Immunologic aspects of the nephrotic syndrome

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The nephrotic syndrome is a clinical entity characterized by proteinuria, hypoalbuminemia, edema and hyperlipidemia. All the features of this syndrome are ultimately related to increased permeability of the glomerular capillary to protein. A specific disease entity in its mildest form may result in mild proteinuria insufficient to cause hypoalbuminemia and the other physiological manifestations of the nephrotic syndrome; the same disease in another patient or at another time in the same patient may cause marked proteinuria and the nephrotic state. The principal difference between proteinuria alone and that associated with the nephrotic syndrome in any specific disease would therefore appear to be quantitative, although it is likely that other factors play a role.

The glomerular capillary wall is composed of a fenestrated endothelium, the glomerular basement membrane (GBM) and the epithelial cell with foot processes that abut on the GBM. It is through this structure that filtration and selective impedance to the passage of protein occur (Fig. 1). The permeability characteristics of the capillary result in the virtual exclusion of proteins like albumin from the glomerular filtrate but permit complete penetration by smaller molecules such as inulin. The evidence that an alteration in this capillary barrier is responsible for proteinuria and the nephrotic syndrome includes the following [reviewed in reference 1]: *1)* histologic evidence of glomerular disease, deposition of immunoglobulin and complement components along the glomerular capillaries and fusion of the glomerular epithelial cell foot processes have been regularly seen in various forms of glomerulonephritis associated with proteinuria; *2)* in certain forms of experimental immune renal disease (e.g., antigen-antibody complex disease and nephrotoxic nephritis) there is clear evidence of glomerular capillary injury, which is often associated with proteinuria and the nephrotic state; *3)* in aminonucleoside of puromycin nephrosis in rats morphologic studies have demonstrated fusion of the

foot processes and decrease in colloidal iron and alcian blue staining reactions of the epithelial glomerular polyanion [2, 3]. This negatively charged macromolecule has been shown to be a sialoprotein that lines the epithelial cell membrane and foot process [3–6]. Whether this polyanion plays a role in the impermeability of the filter or maintains the foot process architecture is unknown. In this experimental form of nephrotic syndrome, increase in the permeability of the glomerular capillary has been demonstrated by micropuncture [7] as well as by ultrastructural studies using marker proteins such as ferritin or catalase [8–11]. These latter studies suggest that the permeability barrier resides in the GBM and the epithelial slit pore; *4)* physiologic studies in human renal disease
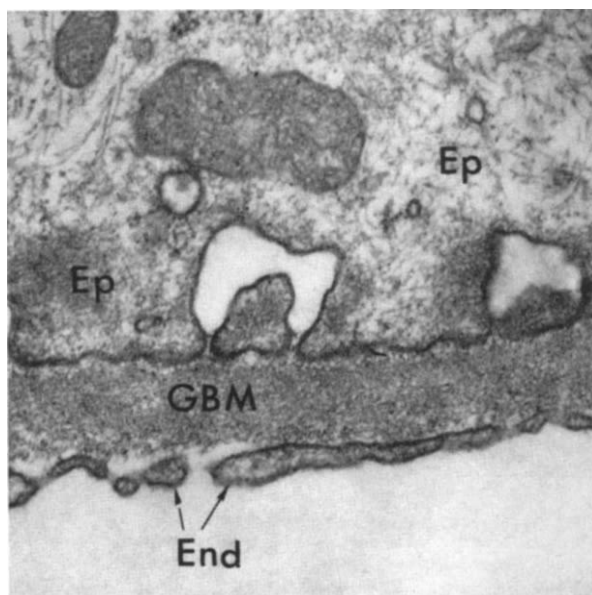

Fig. 1. *Electron micrograph of the normal glomerular capillary filter demonstrating the fenestrated endothelium (END), the glomerular basement membrane (GBM) and the epithelial cell (EP). The epithelial slit pores and membrane can be seen between the foot processes of the epithelial cell (× 52,300).*

have provided indirect evidence that proteinuria is related to altered glomerular permeability [12–14]. There is little evidence to support alternative explanations for proteinuria in nephrotic states, such as the possibility of decreased tubular reabsorption of protein as a major factor.

