IMMUNE COMPLEX GLOMERULONEPHRITIS

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I. INTRODUCTION

Heightened awareness in present medical practice regarding the role of immune complexes in pathogenesis of clinical disease states devolves from several factors--principally successes in manipulation and exploration of research models of immune complex disease, improved technology for detection and measurement of circulating immune complexes, and description of several disease states in which circulating immune complexes have been pathogenetically implicated as having a central role.

Human glomerulonephritis, like animal models, is caused by one of two generally accepted immunopathogenetic mechanisms: specific injury caused by antibodies operationally directed toward structural antigens associated with the glomerular basement membrane or fortuitous injury consequent upon glomerular deposition of circulating immune complexes (1). The latter mechanism is acknowledged as the predominant mechanism operating in spontaneously occurring glomerulonephritis in man associated or not with recognizable underlying systemic disease (2-5).

TABLE I.

INCIDENCE OF APPARENT IMMUNE COMPLEX GLOMERULONEPHRITIS IN HUMAN RENAL BIOPSY MATERIAL (REF 19)

	TOTAL	%
TECHNICALLY SATISFACTORY BIOPSIES	213	
IMMUNOFLUORESCENT NEGATIVE, APPARENT MINIMAL CHANGE	67	31
IMMUNOFLUORESCENT POSITIVE	146	69
IMMUNE COMPLEX	141	(96.5)
ANTI GBM	5	(3.5)

Because of its frequency, importance, and the gradual evolution of interrelating concepts, it is prudent to consider in more detail general concepts regarding immune complex diseases in animals, the distribution, fate and metabolism of circulating immune complexes, and their nephritogenicity. It will be relevant to make some comments regarding glomerular organization, functions, and ultrastructure, and to consider newer information regarding glomerular receptors. Finally, based on circumstantial data, we have the options of broadening our concepts of immune

complex glomerulonephritis or acknowledging a third general immunologic mechanism of renal injury.

II. EXPERIMENTAL MODELS

Experimental immune complex-induced glomerulonephritis in laboratory animals is spontaneous or induced: the spontaneous lupus erythematosus-like disease of NZB and NZB/NZW hybrid mice and Aleutian mink disease have been studied extensively. The principal induced experimental diseases which have contributed to our present understanding are serum sickness and autologous immune complex glomerulonephritis; the first utilizes a soluble heterologous protein whereas the latter is induced with a nonglomerular, renal antigen.

The utility and importance of these experimental models is rooted in their susceptibility to qualitative identification of antigens and antibodies, quantification of the component mechanisms, manipulation of variable contributory and amplification mechanisms, and identification of effector injury systems. From this experience we can synthesize requirements for rigid proof of immune complex pathogenesis:

1. Qualitative identification of antigens and antibodies.
2. Antigen and antibody should be quantitatively related.
3. Concentration of specific antibody in eluates should be enhanced over serum concentrations.
4. Critical manipulations should enhance or abrogate glomerular deposits.

Whereas these tests applied to experimental systems have met expectations generally, relatively few instances of human immune complex glomerulonephritis have been tested so rigorously (6,7) and the antigen-antibody system(s) responsible for the overwhelming majority of such cases has not been identified.

III. EXPERIMENTAL SERUM SICKNESS

The great bulk of current data regarding the in vivo fate of circulating immune complexes derives from experiments with the serum sickness model of immune complex disease and from injection of preformed immune complexes. Early studies established that there were limitations on the distribution of circulating colloidal, aggregated, and macromolecular materials (8) and that intimal deposition in arteries, venules and endocardium required the active participation of ancillary mechanisms causing release of vasoactive amines (9). Although several different mechanisms can initiate their release from storage sites, the reaction in which sensitized basophile leucocytes, in the presence of specific antigen, generate a platelet aggregating factor that causes vasoactive

amine release from platelets correlates best with induction of experimental arteritis and glomerulonephritis in acute and chronic serum sickness in rabbits. Its operation in a state of antigen excess seems particularly important (10).

