

SOME QUESTIONS ON THE PATHOGENESIS OF GLOMERULONEPHRITIS

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INTRODUCTION

About twenty years ago, there was a general feeling that the problems of glomerular disease were very near solution. As a result of almost 70 years of experimental work culminating in the contributions of Germuth¹ and Dixon,² it was clear that two mechanisms produced glomerular damage in animals, and evidence from immunofluorescent methods strongly suggested that they applied also to man.

In the first of these, damage was produced by antibody to glomerular basement membrane (GBM), the most clear cut manifestation morphologically being the smooth linear deposition of immunoglobulin on the GBM as seen by immunofluorescence.

The other mechanism appeared to involve immune complexes (IC) formed between antibodies and a circulating foreign antigen which localised in the glomeruli (visible as discontinuous granular deposits on immunofluorescence) and initiated inflammatory damage. The animal model of acute serum sickness, which was thought to resemble acute proliferative glomerulonephritis, suggested that IC were probably formed in the circulation, and that the very small amounts localised in the kidney were sufficient to cause inflammation. The chronic serum sickness model showed that a variety of patterns of glomerular injury could occur, depending on the quantity and avidity of antibody produced, so that it seemed reasonable to believe that only technical problems stood in the way of identification of the antigens involved in human glomerulonephritis.

In retrospect, the optimism seems to have been misplaced and twenty years later there are very few areas in which knowledge of the pathogenesis of a nephritis is complete.

This review deals briefly with some of the areas in which there has been a substantial expansion in our knowledge about mechanisms of damage or a modification of views about the interpretation of the animal models.

How important is anti GBM disease and does it really resemble experimental nephrotoxic serum nephritis?

Anti GBM disease was originally thought to account for 5--10% of human glomerulonephritides but is clearly much less common than originally thought, with a population incidence in the U.K. of one per million per year. Presentation may be with focal segmental or with crescentic glomerulonephritis and there may be associated lung haemorrhage (Goodpasture's syndrome) for which smoking is a strong predisposing factor.³

The target antigen in the glomerulus has not yet been precisely defined. It is present in basement membrane at sites other than kidney and lung (as shown by immunofluorescence), but is not demonstrable by that technique in all basement membrane.⁴ All human anti GBM sera recognise the same four bands as shown by immunoblotting of collagenase digests of normal GBM and the epitope may be close to, though possibly not identical with, that recognised by a mouse monoclonal antibody to GBM(P1).⁵

In sheep injected with heterologous GBM in Freund's adjuvant, the nephritis which develops (Stebly nephritis) probably involves the same antigen,⁶ but this is not the case with most experimental heterologous serum nephritides.⁷

In human anti GBM disease, the elevation of antibody titres is not a permanent phenomenon and in the normal course of events basal levels are reached in a few years in survivors. This fall in antibody titre can be expedited by immunosuppression and plasma exchange,⁸ though whether this alters the prognosis of the renal disease is still argued.⁹ Clinical disease activity and antibody level are not closely related: cigarette smoke inhalation and intercurrent infection¹⁰ may be associated with rapid deterioration, though in neither case is the exact mechanism known.

Experimental nephrotoxic serum nephritis differs markedly from species to species and

with the experimental protocol, and it is not clear that it relates to spontaneous human disease.

In the *heterologous* phase proteinuria may be produced by antibody alone,¹² and enhanced by complement, but in many models is mainly dependent on complement dependent injury mediated by polymorphs.¹²

The *autoalogous* phase of nephrotoxic nephritis involves a host response against foreign immunoglobulin on GBM (i.e. a planted antigen) and is not strictly analagous to anti GBM disease. Its chief value has been as a model for studying crescent formation.

It seems unlikely that complement is essential to the damage in human anti GBM disease, as it is only present in the glomeruli in a proportion of cases.

Are granular deposits of immunoglobulin in the glomerulus reliable evidence of tissue deposition of immune complexes?

