groups, some two-thirds of those with proliferative glomerulonephritis will be left. We know very little about the nature of these patients' disease. Their kidney biopsy specimens show variable scarring, and their prognosis is also variable. Controlled trials have shown that neither corticosteroid nor azathioprine treatment affect prognosis; there is some uncontrolled evidence that cyclophosphamide may be of benefit, especially in children.

Chronic Renal Failure

By the time uraemia with symptoms appear the kidney is usually so scarred that secondary pyelonephritis and vascular glomerulosclerosis obscure the nature of the original disease ("end-stage" kidney). Many such kidneys as these have been

called "chronic pyelonephritis" in the past, and it is not sufficiently realized that various forms of glomerular disease—principally proliferative glomerulonephritis—account for two-thirds of the patients placed on dialysis or treated by transplantation. The most effective method of delaying decline in renal function from any cause is, of course, strict control of the severe hypertension. This is almost invariable in any form of proliferative glomerulonephritis leading to advanced renal failure.

Acute Renal Failure

Rapidly progressive glomerulonephritis with crescent formation, as discussed above, may sometimes present in this fashion. Some patients will turn out to have some underlying vasculitis, or Goodpasture's syndrome.

Further Reading

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ANY QUESTIONS?

We publish below a selection of questions and answers of general interest.

Vaginal pH

Q.—Does the vaginal pH vary with the stage of the menstrual cycle and is it a guide to ovulation? Is there a simple method of ascertaining its acidity or alkalinity at any given time? Is the sex of a child influenced by the pH of the vagina at the time of conception, and, if so, could douching with, say, weak acid or weak alkali before intercourse influence the sex of the conceptus?

A.—The pH of the vagina is dependent on its cellular glycogen content acted upon by Doderlein's bacilli to produce lactic acid. The secretions of the cervix are relatively more alkaline than the vagina and so may modify the pH. Seminal fluid is also more alkaline than the vagina.

Karnaky¹ studied the vagina from top to bottom and on all four walls with an electronic recording machine. He found that there was no gradient in pH from top to bottom, and it varied from 3.5 to 4.2. Jeffcoate,² how-

ever, thinks that the pH is higher nearer the cervix because of the cervical secretions. Also he believes that the pH range is from 4.0 to 5.5 with an average of 4.5. Fluhmann³ suggests that the pH varies during the menstrual cycle, being 4.0 to 4.2 in the pre-ovulatory phase, rising to 4.5 to 5.8 at ovulation. Within 48 hours it drops to 4.0, rising again to 4.4 about two days before menstruation.

It seems probable that these changes are to be correlated with the changes of cervical secretion. The Geigy scientific tables⁴ give the pH of cervical secretion as 7.8. Of course the pH of the vagina changes during menstruation as the slightly alkaline blood streams into it. Seminal fluid has a pH of 7.2 to 7.39,⁴ so that after intercourse the pH of the vagina is altered. The pH of the vagina also changes with vaginal infections and during pregnancy, and when there are cervical lesions such as ectropion.

The clinical history, the temperature rise after ovulation, and the changes in the

crystallization pattern of the cervical mucus are better and simpler guides to ovulation than pH, which is not therefore used. The various colour indicators for pH have such relatively wide pH ranges⁴ that they are of little use in detecting minor changes.

Claims have been made that the pH of the vagina influences the sex ratio at fertilization. The claims have not been substantiated. Bicarbonate or vinegar or lactic acid douches may change the pH and have been advocated to influence the sex of the child. Shettles⁵ suggests that coitus at the time of ovulation, female orgasm increasing cervical secretions, or precoital alkaline douches increase the chances of a male child being conceived.

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