Size of immune complexes has a critical importance that has been demonstrated in passive complex administration and in in vivo immune complex formation in acute and chronic serum sickness: larger complexes, in excess of 19 S, become entrapped by a limiting filtration membrane and can initiate pathogenic lesions whereas smaller complexes do not (11,12). The principal role of complement as a mediating and amplifying system in the Arthus reaction and in serum sickness has been the attraction of polymorphonuclear leucocytes to sites of immune complex deposition. Hence, the central features of immune complex disease are:

1. Increased permeability
2. Deposition of circulating complexes along a membrane
3. Inflammation

IV. DISTRIBUTION, FATE, AND METABOLISM OF IMMUNE COMPLEXES

The kinetics of immune complex distribution and disposal have been defined by Mannik, Arends and coworkers in a sophisticated, systematic series of experiments utilizing passive administration of a variety of purified, preformed immune complexes made at five times antigen-excess. Their studies showed that such preparations contained a polydisperse series of immune complexes definable by physical properties and biological activity, with differing kinetic characteristics in vivo. The size of immune complexes, defined by molar ratio rather than molecular weight, dictated that very large complexes, which fixed complement effectively, were removed from the circulation

TABLE 2

DISAPPEARANCE OF HSA-a-HSA COMPLEXES FROM RABBIT CIRCULATION (HOURS)

	FASTEST		SECOND		THIRD	
	T 1/2	%	T 1/2	%	T 1/2	%
HSA-a-HSA	.21	41	3.6	40	40	19
HSA-a-HSA REDUCED, ALKYLATED	1.98	43	63	54		
HSA-a-HSA COBRA VENOM	.18	47	4	38	53	16

very quickly, with half-time measurable in minutes, whereas smaller complexes circulated for prolonged periods of hours to days. Intact IgG antibody chains were necessary for complement fixation, normal kinetic performance, and disposal by the fixed macrophages of the reticuloendothelial system; however, complement apparently is not involved in the uptake and removal of these complexes (13,14). Other kinetic analyses defined that the largest complexes were cleared primarily by the liver and that this was a saturable system; circulatory kinetics further showed

Table 3

TISSUE DISTRIBUTION OF IgG-a-IgG COMPLEXES AT 40 MINUTES

ALTERATION OF ANTIBODIES	COMPLEMENT REDUCTION	DISTRIBUTION OF INJECTED COMPLEXES (%) LIVER	SPLEEN	LUNG	KIDNEY
NONE	NONE	54.2	0.1	0.5	0.2
		42.5	0	0.3	0.5
REDUCTION AND	NONE	8.2	0.1	0.3	0.2
ALKYLATION		10.1	0.1	0.2	0.4
NONE	COBRA VENOM	42.2	0	0.4	0.4
NONE	AGGREGATED γG	43.2	0	0.3	0.4

that glucocorticoids blocked the early removal of very large (greater than $Ag_2\ Ab_2$) complexes by the liver, resulting in their prolonged circulation (15), and enhanced and prolonged glomerular uptake in mice (16,17).

V. SERUM SICKNESS NEPHRITIS

Quantitative studies of serum sickness also have been performed in the rabbit, emphasizing several dynamic considerations (18). In acute serum sickness glomerulonephritis, for example, both kidneys of animals sacrificed when they had eliminated greater than 99% of the

Table 4

ACUTE SERUM SICKNESS GLOMERULONEPHRITIS

IMMUNE ELIMINATION DAY	MEAN BSA, BOTH KIDNEYS	GLOMERULONEPHRITIS BY HISTOLOGY	PROTEINURIA	BSA BY IMMUNOFLUOR.
	mcg			
10-12	18	20/20	17/20	20/20
13-15	11	9/9	4/9	4/8
>15	4	4/9	1/9	0/9

500 mgm/kg BSA antigen dose contained an average of 18 micrograms of complexed antigen; calculations of half-disappearance times suggested approximately 10 days. In contrast, similar measurement in chronic serum sickness glomerulonephritis defined a more complicated situation: the total amount of complexed antigen depositing in animal kidneys depended on their antibody responses, but approximated .04% of the

Table 5

CHRONIC SERUM SICKNESS GLOMERULONEPHRITIS

	RABBITS STUDIED BEFORE ONSET OF GLOMERULONEPHRITIS		RABBITS STUDIED AFTER ONSET OF GLOMERULONEPHRITIS	
	STUDY DOSE 10-40 mg	STUDY DOSE 50-200 mg	STUDY DOSE 10-40 mg	STUDY DOSE 50-200 mg
RENAL BOUND BSA (mcg)	7	47	112	601
% INJECTED DOSE IN BOTH KIDNEYS	.04	.04	0.6	0.5
DISAPPEARANCE RATE OF RENAL BOUND BSA T 1/2; DAYS	5.1	5.8	6.9	37

daily antigen dose injected prior to the onset of proteinuria. After onset of proteinuria 0.5 to 0.6% of the antigen was fixed in nephritic kidneys; half-disappearance times of radiolabelled antigen from the kidneys approximated 5 days and could be shortened markedly by huge doses of excess antigen.

To summarize to this point: experimental, exogenous, immune complex disease due to non-living antigens, whether actively or passively induced, has the following characteristics:

1. Requires an active response by the experimental animal.
2. The active response involves mediators which increase vascular permeability.
3. Only immune complexes, aggregates, or macromolecules in excess of critical size deposit.