It is difficult to develop a meaningful classification of the various diseases that lead to the nephrotic syndrome, since the precise pathogenetic mechanisms have not been satisfactorily explained. Evidence that immunological mechanisms play a role in the pathogenesis of some forms of human nephrotic syndrome is derived from immuno-pathologic studies, by analogy to certain diseases in animals that are naturally occurring or induced by im-munological manipulation, and by alterations in the levels of serum complement and complement components. On the basis of available evidence and considerable liberty, the classification noted in Table 1 is suggested. No attempt will be made to describe these diseases in detail.

Immunopathologic studies

During the course of the last decade numerous studies have demonstrated the regular occurrence of immune reactants within the glomerulus in a variety of forms of glomerulonephritis [15, 16]. The distribution and local-ization of immunoglobulins and complement has been useful in a number of instances in separating diseases into various categories. These data are summarized in Table 2. The recognition of an ultralinear immunofluorescent pattern indicating the presence of immunoglobulin within

Table 1. Classification of the nephrotic syndrome

I. *Immunologic glomerular capillary injury*
  A. *Presumed antigen-antibody complex disease*
    Acute poststreptococcal glomerulonephritis
    Lupus erythematosus
    Chronic membranoproliferative glomerulonephritis
    Glomerulonephritis associated with certain infections
    Rapidly progressive glomerulonephritis
    Membranous glomerulopathy (with or without renal vein thrombosis)
    Glomerulonephritis associated with certain malignancies
    Glomerulonephritis associated with certain drugs (e. g., penicillamine)
  B. *AntiGBM antibody disease*
    Goodpasture's disease
    Rapidly progressive glomerulonephritis
  C. *Unknown mechanism*
    Anaphylactoid purpura glomerulonephritis
II. *Mechanism of glomerular capillary alteration unknown*
  A. *Idiopathic nephrotic syndrome*
    1. With nil or minimal glomerular alteration
    2. With mesangial proliferation
    3. With glomerular sclerosis
  B. *Other causes*
    Congenital and familial nephrosis, amyloidosis, diabetic nephropathy, chemicals (e. g., tridione and mercury), sickle cell anemia, Hodgkin's disease, etc.

the GBM and the presence of antiGBM antibody has been helpful in the diagnosis of Goodpasture's disease and certain forms of rapidly progressive glomerulonephritis [17, 18]. In our experience, this is a rare lesion. The immuno-

Table 2. Summary of immunopathologic observations and alterations in serum complement in various forms of nephrotic syndrome

Disease	Serum levels of complement[c]					Glomerular deposits of immunoglobulins and β1C by immunofluorescent microscopy	
	CH_{50}	C1	C4	C2	C3	Distribution	Pattern
I. *Immunologic glomerulonephritis*							
Acute poststreptococcal	R	N or R[a]	N or R	R	R	GBM, extra-GBM, mesangial	Granular or nodular
Lupus erythematosus	R	R	R	R	R	GBM and mesangial	Granular; linear
Membranoproliferative	R	N or R[a]	N or R[a]	N	R	GBM; infrequent mesangial	Peripheral lobular
Nephritis with infection	N or R	(R[b])	(R[b])	(R[b])	N or R	GBM, mesangial	Granular; focal linear
Rapidly progressive	N				N	GBM and mesangial; occasionally no deposits	Granular
Membranous	N				N	GBM and epimembranous	Granular or nodular
AntiGBM (Goodpasture's or Rapidly Progressive)	N				N	GBM	Ultralinear
Anaphylactoid purpura	N				N	Mesangial; rarely GBM	Arborized; focal linear
II. *Idiopathic nephrotic syndrome*	N or R	N or R	N	N	N	Negative or stalk and mesangial	
Congenital nephrotic syndrome	N or R				N	Negative	

[a] Several low values obtained by hemolytic assay in one investigation [37].
[b] In one instance with shunt nephritis [41].
[c] N—normal; R—reduced.
  (Data derived from references 37, 41, 60–64, 68, 73–76.)

fluorescent pattern frequently seen in diabetic nephropathy may be indistinguishable from that of antiGBM antibody disease [19, 20]. In diabetes, renal tissue from over 50% of patients show this ultralinear distribution for IgG usually associated with the presence of other proteins such as albumin, fibrinogen and ceruloplasmin [20]. The presence of these proteins, the inability to demonstrate that eluted IgG fixes to GBM and the absence of *in vitro* complement fixation strongly suggest that the proteins are present on the basis of a nonimmunological mechanism. These findings may reflect some intrinsic abnormality of the GBM in diabetes. We have observed this distribution of proteins in the GBM of children as early as two years after onset of diabetes at a time when there were no significant glomerular abnormalities by light microscopy. Lesser quantities of IgG in an ultralinear distribution similar to that described for Goodpasture's disease and diabetic nephropathy may also be seen in the normal kidney; in this circumstance it is quantitatively less intense and usually associated with the presence of other proteins such as albumin and fibrin. These immunofluorescent findings probably reflect the presence of small quantities of entrapped proteins within the GBM which we have been able to detect by immunochemical techniques in normal isolated GBM [21].