Granular glomerular deposits of immunoglobulin were originally thought to be pathognomonic of "trapped" IC, but the work of Hoedemaeker and colleagues¹³ and of Couser's group¹⁴ showed that the nephritis produced in rats by immunisation with kidney tubule brush border fractions (Heymann nephritis),¹⁵ or conveyed by the serum of such animals is not an immune complex disease, even though it produces granular deposits of immunoglobulin and complement beneath the foot processes of the podocytes. It is in fact due to an auto antibody directed at a podocyte membrane glycoprotein present on the coated pits.¹⁶

The model has a close histological similarity to membranous glomerulonephritis in man and it has been suggested by Japanese workers¹⁷ that it has a similar mechanism, though this was not supported in U.K. cases.¹⁸

Another circumstance in which granular glomerular deposits are not due to circulating immune complexes is provided by a spontaneous glomerulonephritis in rabbits.¹⁹ An auto antibody fixes to a non-linearly distributed glomerular antigen which appears unrelated to the Heymann antigen.

How well characterised are the IC of human **glomerular** disease?

The best characterised immune complex mediated glomerular disease is that associated with mixed monoclonal and polyclonal cryoglobulinaemia. The complex is a monoclonal immunoglobulin (usually IgM k) which has rheumatoid factor activity and therefore binds to polyclonal IgG as its antigen. It is present in large amounts in the plasma

and is characteristically associated with mesangiocapillary glomerulonephritis (MCGN) Type I (less commonly a mesangio-proliferative, or focal segmental nephritis), the cryoglobulin components being present in the mesangium and subendothelial space as an electron dense deposit.

In most other types of MCGN Type I the antigen is less certain. In some cases, there are clinical clues – association with hepatitis B, malaria, schistosomiasis, an infected **ventriculo-atrial** shunt or **subacute** infective endocarditis – and tentative identifications of antigen have been reported²⁰ but the technical problems of quantifying an antigen in the presence of an unknown amount of antibody to it have not been solved either for circulating IC or for the much smaller quantities of tissue IC. Although antigens can be demonstrated in tissue IC, they have rarely been shown to be quantitatively important rather than passively trapped contaminants.

Are glomerular complexes derived from circulating soluble complexes?

Attempts to reproduce the effects of serum sickness by the passive infusion of IC in experimental animals produced effects which were on the whole disappointing. Large complexes were rapidly phagocytosed, and many soluble IC behaved like colloidal molecules:²¹ they were filtered into the subendothelial space, transferred to the mesangium and eliminated from the glomerulus within 24–48 hours. Often there was minimal inflammatory change, though increasing amounts of C₃ were demonstrated on the aggregated complexes in the glomerulus.

Much effort was devoted to developing assays for IC in man and at least 50 different methods have been published. These do not necessarily correlate since they measure different properties, and in most cases they give no information on the antigen content of the complex.

Assays are positive in a wide range of conditions ranging from malignancies to cardiac infarction and although conditions such as mixed cryoglobulinaemia, systemic lupus erythematosus and Henoch Schonlein purpura are positive, in some types of nephritis IC are not regularly demonstrable.

It is now appreciated that serum assays are artefactual in that in the blood much IC transport is on erythrocytes.²²

What is meant by in-situ complex formation?

An alternative to the possibility of "trapping" of circulating ICs is that ICs are

assembled in the tissue. Foreign nephrotoxic immunoglobulin is an example of a substance which, having adhered (immunologically) to host glomeruli, subsequently acts as an antigen and combines with host immunoglobulin and complement. Other foreign antigens may adhere to the glomerulus by a charge effect: since the GBM has a net anionic charge these would be polycations. Lange *et al.* (1983)²³ have suggested that this mechanism operates in post-streptococcal glomerulonephritis i.e. streptococcal cationic proteins adhere to the GBM and antibody subsequently combines with them.

Other possible mechanisms of binding of the antigen to the glomerulus could involve a lectin type of interaction (Bartolotti and Evans - unpublished) or an interaction with fibronectin.

How does complement produce glomerular damage?