4. Deposition occurs along some limiting membrane
5. Inflammatory sequelae ensue
6. Involves crucial quantitative and dynamic considerations

VI. CLASSIFICATION OF GLOMERULONEPHRITIS

Germuth has proposed a classification of glomerulonephritis (19)

Table 6

IMMUNE COMPLEX GLOMERULONEPHRITIS

CHARACTERISTIC LOCATION OF DEPOSITS	PROPOSED NOMENCLATURE
I. BENEATH EPITHELIUM	I. CLASS I IMMUNE COMPLEX DEPOSIT DISEASE
A. AT EPITHELIAL SLITS	A. TRANSMEMBRANOUS GLOMERULONEPHRITIS
B. SUBEPITHELIAL SPACE	B. TRANSMEMBRANOUS GLOMERULOPATHY
II. SUBENDOTHELIAL-MESANGIAL SYSTEM	II. CLASS II IMMUNE COMPLEX DEPOSIT DISEASE
A. SUBENDOTHELIAL SPACE	A. ENDOMEMBRANOUS GLOMERULONEPHRITIS
B. LAMINA DENSA	B. LAMINAL GLOMERULONEPHRITIS
C. MESANGIUM AND ADJACENT LOOP	C. MESANGIOPATHIC GLOMERULONEPHRITIS

which is rooted in known characteristics of the glomerulus and his own considerable experience with the experimental models of glomerulonephritis. First, a number of observations point to an important function for the renal mesangium and mesangial cells, and implicate this structure (s) as a component of the reticuloendothelial (monuclear phagocyte system) (20-22). These observations include structural as well as functional differences of mesangial cells, the important function of mesangium in disposal of intravascular aggregates of colloids and macromolecules, and characteristics of dissociated and cultured glomerular cells (23).

Secondly, correlative experimental studies in acute and chronic BSA serum sickness in Germuth's hands indicates that peripheral glomerular loop deposition of immune complexes in subepithelial location was a characteristic of smaller immune complexes, capable of penetrating the lamina dense of the GBM. These complexes, so called type I complexes, are formed in antigen excess. In contrast, larger complexes (type II complexes) are less soluble, are restrained by the lamina densa, and are deposited in the subendothelial area of glomerular wall and mesangium preferentially (12,24).

Recent experiments contrasting the two principal models of chronic BSA serum sickness glomerulonephritis are informative in emphasizing the differences between "membranous" deposition of type I complexes formed in relative antigen excess and "mesangiopathic" deposition of type II complexes formed in antibody excess (25). Moreover, this same study demonstrates effectively the quantitative impact that larger antigen dose (and more voluminous immune complex deposition) has in inducing extracapillary-wildly proliferative-glomerulonephritis, due apparently to deposition of similar type I complexes.

Table 7

CHRONIC BSA-RABBIT SYSTEM GLOMERULONEPHRITIS

DOMINANT GLOMERULAR LESION	GROUP I (12.5 mg BSA/dy) NO. RABBITS	%	GROUP II (VARYING BSA DOSE) NO. RABBITS	%
CRESCENTIC GN	0		7	37
MEMBRANOUS GN	9	82	4	21
MESANGIOPATHIC GN	2	18	8	42

VII. GLOMERULAR STRUCTURE AND "BINDING SITES"

The structural characteristics of the glomerular capillary wall undoubtedly have primary importance in its role physiologically as an ultrafilter (26,27) and immunologically as a site of immune complex deposition, fixation, and movement. Long thought to be a simple and passive structure,the components have been shown structurally and functionally to be much more complex. Poorly staining areas such as lamina rara interna and externa, and more well defined structures, such as epithelial cell foot processes, can be stained by a number of reagents with binding characteristics preferential for acidic glycoproteins (28-30). Moreover, disruption of these moieties by physical, chemical or immunologic manipulations can result in profound alterations in their fine organization, gross morphology, and filtration characteristics. The extent to which, and the mode by which, the structural characteristics of the glomerular capillary wall dictate the passage and/or restraint of impinging immune complexes is not known precisely at this time, but undoubtedly involves organization, density, chemical composition, and perhaps electrical charge and biological receptors.

Recent immunohistologic observations have introduced a complicating, or enhancing, new dimension to insights regarding glomerular binding of immune complexes. Although some aspects of the observations are apparently conflicting, there are binding sites (receptors) in human glomeruli for the C_{3b} component of complement (31-34). Tested *in vitro*, human glomeruli bind EAC--coated red cells and particles. Moreover, receptors for immunoglobulin Fc fragment were detected on glomerular cells in tissue culture (23). In sections from diseased human kidneys with C_3 deposits in mesangium or in subepithelial sites receptors appear to be blocked from uptake of *in vitro* adherent test materials, but these sites can be unblocked by chemical and enzymatic techniques. The role that these receptors for an activated complement component play *in vivo* in localization or deposition of complement-binding immune complexes is conjectural, but they may prove to be an important link in local metabolism and degradation of deposited immune complexes.