Patterns of immunofluorescence that are not of the antiGBM variety are often described under a great number of different and conflicting terms which mean different things to different investigators. This confusion arises in part because of the difficulty in defining precise location of immune reactants within the glomerulus in some diseases. The presence of discrete nodular deposits along the GBM is a characteristic feature of antigen-antibody complex disease because the appearance is similar to that observed in experimentally induced serum sickness or chronic complex disease (Figs. 2 and 3). In addition, there is often an assumption that any variety of globulin deposition, which is not characteristic of antiGBM disease, represents an immune complex mechanism. This assumption is unwise, as pointed out by McCluskey [16], since direct proof of an immune complex pathogenesis would require demonstration that antibody in the glomerulus forms a complex with a specific antigen—evidence which has been substantiated only in lupus erythematosus, where both antibody [22–24] and antigen [24] have been demonstrated, possibly in poststreptococcal glomerulonephritis [25–27] and certain instances of glomerulonephritis associated with infection [28–30] and malignancy [31]. No attempt will be made to depict the various patterns of glomerular deposition of immunoglobulin in various forms of glomerulonephritis since these have been described in prior publications.

In some diseases, the immunoglobulin within glomerular deposits reacts with certain antigens following elution with solutions known to dissociate antigen-antibody complexes. In Goodpasture's disease, the antibody has been shown to have specificity for the GBM *in vitro* by immunopatho-
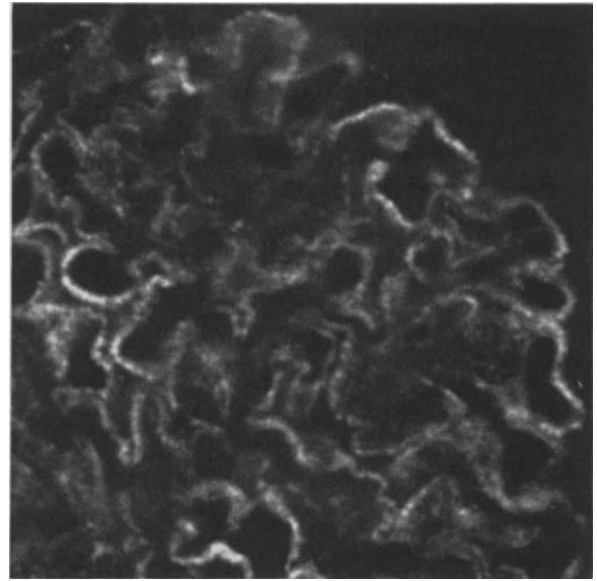

Fig. 2. *Tissue from a patient with nephrotic syndrome and histologic evidence of membranous glomerulopathy.* The patient ultimately developed DNA antibody and other evidences of lupus erythematosus. Note the granular deposits of IgG along the GBM demonstrated by immunofluorescent microscopy.

logic techniques and to react *in vivo* in monkeys causing glomerulonephritis [18, 32]. Antibody eluted from kidney of patients with lupus erythematosus reacts with nuclei, desoxyribonucleoprotein and DNA (see Agnello, Koffler and Kunkel, this issue).

Analogy to experimental forms of renal disease induced by immunological manipulation

The analogy of certain experimental forms of immune renal disease to human glomerulonephritis has been a major factor in developing ideas regarding the pathogenesis of human disease. The outstanding studies of Dixon and his colleagues and many other workers have developed the concepts of antigen-antibody complex disease and its unique difference from antiGBM disease [33]. These studies will not be reviewed here.