A comprehensive review of the mode of complement activity is beyond the scope of this short article. There is much detailed information available on the twenty proteins involved as well as their receptors and regulatory proteins.²⁴

It is clear that there are two independent modes of action, the generation of a "killer" molecule, the so-called membrane attack complex (MAC),²⁵ and the activation and recruitment of leucocytes.

The enzymic cleavage of C₃ is the pivotal point of the complement system, and it is well established that it may be brought about by two different enzymes generated by the classical or alternative pathways. When C₃ is split, the C3b fragment formed is highly reactive and may bind covalently to -OH and -NH₂ groups. It also assists the enzyme generating it (i.e. classical or alternative pathway C₃ convertase) to split C₅, thereby forming C5b and initiating assembly of MAC by the non-enzymic interaction between C5b and C6, C7, C8 and C9. C5b-C6-C7 is first formed in the fluid phase and if it does not react with an inhibitor, it attaches to membrane: C8 is then bound and is able to penetrate the hydrophobic core of the lipid bilayer. This produces a small pore sufficient to lyse an erythrocyte but not to kill a nucleated cell: to complete MAC formation a single molecule of C9 added produces cytolytic activity. Polymeric addition of up to 17 molecules of C9 produces the characteristic membrane hole.

MAC can be demonstrated in many forms

of human glomerulonephritis but its functional significance is only readily assessed in experimental models.

In Heymann nephritis in the rat antibody attaches to the coated pits on podocyte surface membrane but only if MAC is generated does proteinuria occur.⁵ Presumably this is because the podocyte is forced to shed membrane as a defensive mechanism and this interferes with its normal function in maintaining the glomerular permeability barrier.

MAC also appears to have a role in generating the large subepithelial deposits in serum sickness in the rabbit as these are not seen in C6 deficient animals: the exact mechanism is not determined, but it may be by an indirect effect on leucocytes.

Generation of C3b by the classical pathway requires the activation of C1 which will then generate the classical pathway convertase C42. The most familiar interaction which activates C1 is the binding of C1q to various aggregated immunoglobulins or immune complexes, but many other mechanisms can be demonstrated in the laboratory, including proteolytic activation of C1r and C1s, and interaction of C1q with non-immunoglobulin activators, such as complexes of polyanions and polycations, viral proteins, and a component of bacterial endotoxin.

The alternative pathway convertase C3B is unusual in that it is generated by the reaction product C3b. Once formed, it is theoretically capable of exhausting C3 in the absence of controlling factors to inactivate it (factors H and I). Removal of these factors from normal serum results in total C3 depletion without the necessity for any additional activators, which implies that in normal circumstances the alternative pathway "ticks over".

Stimulation of alternative pathway activity occurs whenever the rate of C3b formation is increased and this may be the consequence of triggering the classical pathway, activation of plasmin, release of leukocyte proteases, or stabilisation of the C3B convertase.

In the laboratory, it can be shown that a normal serum protein, properdin, functions as a stabiliser of C3B but factors controlling this interaction are not well defined.

Abnormal stabilisation of the C3B convertase is present in certain hypocomplementaemic patients, and this is due to a circulating factor which was originally called C3 Nef or nephritic factor (because the patients had nephritis). It is now known that it is an auto antibody which will stabilise C3B²⁶ and that it is not restricted to patients with nephritis.²⁷

Three of the fragments formed during complement activation have effects on leucocytes – as chemotactic agents, promoters of granule release and cell activators. These are C3b, C3a and C5a. C5a is particularly notable as a chemotactic agent for polymorphs and C3a, C3b have striking effects on the activation of monocytes.

Does complement have only adverse effects on nephritis?

Although in the previous section the stress has been on the adverse effects of complement in damaging cells, it is clear that impaired complement function predisposes to glomerulonephritis.^{2,8} Complement is able to disrupt and solubilise some classes of insoluble tissue deposited complexes, but its main function in nonnal circumstances is probably to facilitate disposal of IC. These are bound through a C3b receptor to the erythrocytes.

