During the past ten years there have been rapid advances in immunology and nephrology, but very little has yet been assimilated into a clear and rational body of knowledge. It is still impossible, therefore, to identify those patients whose renal disease is immunologically based, and to foresee the response to treatments specifically aimed at suppressing the immunological response or lessening its damaging effects. Also, it is important not to increase confusion by overdifferentiation of a group of conditions that may all have much more similar aetiologies than is now apparent.

There is clinical evidence of immune involvement in many cases of glomerulonephritis and I shall try to indicate the ways in which our limited knowledge can be used to clarify the situation.

THE HETEROGENEITY OF GLOMERULONEPHRITIS

Glomerulonephritis is not a single disease, but a group of diseases. Examination of renal biopsies has shown a wide variety of histological lesions associated with the syndromes of nephritis (Brewer, 1964) and now the clinical progress of many patients, with or without treatment, can be predicted with some accuracy from the biopsy appearances (Hardwicke et al., 1967). The capacity of the glomerulus to respond to noxious stimuli is clearly limited and the very high proportion of the cardiac output it receives makes it particularly susceptible to circulating pathogenic influences. Until aetiological factors can be positively identified we must bear in mind two points:

(a) Two or more agents may give rise to identical clinical syndromes and histological appearances just as clinically identical allergies may be due to a wide range of antigens.

(b) The same aetiological agent may produce lesions of widely varying severity and appearance in different subjects. Similarly, atopic subjects are much more susceptible to allergies than the bulk of the population.

Some forms of glomerular damage are closely associated with systemic disease such as systemic lupus erythematosus, but I shall deal only with those in which glomerular involvement appears to be primary. By using a com-
combination of histology and function testing, and observing clinical progress and response to treatment, we can now differentiate this group into four clear entities, which will be discussed in more detail later.

EVIDENCE OF IMMUNOLOGICAL INVOLVEMENT

Direct

(a) The demonstration of circulating antibody to glomerular or renal components, or the finding of immunocompetent cells specifically sensitised to such components.

(b) The demonstration of circulating antigen-antibody complexes, combined with their deposition in glomeruli and associated glomerular damage.

(c) Deposition in the glomeruli of one or more immunoglobulins with affinities for specific antigens.

Indirect

(a) High serum levels, or increased turnover rates, of immunoglobulins in association with active disease.

(b) Similar evidence in relation to the complement system.

(c) The association of glomerular damage with allergic disease affecting other body systems, and a reciprocal relationship of activity between the two manifestations.

THE MECHANISM OF IMMUNOLOGICAL DAMAGE

The mechanism of immunological damage varies with host response and with the type of antigen used. On this basis Gell and Coombs (1968) have defined four types of immunopathological response. Different species may show different types of response to the same antigen and even in a single species, using genetically defined strains, variability can occur. This makes hazardous the interpretation of human responses in the light of animal studies.

Current evidence suggests that the mere presence of antigen-antibody complex may not be damaging, but it can set in train a series of reactions that are mediated by activation of the complement system. These include the release of vasoactive peptides, with increased vascular permeability, the attraction of one or all of the circulating leucocyte types, activation of clotting factors, with platelet aggregation and fibrin deposition that can lead to secondary fibrosis and scarring, and possibly to the activation of specifically cytotoxic antibody (Cochrane and Dixon, 1968).

Consequently, any therapeutic agent that will inhibit one or all of these secondary manifestations may be of value in any immunologically based disease; conversely, the inhibition of these secondary effects could also lead to failure of removal of the original complex, and perpetuation of the un-
desirable reaction in a subacute form leading to chronic damage in a situation in which the original lesion was self-limiting (Germuth et al., 1968; Valdes et al., 1969).

TYPES OF GLOMERULONEPHRITIS IN MAN
The three major types, based on renal histology and supported by clinical evidence, are:

(a) Minimal change disease.
(b) Membranous glomerulopathy.
(c) Proliferative glomerulonephritis.

The first two of these are well-defined clinical and pathological entities, although their aetiology remains obscure. The third encompasses such a wide variety of histological lesions, clinical symptoms and signs, and varieties of prognosis that it almost certainly includes many aetiological agents, only one of which, the nephritogenic streptococcus, is in any way defined.