The change in the permeability barrier occurring after immunologic insult (antigen-antibody complex nephritis or antiGBM nephritis) is mediated by a variety of effector mechanisms. The extensive studies of Cochrane and Henson [34–36] have clearly demonstrated a major role for complement, leukocyte and platelets in the proteinuria of antiGBM nephritis. The release of various mediators, cathepsins, cationic proteins and other enzymes such as collagenases from lysosomal granules probably plays a major role in altering the filter, resulting in nonselective proteinuria and the release of fragments of GBM into the urine. In contrast, depletion of C3 by cobra venom factor or leukocytes does not alter the glomerular histology or proteinuria in acute experimental immune complex disease in rabbits,
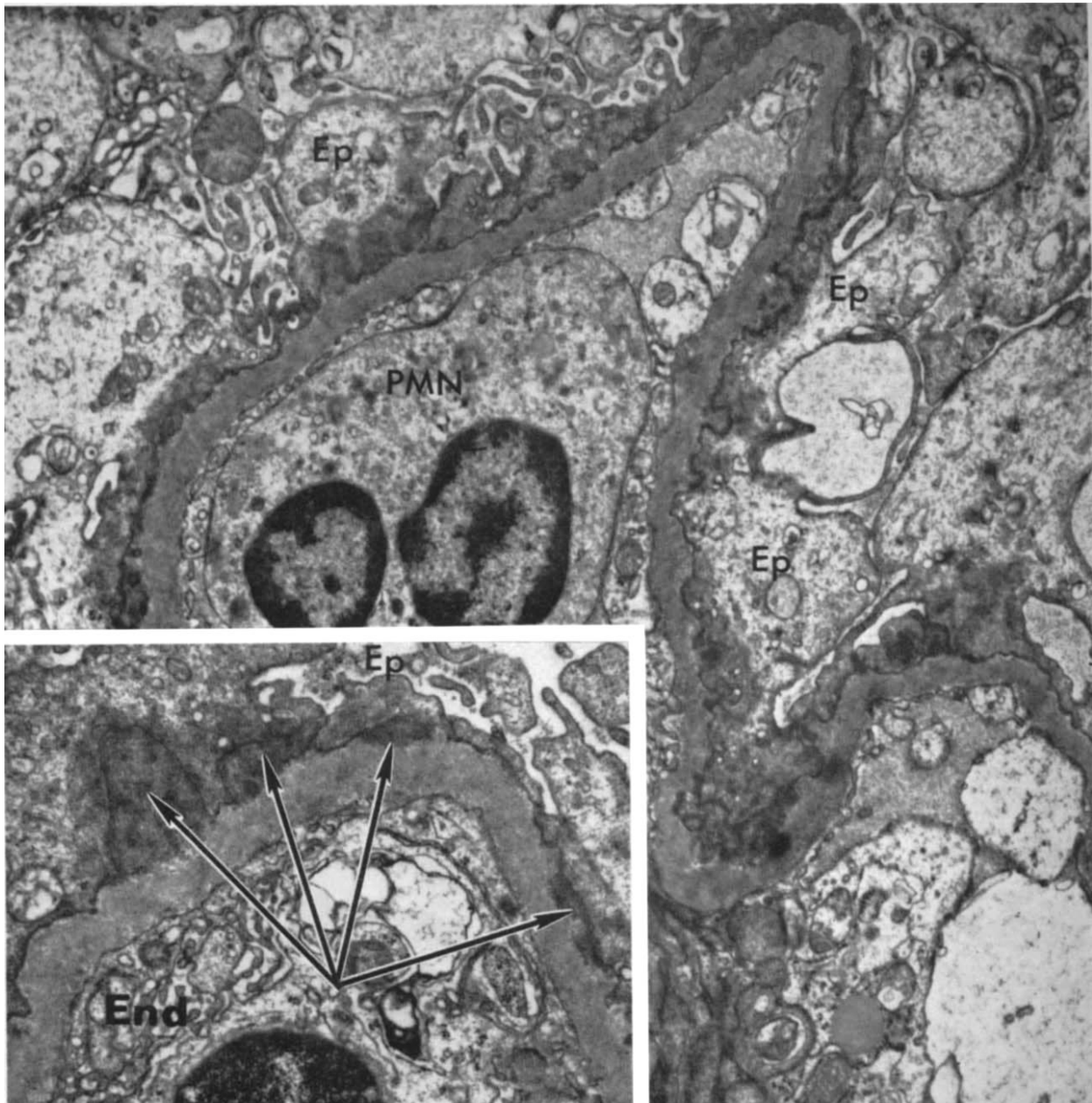
Fig. 3. *Electron micrograph of a part of a glomerular capillary from the same patient described in Fig. 2, showing early morphologic changes of membranous glomerulopathy.* The larger figure demonstrates variable-sized densities accumulating primarily beneath the limiting membrane of the epithelial cell and the GBM. Note that the epithelial surface of the GBM projects in "peglike" protrusion into the epithelial cell in several loci. These protrusions are the silver-positive spikes seen by light microscopy. The insert demonstrates variable-sized deposits of dense material in this same locus and emphasizes the probable sequence of development of such epithelial deposits. EP—epithelial cell; END—endothelial cell; PMN—a partially degranulated polymorphonuclear leucocyte. (× 16,000; insert × 22,000).

