Hospital Topics

Bright's Disease Today: The Pathogenesis and Treatment of Glomerulonephritis*—II

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Most doctors treat human beings rather than rats, mice, or rabbits, and we may ask what we can learn from elegant experimental models which will help us with patients suffering from glomerulonephritis. The answer is that we can learn much but that in most cases of human glomerulonephritis we have as yet no evidence of similar pathogenesis.

Soluble Complex Disease

The first suggestion that human glomerulonephritis might relate to infection and immunity came from observations of glomerulonephritis following scarlatina and Schick's suggestion in 1907⁴⁵ that the antecedent streptococcal infection might have induced an immune reaction affecting the kidney similar to the events of serum sickness. Many other observations fit with the idea that acute nephritis in man is an *acute soluble complex illness* with streptococcal antigens as the initiating event⁴⁶—for example, the latent period after the infection, the presence of extracapillary "humps" containing antibody and complement during the first few weeks of the illness, and the generally benign course.

Several facts, however, do not fit so well. Firstly, we need an explanation of why some streptococci (types 12 and 2 in the throat, types 49 and 57 in the skin) are much more commonly associated with nephritis than others. It has been suggested that these are varieties more apt to give soluble cell wall antigens than other strains.⁴⁷ Secondly, in soluble complex nephritis in animals the serum concentrations of all the components of complement are depressed during the early stages of the disease. In human acute glomerulonephritis only the later components are consistently depressed. Finally, although it has proved possible to show streptococcal antigens in the mesangial regions of the glomerulus, it has not yet been possible to show these in the extracapillary immune deposits where one might expect them. Thus some additional pathogenetic mechanism may be operating, and this may relate to the cross-reactions between streptococcal membrane antigens and other human membrane antigens, including glomerular basement membrane antigens⁴⁸ and HI-A antigens.⁴⁹

The less well-studied, non-streptococcal acute nephritis occurring after virus and pneumococcal infection presumably operates through similar mechanisms. The glomerulonephritis associated with secondary syphilis^{50 51} appears on morphological

grounds to be acute soluble complex nephritis, but only a handful of cases have been reported.

It is, however, the role of *chronic soluble complex deposition* in human disease that is the more important question. We have two forms of chronic nephritis in man, in whom it has been established beyond reasonable doubt that chronic soluble complex deposition plays a major part in pathogenesis. These are the nephritis of systemic lupus erythematosus^{52 53} and the nephropathy associated with quartan malaria.^{53 56} Here the antigens (DNA and *Plasmodium malariae* respectively) have been found in the immune deposits within the glomeruli, and specific antibody can be eluted from the renal tissue. It might be argued that the formation of complexes is an epiphenomenon of the disease, but the fall in the incidence of the nephrotic syndrome in Guyana when *P. malariae* infestation was eliminated⁵⁷ is very impressive (see Table). It is appropriate that we know a great deal about one of the commonest forms of chronic glomerulonephritis in the world as a whole.

Incidence of Nephrotic Syndrome

	Country	Hospital	Admission Rate %	Malaria
Africa	Nigeria	Ibadan	2.4	+
	Uganda	Fort Portal	1.8	+
		Mulago	2.0	+
S. America	Rhodesia	Harari	0.7	+
N. America	Guyana	Mackenzie	2.8	—
	U.S.A.	Mackenzie	0	—
		L.A. County	0.03	—

From Kibukamusoke *et al.*⁵⁸.

Recently there has been much interest in the very rare association of tumours with renal lesions, and tumour antigen and antitumour antibody have been shown in the glomeruli of one patient.⁵⁸ Other rare but well-studied instances of antigens causing chronic soluble complex disease in man are Australia antigen,⁵⁹ staphylococcal infection of subarachnoid-jugular shunts for hydrocephalus^{60 62} and in subacute endocarditis,^{63 64} mixed cryoglobulin,⁶⁵ and thyroglobulin.⁶⁶

Obviously other antigens responsible for progressive human glomerulonephritis will be identified, and the search for chronic viral disease analogous to the infections in mice should prove rewarding. On the other hand, patients with known viral diseases should be screened for nephritis. For example, one might predict that some patients suffering from kuru, measles encephalitis, or chronic Australian antigenaemia might develop chronic soluble complex disease affecting the kidney.