Minimal Change Disease
On light microscopy the glomeruli are normal; on electron microscopy only the foot processes of the epithelial cells are damaged and the cytoplasm vacuolated. Clinically, massive proteinuria is usually the sole functional abnormality. This usually resolves with steroid therapy, with concurrent recovery of the histological damage.

There is no direct evidence of immunological involvement in this condition; the glomeruli are free of immunoglobulin and circulating antibody has not been found. There is, however, some indirect evidence that this lesion can involve immunological mechanisms; some cases have been shown to be associated with hypersensitivity but they are not histologically specific and also respond to steroid therapy. In most cases the serum complement is normal; however, there are occasional cases in which attacks and relapses are associated with marked falls in haemolytic complement (Hardwicke, 1965).

In rats and dogs an identical lesion can be induced with Puromycin amino-nucleoside; this lesion is reversible initially but its response to steroids is equivocal.

Membranous Glomerulopathy
If any form of glomerular disease merits the term Ellis Type II nephritis, it is this lesion. Oedema of insidious onset is the presenting symptom, and the course is usually slow and unrelentingly downhill to renal failure (Hardwicke
Histologically there is thickening of the basement membrane without gross cellular proliferations. Silver stains show this thickening to be nodular, the lumps being on the outside of the membrane. Electron microscopy reveals deposits within the substance of the membrane itself, and, on immunofluorescence, these prove to be immunoglobulin. In spite of this direct evidence of immunological involvement there are no accompanying systemic signs of allergy. Serum levels of immunoglobulin and complement are normal, and there is no evidence of allergic involvement in any system other than the kidney. The histological appearances can be reproduced experimentally only in rats, by the injection of preparations of subcellular components of renal tubules in Freund’s adjuvant. The specific antigen is brush-border, and the disease can be induced by using autologous kidney from unilaterally nephrectomised animals. This true autoimmunity is self-perpetuating until the kidney fails. Similar regimes can produce renal disease in other animals, but the histological appearances differ.

**Proliferative Glomerulonephritis**

This type comprises over 50 per cent of all cases of glomerulonephritis, and is very heterogenous both in clinical course and histological appearances (Hardwicke et al., 1967). The best defined entity is acute streptococcal glomerulonephritis, although it is probable that other infections may produce a similar syndrome.

**Acute glomerulonephritis** is a condition in which there is clear evidence of an immunological basis. Some 10 to 15 days after infection with a nephritogenic organism an acute haematuria presents. The serum immunoglobulin is raised and the complement low, and specific antibodies to the organism may be found in the circulation. The glomerulus shows proliferation of the endothelial cells and infiltration with eosinophils and polymorphs. In very severe cases there may be fibrin thrombi present, fibrinogen in Bowman’s space, and gross epithelial cell proliferation leading to crescent formation. Electron microscopy shows characteristic deposits in the epithelial cells on the outer side of the basement membrane, and these stain positively for IgG and complement. In most patients the disease resolves spontaneously. Occasionally, severe crescent formation leads to acute renal failure, while slow recovery is associated with mesangial cell proliferation and the appearance of a lobular glomerular tuft.

The experimental lesion most closely resembling this is acute serum sickness. Rabbits given a single injection of foreign protein develop antibodies at 5 to 10 days, initially circulating as antigen-antibody complex soluble in antigen excess. As the complexes reach a critical size they deposit from the
circulation in vascular endothelium, leading to a variety of systemic effects such as urticaria and arthritis; at about the same time proteinuria and haematuria appear and all the residual antigen disappears rapidly from the circulation. In human acute serum sickness that may follow intravenous injection of foreign proteins, proteinuria, and microscopic haematuria are the rule, although with nephritogenic organisms renal involvement is more striking than systemic damage. It is not known why this selective damage occurs but it has been suggested that there is cross reactivity between infective antigens and glomerular structural protein.

These patients represent the majority of those with acute disease, but in a small proportion a very striking lesion occurs, with massive crescent formation, early and persistent oliguria, and often haemoptysis. This is Goodpasture’s syndrome in which the glomerular deposition of IgG is linear and subendothelial, and the presence of specific antibody to basement membrane can be demonstrated, either by elution from the glomeruli following nephrectomy, or circulating free in the serum. This rare condition is analogous to the nephritis induced in rabbits by injecting heterologous anti-rabbit-kidney serum, and to the nephritis that appears in sheep following the injection of heterologous kidney preparations. In addition to producing hetero-antibodies, such sheep also produce autoantibody to their own glomeruli, and a progressive fatal disease ensues.