VIII. ANOTHER MECHANISM OF GLOMERULAR IMMUNE INJURY

Structural and functional characteristics of glomeruli *in vitro* and *in vivo* together with experimental data point to the potential for an anomalous mechanism of renal injury; this may be a valid and relevant third immunopathogenetic mechanism of glomerulonephritis. As referenced earlier, the renal mesangium performs an apparently active, clearing function for intravascular macromolecules, colloids, aggregates, and immune complexes. Moreover, intact glomeruli and GBM, because of their chemical composition, can bind lectins (35); this binding may be particularly persistent. Intravascular aggregates and/or immune complexes that are trapped in the mesangium, or lectins-such as bacterial or tissue constituents-that bind to glomerular structures, may provide the nidus for binding of circulating free antibodies or immune complexes. This latter potential has been realized in the case of passive administration of antibody (36), and has been suggested as a mechanism for in *situ* formation of immune complexes in animals (37). Such a role has also been inferred for IgM rheumatoid factor in a case of human glomerulonephritis (38).

This postulated mechanism similarly may have relevance in the pathogenesis of acute poststreptoccal glomerulonephritis (PSGN). Free antigen may be detectable in mesangial sites of renal biopsies early in the course of acute PSGN, and these sites become unavailable to antibody binding in biopsies tested during convalescence (39). It might be hypothesized that during bacterial infections-such as streptococcal pharyngitis or impetigo-that bacterial antigen circulating in the blood binds nonspecificially as lectin to glomerular structures.

As antibodies are induced in the individual previously non-immune to the particular nephritogenic strain of bacteria, immune complexes are formed in the circulation and may lodge in the glomeruli. Similarly, free antibodies or circulating immune complexes may bind to-and cover-bacterial lectin already fixed in glomeruli. Whether or not such bacterial lectins have any role in elicitation of crossreactive basement membrane antibodies, and development of chronic glomerulonephritis is unknown at this time, but has been implied.

IX. GLOMERULONEPHRITIS AND SYSTEMIC DISEASE

It is beyond the intent of this presentation to discuss specific clinical entities associated with human immune complex glomerulonephritis, except to point out the obvious: the foregoing discussion has emphasized the renal glomerulus as target and has ignored non-glomerular and non-renal considerations. Nevertheless, immune complex glomerulonephritis occurs in a setting of systemic immune complex disease (40), although systemic features of the immunopathologic disease usually may be inapparent (41).

Hence, there are several clinical points to emphasize:

a. The antigen exciting immune complex glomerulonephritis should always be sought. To the extent that it is recognizable, removable, or treatable, a specific and definitive curve may be presently or ultimately available (42).

b. Idiopathic immune complex glomerulonephritis may have systemic correlates: symptomatic, or inapparent except to zealous scrutiny.

c. The determinants of immune complex localization to major, large blood vessels disproportionately in patients with periarteritis nodosa in contrast to the kidney, in such clinical problems as SLE and PSGN are largely unknown, but are inferred to be derived from immune complex size. A similar enigma is noted in acute serum sickness where coronary arteritis is the conspicuous hallmark of disease, whereas this lesion does not occur in chronic serum sickness.

X. MEASUREMENT OF IMMUNE COMPLEXES

Finally, laboratory techniques are evolving which lend promise of objective data and quantitative criteria for diagnosis and management of immune complex glomerulonephritis (43). Most of these techniques are

indirect; that is, they utilize some indirect reactant or property of immune complex material to bind to a detector system: binding to C_{1q}, or rheumatoid factor, complement activation, cell binding, or induction of a biologic end-point such as histamine, release, PMN chemotaxis, platelet aggregation, etc. Direct tests include analytic ultracentrifugation, measurement of cryoglobulins, differential solubility precipitation etc. All tests so far have an apparent inverse relationship between sensitivity and specificity, and suffer three important handicaps:

a. It is not certain that the levels of circulating complexes are indicative of the nephritogenic complexes.
b. Present assays detect circulating immune complexes in only a variable fraction of patients who appear to have ICGN.
c. There may be substantial spontaneous variation in concentrations of circulating immune complexes.

To date, clinical managment of immune complex disease by serial sampling of circulating immune complexes has not been practical (44-46), although it is the real hope of clinical therapists.

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