What proportion of chronic nephritis will ultimately be shown to be soluble-complex dependent, however, is quite unknown and we should not yet assume that forms of human glomerulonephritis without obvious associations are dependent on this mechanism—or are, indeed, primarily immunological diseases at all. In puromycin-treated rats proteinuria appears within a few days, but after 10–14 days IgG can be seen in the

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glomeruli, presumably as a non-specific reaction. Fixation of IgG may even be seen in the glomeruli of pyelonephritis and polycystic kidney disease. The presence of irregular or granular deposits of IgG in most chronic forms of glomerulonephritis is a clue, not a conclusion.

Antikidney Antibody Nephritis

There is less evidence for the participation of *anti-kidney antibody* in human glomerulonephritis.⁶⁷ The best defined group are those rare patients with rapidly progressive glomerulonephritis and extensive periglomerular crescents of epithelial cells, in whom IgG can be identified in a smooth linear pattern along the glomerular basement membrane.⁶⁸ Most of these patients show also pulmonary haemorrhagic lesions, and the name Goodpasture's syndrome is usually applied to this combination (without good reason, as is often the case with eponyms). Probably this may represent anti-glomerular-basement-membrane antibody which cross-reacts rather more widely with other basement membranes than in the patients where the attack is only on the kidney.⁶⁹ When the kidneys are removed the lung lesions may eventually disappear.⁷⁰ At this point free antibody is also found in the circulation.

The rare form of nephritis in Goodpasture's syndrome is of great importance, since it has proved possible to elute enough antibody from a kidney with this disease to induce a similar pattern in a squirrel monkey by injecting the antibody.²⁷ This variety of glomerulonephritis also transmits to allografted kidneys, although not always with acute destruction of the graft.⁷¹ Dixon *et al.*⁷² advocated nephrectomy and immunosuppression for some months before transplanting these patients on the grounds that in the few successful grafts in their patients these manœuvres were adopted. Where does this anti-glomerular-basement-membrane antibody come from? The analogy may be closer with the form of nephritis produced by repeated injections of homologous antigen. Lerner and Dixon⁷³ showed that normal individuals release small amounts of glomerular-basement-membrane-reacting fragments into both plasma and urine all the time, and this may be the immunogen under particular circumstances.

As with the attribution of soluble complex disease in all patients with granular or lumpy deposits containing IgG or C3, one must be cautious before assuming that the "linear" pattern of immunofluorescence necessarily implies anti-glomerular-basement-membrane nephritis. Several workers have observed linear patterns in patients without demonstrable anti-kidney antibody,⁷⁴⁻⁷⁷ interestingly in some patients with diabetic glomerulosclerosis. Also, if sensitive tests are used anti-glomerular-basement-membrane antibody can be found much more commonly in proliferative glomerulonephritis, in which the rare linear immunofluorescent IgG pattern is observed.¹⁸ The significance of this needs further study.

Mechanisms of Glomerular Injury

I have left until now consideration of the events which follow on antigen-antibody combination, which is in itself relatively innocuous, to relate possible therapeutic approaches to modification of glomerular injury. Two mechanisms seem to be concerned—the complement system (Fig. 1) and the coagulation cascade (see part I, Fig. 2). It has become evident in the past few years that these two complex biological systems and the kinin system (Fig. 2) may interact at many levels and that their apparently separate operation has largely been an artefact of investigative laboratory techniques.

FIG. 1—Simplified diagram of complement system and some results of complement activation (see text).

FIG. 2—Activation of complement by components of the coagulation cascade. Several routes of activation are already known, while simultaneously the kinin system is also activated and reinforces the complement-induced inflammation.