The binding of C3 to IC also inhibits the formation of large insoluble complexes. It is now clear that these are formed mainly by Fc interactions rather than by the formation of an infinite antigen antibody lattice; the binding of C3 inhibits these Fc interactions.^{2,2}

Is there a significant association between glomerulonephritis and HLA antigens and, if so, what does it mean?

Studies by workers on tissue transplantation led to the identification of a group of genes known as the major histocompatibility complex (MHC), and it has subsequently been found that these genes have important general functions in the immune response. In man MHC Class I products (HLA-A, B, C) are essential participants in the cytotoxic T cell killing of cells whose surfaces have been altered, for example, by viral infection. Class II antigens (HLA DR, DC and DQ) are essential for antigen presentation and cell collaboration in the immune response: they determine the repertoire of antigenic epitopes to which response occurs, i.e. they are immune response genes.

It is only possible to study genetic linkage of a disease if there is an appreciable familial incidence and this is not the case in nephritis, but because Class I and Class II products are highly polymorphic, it is quite easy to look for associations by comparing patient groups with a control population. Because of racial variation in HLA, this can only readily be done in homogeneous populations. True associations may be concealed if the patient group is nosologically heterogeneous. The

subject is well reviewed by Rees.^{2,9}

Clear cut associations are documented in several disease groups (see Table 1), but what do they mean?

In animals, MHC linked differences can be seen in the response to synthetic antigens having a single repeated epitope.^{3,0} Similar MHC restriction is seen in various experimental autoimmune diseases.^{1,3,2} It seems probable that the HLA-DR2 linkage of anti GBM antibody disease is due to responsiveness to a single epitope in the GBM. The link between development of C3 Nef and HLA.DR7 may be of similar type.

Other possible less specific ways in which MHC could influence disease development is by an effect on the efficiency of antigen processing or the magnitude of antibody response.³

Why do not all individuals with HLA.DR2 develop anti GBM disease? Several explanations are possible: it may be that there is implication of genes outside the MHC complex and that environmental factors are also of importance. Thus, in the rat, development of anti GBM antibody may be produced by mercuric chloride only in the presence of the MHC gene (RT1ⁿ) and one or two genes at unlinked loci.^{3,3} It is further possible that serologically homogeneous HLA antigens are structurally heterogeneous and that this is reflected in function.⁴

What circulating elements are involved in glomerular damage and how?

Polymorphs and monocytes may adhere to immunoglobulin fixed on basement membrane or in immune complexes by their Fc receptors, or by their C3b receptors to complement fixed on immunoglobulin or other molecules. If phagocytosis is impossible, exocytosis of enzymes will occur and for many years it was assumed that the chief mechanism of damage was release of these proteolytic enzymes.⁵ More recently, interest has focussed on the generation of superoxide, hydroxyl radicals or halogen radicals by polymorphs and monocytes^{3,6,3,7} which can be shown to cause damage in certain experimental models.

The role of the lymphocyte is more problematical. Although it mediates an experimental nephritis in the bursectomised chicken,⁸ most experimental nephritides are independent of lymphocytes, though it has been suggested that in antibody mediated disease (especially crescentic nephritis) they may assist in recruiting monocytes.⁹

TABLE I
HLA AND NEPHRITIS

Disease	HLA antigen	Relative risk	Etiological fraction	
Anti GBM nephritis	DR 2	36	0.86	
	B 7	5	0.47	
Membranous nephritis				
	Europe and U.K.	DR 3	3.0–11.8	0.35–0.58
U.S.A.	DR 3	1.9	0.16	
Mesangial IgA disease				
	Japan	DR 4	1.6–3.0	0.20–0.45
		BW 35	1.0–2.7	0–0.18
	BW 54	1.5–2.4	0.07–0.35	
Minimal change nephritis				
	in children in Europe	DR 7	4.2–5.9	0.50–0.62
		B 8	1.6–3.6	0.09–0.46
		B 12	0.5–6.3	Up to 0.45
	in children in Japan	DR 8	10.1	0.42

It has been proposed that soluble factors produced by lymphocytes may be of importance in minimal change of glomerulonephritis⁴¹ and lymphocytes have been shown to have enzymes capable of degrading heparan sulfate (which is part of the glomerular permeability barrier) but whether these mechanisms are indeed of importance is not yet established.