Progressive glomerulonephritis is the most common type of proliferative glomerulonephritis. A wide variety of histological lesions are seen: involvement may be diffuse or focal, cellular proliferation may affect endothelial, epithelial or mesangial cells, and polymorph infiltration may be found. All show deposition of immunoglobulins in the glomeruli, although the severity, localisation and type of immunoglobulin may vary, and the deposition of complement is variable. Indirect evidence of immunological involvement is also variable; serum immunoglobulins may be raised or lowered, serum complement may be low or normal and occasionally there is evidence of immune disease affecting other systems. Efforts to classify these patients on a purely histological basis have led to a confusing multiplicity of diagnoses, and it is still possible that they all represent responses to a single pathogenetic mechanism of widely varying severity.

In the majority of cases the deposits of immunoglobulin are sub-endothelial and patchy in distribution, suggesting that deposits of antigen-antibody complexes are involved. For this reason the effects of prolonged antigen administration to animals have been carefully studied (the ‘chronic serum sickness’ model.) With carefully graded doses of antigen given intravenously (12.5 mg/kg/day of BSA) to rabbits it is now possible to produce persistent
proteinuria in a proportion of animals. The sequence of events is illustrated in Fig. 1. An initial bout of proteinuria occurs at the time at which animals first pass into antibody excess 24 hr after each intravenous dose of antigen; this is analogous to acute serum sickness following a large single dose of
antigen. After a varying period in antibody excess, some animals develop increasing immunological paralysis; at about the time at which daily antibody production is only just enough to destroy the injected antigen in 24 hr, a second bout of proteinuria and glomerular damage occurs, which may become progressive. Only those animals that show persistence of antibody production at a relatively low level are affected. The histological nature of this lesion is remarkably mild and even those animals that die show only progressive hyalinisation of glomeruli as renal function declines, with very little inflammatory change or cellular proliferation.

While it still seems very probable that soluble complexes with a particular affinity for renal glomerular capillaries are the cause of the pathological change in many patients with proliferative lesions, this still remains to be proved. In animals, complexes can be readily demonstrated in the circulation (Boynes and Hardwicke, 1968). In man, the presence of IgG molecules of abnormally high molecular weight with the characteristics of soluble antigen-antibody complex have been found only in SLE. No studies have yet been reported on the search for such complexes in acute nephritis. In malarial nephrosis some suggestive changes in complement have been reported (Soothill and Hendrickse, 1967), and we have examined sera from similar patients, but can find no evidence of circulating IgG complexes (Hardwicke and Kibukamusoke, 1970).

CONCLUSIONS
There is fairly convincing evidence that all forms of 'primary glomerulonephritis' are associated with some form of immunological mechanism. On the basis of animal experimentation Dixon (1968) has classified such renal disease into two forms—soluble complex disease and disease caused by damage due to circulating anti-kidney antibody. In my opinion this is a very useful working hypothesis, but much more evidence is required before it can be accepted in human disease.

To attempt a classification of human glomerulonephritis on the basis of immunopathology would be premature and, as yet, have no relevance to treatment; the histological classification, admittedly unsatisfactory, has such relevance (Hardwicke et al., 1967).

With the passage of time the situation may well be reversed and the identification of specific antigen and antibody may give us a positive aetiological diagnosis. Potentially helpful lines of work would include the search for specifically immunocompetent cells or circulating antibody directed against antigens native to the kidney or shown to deposit preferentially therein, for circulating soluble complexes in nephritis, and the identification, after elution,
of antibody deposited in the glomeruli. Assessing the effect of chemotherapeutic agents is particularly difficult in nephritis, as frequent biopsies are not possible, and improvement or deterioration cannot be assessed satisfactorily with existing tests of function. A promising development is the detection by immunochemical methods of increased amounts of structural elements of tubules and glomeruli in the urine of patients with active disease. If their quantitative output is found to reflect destruction of glomeruli, this estimate may prove a most useful indicator of drug effectiveness.

New techniques in immunology appear almost daily, and it is not therefore surprising that it is sometimes difficult to interpret their exact significance. Even five years ago it was not easy to see how this field would advance, but now it seems that any day we may read that crucial paper which will lead to a clarification of the whole situation.

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