COMPLEMENT SYSTEM

The complement system⁷⁸ consists (Fig. 1) of nine main proteins and a number of associated ions and cofactors. When activated it leads through its cell-bound components to cytotoxicity.⁷⁹ Recently more interest has centred on the soluble factors released into the surrounding fluid. These lead to several events—immune adherence, attraction and application of polymorphonuclear leucocytes, and through anaphylatoxin to the secondary release of histamine, serotonin, and SRS-A (slow reacting substance).⁸⁰ Thus complement activation leads to all the components of inflammation.

"Classical" complement activation (Fig. 1) occurs when antibody combines with antigen. The "tail" or Fc portion of the antibody (which does not combine with the surface) undergoes some steric change which enables it to activate the first component of complement (C1). This type of activation presumably takes place wherever antibody-antigen complexes are found, both in the circulation and in the kidney, and where antibody is applied to non-phagocytosable antigen of the basement membrane, as in anti-glomerular-basement-membrane nephritis.

The complement system can also be activated at the C3 level by a recently described "alternate" pathway⁸¹ (Fig. 1). How often this pathway leads to complement activation is still not clear, but its clinical importance is already established, since endotoxin triggers the system by this route. Possibly this recently recognized pathway is at least as important as the so-called "classical" activation; and, of course, both may operate together under some conditions.

The principal mode of glomerular injury in both the main forms of experimental chronic glomerulonephritis (soluble complex and anti-glomerular-basement-membrane) appears to

be activation of complement and the attraction and application of leucocytes.^{37, 82} These events are followed by release of enzymes from the granules of the leucocytes⁸³ with digestion and destruction of tissue. The accompanying inflammation also facilitates the further deposition of soluble complexes in the glomeruli. Depletion of animals of either complement or leucocytes will limit the injury to the glomerulus.

Some injury, however, is mediated by mechanisms other than complement and leucocytes in both soluble complex and anti-glomerular-basement-membrane nephritis. Complement and leucocyte depletion only limits but does not inhibit the injury entirely, and duck antibody against glomerular basement membrane (which is not complement-fixing) can produce nephritis. Soluble complexes are capable of several activities besides complement activation, particularly with regard to coagulation (Fig. 3), which is discussed below.

FIG. 3—Biological effects of soluble complexes—illustrating possible modes of injury to the glomerulus and indicating close relation between complement, coagulation, and kinin systems.

COMPLEMENT IN HUMAN GLOMERULONEPHRITIS

The evidence that complement is involved in human glomerulonephritis is good.⁸⁴ Gunn⁸⁵ noted in 1914 that the level of haemolytic complement in the serum was low in the early phases of acute post-streptococcal glomerulonephritis, and this has been confirmed. Complement components are also reduced, especially C3.⁸⁶ The early components (C1, C4, and C2) are not always reduced in serum concentration, which brings into question whether the classic activation pathway is always in action.⁸⁷ In lupus nephritis serum concentrations of all complement components fall and rise with exacerbations of the disease.⁸⁸ Finally, complement components (of which by far the most extensively studied has been C3) can be found by immunofluorescent tracing techniques in the glomerulus, usually in the same distribution as the IgG antibody.

Membranoproliferative (mesangiocapillary) glomerulonephritis is of particular interest, in that C3 is frequently seen in the glomeruli in isolation without any immunoglobulin being detectable, and persistent hypocomplementaemia is the rule. This form of glomerulonephritis has occupied our attention for some years,^{89, 92} and it illustrates some of the problems of interpretation. The levels of haemolytic complement and C3 are low in most patients for years at a time.⁸⁹ The concentrations of the early components of complement (C1, C4, C2) are normal, suggesting activation at C3. Vallota *et al.*⁹⁴ found, and we have confirmed,⁹¹ the existence of a C3 activating factor, called by Vallota *et al.* C3NeF. This is associated with IgG, particularly IgG of subclass 3,^{95, 96} and a point of active investigation at the moment is whether this operates on C3 in a manner distinct from the "alternate" pathway of C3 activation mentioned above (Fig. 1). Both the C3NeF and the low C3 concentrations persist after bilateral nephrectomy. This condition illustrates the danger of trying to force the variety of clinical renal disease in man into a straitjacket defined by the range of experimental disease in animals (since there is as yet no animal equivalent).