What is the role of mediators such as PAF, IL-1, TNF, leukotrienes, prostaglandins and thromboxane in glomerulonephritis?

Although there is much information about the various mediators in inflammation in general, it is very difficult to decide how relevant a particular mediator is in glomerulonephritis, especially bearing in mind the wide range of human glomerulonephritides. General reviews are available for the interested reader⁴¹ and there is space for only a few selected points.

Platelet activating factor (acetyl glyceryletherphosphorylcholine). PAF is produced not only by leukocytes but also by mesangial and endothelial cells. Logically it can be put in the class of autocoids – substances which are produced and act locally, like the prostaglandins. Its name is somewhat misleading: in the rat, platelets resist its action but it has marked effects on vascular

permeability. In isolated perfused animal kidneys it produces proteinuria.

Leukotriene B4 (LTB 4) is produced in mast cells, basophils, neutrophils and monocytes (possibly also lymphocytes) and influences leukocyte activation. It stimulates PAF production by human neutrophils and might therefore have a role in proteinuria. Although fixed tissue cells such as keratinocytes produce LTB 4, production by glomerular cells does not appear documented.

Leukotrienes C, D, E (SRS) are mainly derived in man from IgE (or IgG4) dependent release by basophil and mast cells and except possibly in serum sickness appear unlikely to have a major role in glomerular disease, though LTC 4 has been shown to stimulate glomerular epithelial cells in culture.

Thromboxane B2 formation is increased in glomeruli in some animal models of nephritis, both acute (such as in-situ IC nephritis) and chronic, such as murine lupus.⁴² Elevated levels of thromboxane B4 have been reported in human SLE during episodes of deterioration, but have not been clearly linked to morphological events.⁴³

Prostaglandins are thought to play an important part in the control of the glomerular circulation, and it has been known for almost ten years that they may be produced in

glomeruli. In animal models (nephrotoxic serum nephritis) there is evidence of increased production of PGE₂.⁴⁴ Cultured mesangial cells produce PGE, and this can be stimulated by IL-1 derived from leukocytes or from the mesangial cells themselves.⁴⁵

Interleukin 1 was first defined as a protein produced by macrophages which activated lymphocytes. It has multiple other actions acting as endogenous pyrogen, a chemottractant for leucocytes, an inducer of acute phase proteins, a stimulator of bone and cartilage resorption, and a stimulator of synovial fibroblasts.⁴⁶ Many cells synthesise it, including mesangial cells, and *in vitro* it stimulates mesangial cell proliferation (though whether it fulfils a similar role *in vivo* is not yet clear).

Tumour necrosis factor (cachectin) is also a macrophage derived protein with a variety of actions.⁴⁷ Not only does it mediate the lethal effects of bacterial lipopolysaccharide but it also has similar effects to IL-1 on synovium and osteoclasts. It is itself an endogenous pyrogen and induces IL-1 release. In the kidney its chief target would seem to be endothelium: in large doses it has a toxic action but in smaller amounts it influences antigen expression, IL-1 production and cellular reorganisation and it facilitates thrombosis by inhibiting thrombomodulin and inducing procoagulant activity.

CONCLUSION

The delineation of mechanisms of glomerular damage is by no means complete: indeed, it is fair to say that in no single type of human glomerular disease can an exhaustive account be given of the process. The advances outlined in this review have made little impact on the management of human glomerulonephritis: to develop rational therapy a more detailed knowledge of the early pathogenetic events is required and until then therapy must remain empirical. Despite the successes of empiricism, it is to be hoped that elucidation of the pathogenesis will not take a further 20 years.

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