In the great majority of human glomerulonephritis, where C3 may be detected in the glomeruli by immunofluorescent techniques, the concentration of C3 in the plasma is normal—for example, malarial nephropathy.⁹⁷ Evidence of reacted complement components, however, may be found in the plasma.⁹⁸ The amount of complement required to mediate slow injury in the glomerulus is too small to lead to obvious falls in the plasma concentration. In these diseases discussed above, where the concentration falls very low, complement activation is probably taking place in the circulation.

Coagulation

Coagulation leads to local tissue damage through microthrombosis and through inflammation. The inflammation is mediated through factor XII (Hageman factor).⁹⁹⁻¹⁰¹ Factor XII is activated by surface contact but also by antibody-antigen complexes (Fig. 3) and by bacterial endotoxin. Activated factor XII and the plasma it generates promote kinin production from kiniogen¹⁰² (Fig. 2). Both plasmin and thrombin are capable of activating complement.¹⁰³ Platelets may also be involved in the inflammatory reaction, allowing soluble complexes access to vessel wall.³⁷ Coagulation therefore activates complement and initiates inflammation^{100, 104} (see part I, Fig. 2, and the present Figs. 2 and 3).

Complement itself is also involved in coagulation¹⁰⁵ and initiates coagulation¹⁰⁶ by an unknown pathway. Antibody-antigen complexes can activate factor XII, aggregate platelets, and release platelet factor 3 by a complement-dependent mechanism (Fig. 3). The two systems of injury, complement and coagulation, are therefore intimately related and mutually sustaining.

In both experimentally induced and spontaneous nephritis in animals, and in human glomerulonephritis, fibrin (ogen) can be detected in the glomeruli¹⁰⁷ both by immunofluorescent tracing techniques and in some instances by electron microscopy. Platelet aggregates may also be found in glomerular capillaries. In anti-glomerular-basement-membrane nephritis in animals and rapidly progressive glomerulonephritis with crescents in man there is particularly dense extracapillary deposition of fibrinogen in the glomerulus itself.

In many forms of experimental glomerulonephritis and in the human disease with extensive crescents, but also in many forms of proliferative glomerulonephritis, there is excessive excretion in the urine of fibrin degradation products from plasmin digestion of fibrin.¹⁰⁸ The most likely hypothesis is that these fragments result from in-situ degradation of fibrinogen or fibrin-fibrin degradation product complexes deposited in the glomeruli, since glomerulonephritis judged by other criteria to be "active" show excessive fibrin degradation products in the urine. The role of chronic, low grade intravascular coagulation in chronic human glomerulonephritis seems at present to be an important one.

Other Mechanisms

We must not forget that the events discussed above are all potentially reversible, provided that widespread coagulation and infarction does not take place in an acute fashion. The penalty, at most, would be minor glomerular scarring. If, however, repeated or continuous assaults on the glomerulus take place the role of healing becomes particularly important. Many of the histological appearances we call "glomerulonephritis" probably represent attempts at glomerular repair, particularly when the mesangium is involved. These reparative responses probably result in damage, since healing by scarring will almost inevitably distort the delicate glomerular structure (see part I, Fig. 2). We must also consider the role of secondary autonomous phases with production of

secondary antibody against either autologous damaged kidney antigen or non-specific antigen initially deposited as soluble complex.⁵⁶

Finally, what of the rather common condition where no glomerular abnormalities are visible? The nephrotic syndrome, or symptomless proteinuria in association with the so called "minimal-change" lesion (lipoid nephritis⁹²), is most often seen in childhood but may occur at any age.⁹² There is no spontaneous or animal nephritis which bears any resemblance to this condition. In man several clues suggest that immune events may be important. The frequently recurring attacks of nephrotic syndrome may follow immediately on a variety of viral and bacterial infections. A tiny minority of patients have attacks in association with exposure to specific antigens, particularly grass pollen.^{109 110} At the same time there is no evidence that immunoglobulins, cells, fibrinogen, or complement are present in the glomerulus, and how the permeability of the filter is disturbed remains a mystery.

We have been pursuing the idea that IgE-mediated responses, with release of vasoactive substances, might be the mechanism. Mast cells, however, are infrequent in the kidney and absent from glomeruli. We have also studied four patients with specific pollen sensitivity who relapse on exposure to allergen (grass pollen and spring flowers). At the height of pollen-induced relapse in one patient, when plasma IgE levels were at their height, we failed to show IgE in the glomeruli despite careful study.¹¹¹ This is in agreement with other observations in "minimal change" nephrotics.¹¹² The findings of IgE in the glomeruli in "lipoid nephrosis" by Gerber and Paronetto¹¹³ are interesting but require confirma-

FIG. 4—Long-term effect of cyclophosphamide on relapses in nephrotic children with "minimal change" lesions.⁹²

tion. Two further pieces of evidence need to be fitted into the jigsaw. Ngu *et al.*¹¹⁴ found evidence of reacted complement in patients in relapse, and the prolonged remission with eventual relapses after several years induced by cyclophosphamide (Fig. 4) could suggest the participation of some long-lived group of cells. Mallick *et al.*¹¹⁵ suggested that these patients retain cell-mediated sensitivity to kidney antigens but others did not.^{16 18} This approach obviously needs further study, and how and whether such cells might participate in the injury is an interesting subject for speculation.

The conclusion of this lecture will appear in next week's issue, together with a list of references.

New Appliances

Graphic Records in Labour

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R. H. PHILPOTT, Sims-Black professor in obstetrics and gynaecology, University of Rhodesia, Salisbury, Rhodesia, writes: From our experience in the Harare Maternity Hospital, Salisbury, graphic recordings greatly improve the management of labour in the individual and the administration of the labour ward as a whole. They are more efficient than lengthy written notes and provide a pictorial display of all the essential features of a labour and immediately alert the attendant to abnormal developments. Graphic recordings are also of particular value in teaching medical students and pupil midwives the recognition of normal and abnormal labour.

The composite graph used in Harare Hospital has proved to be suitable for use in small peripheral clinics and hospitals in Rhodesia, where staff shortages necessitate a simple, efficient method of recording. It has also been used in several British hospitals, where acceptance has followed introductory explanation (J. W. W. Studd, personal communication, 1971).

The graph (Fig. 1), which measures 25 by 40 cm forms the double-page spread of the centre of the patient's bound maternity record and is attached to a clipboard at the foot of the patient's bed. The recordings are made by the midwife or doctor. The doctor's findings on admission are recorded on the previous page and any extra intrapartum information, such as consultant's comments, are recorded on the succeeding page. The details of the components of the graph have

evolved over the past five years and the graph described below has been in use for the past 12 months in the management of over 8,000 patients. The whole graph revolves around the main feature, which is the cervicographic record of labour progress. The details are given in the order in which they appear on the graph.

Components of Labour Graph

TIME

Zero time is taken as the time of admission to hospital rather than the problematical time of onset of labour. The actual time is recorded on two lines, one for each half of the record. In addition the hours from admission are marked off to alert the observer to the passage of time. Although most labours are completed in less than 12 hours from admission to hospital, we have extended our graph to cater for inductions of labour, which sometimes take a little longer.

FETAL HEART RATE GRADING

The conventional method of recording the fetal heart rate between contractions is too inexact a measure of fetal condition to be of any clinical value. Wood *et al.*¹ showed that the effect on the fetal heart rate of uterine contractions was the earliest sign of fetal distress. We have monitored on the cardiotocograph the deteriorating fetal condition in a few