so that the mechanism of altered glomerular capillary permeability in this disease remains unexplained.

Studies on complement

During the last half-century, numerous studies have shown a reduced serum level of complement in acute post-streptococcal glomerulonephritis. The diseases in which a significant depression in the complement level has been observed are outlined in Table 2. Gewurz et al [37] pointed out important differences between the complement profile in systemic lupus erythematosus and that seen in chronic membranoproliferative glomerulonephritis associated with hypocomplementemia. In the former there was uniform depression of the earlier components in addition to C3t, whereas in the latter C1, C4 and C2 were relatively normal

when compared to a depression of C3t. On the basis of this observation, the possibility was proposed that an alternate system for complement activation might be operative in this disease. An analogy was drawn between the action of antigen-antibody complexes, on the one hand, which result in depression of C1, C4, C2 and C3t, compared with the action of endotoxin or zymosan which activated the terminal components (C3t).

Alternate complement pathway in glomerulonephritis. Although it seems clear that immunological mechanisms may be primary in the pathogenesis of many forms of human glomerulonephritis and nephrotic syndrome, the precise mechanism of this injury is unknown although it appears to be mediated at least in part by the complement system. The evidence that an alternate system for complement activation may be present includes the following: *1)* studies carried out by Pillemer et al [38] nearly 20 years ago elucidated a system in which properdin was characterized as a protein which in the presence of zymosan could be removed from serum at 17° C, and participated in the inactivation of C3 at 37° C. At least two other serum factors were essential—factor A, a hydrazine-sensitive factor, and factor B, a heat-labile factor. The precise relevance of this system to human disease and its role as a unique immunological system were challenged for a number of reasons. A reduction in the activity of serum properdin has been demonstrated in patients with acute poststreptococcal nephritis and in certain instances of chronic glomerulonephritis [39]. We have demonstrated the presence of properdin in the glomerular deposits of all patients with acute poststreptococcal glomerulonephritis and chronic membranoproliferative glomerulonephritis with hypocomplementemia [40, 41]. In other diseases (e.g., lupus erythematosus) deposits of properdin are less frequently observed. *2)* Gewurz et al [42] demonstrated preferential fixation of the terminal six complement components by gram negative bacterial endotoxin although recent studies indicate that earlier components may be necessary. Sandberg et al [43] and Oliveira et al [44] also presented evidence for an alternate system by the demonstration of terminal complement component activation by the F(ab)$'_2$ fragment of gu'nea pig γ1 and γ2 and aggregated gamma globulin. The γ1 antibody showed no interaction with C1, C4 and C2. This contrasted with the activity of γ2 antibody, which activated the entire complement sequence through the Fc fragment. *3)* Müller-Eberhard and Götze [45, 46] have recently presented evidence supporting the existence of a second system for activating complement essentially replacing the need for the first three components. C3 proactivator (C3PA), a beta globulin, with a molecular weight of 80,000 is cleaved into two fragments; the larger one, which has gamma mobility on electrophoresis and a molecular weight of 60,000, has been called C3 activator since it is able to activate and split C3. Certain substances including inulin, endotoxin, cobra venom factor and immunoglobulin aggregates activate the system in the presence of a 3S alpha globulin, C3PA convertase and an activated hydrazine-sensitive factor which is related to C3. C3PA and the glycine-rich beta-glycoprotein have been shown to share antigenic determinants; factor B activity has been described in both C3PA and the glycine-rich beta-glycoprotein [47, 48]. There has been considerable debate regarding the precise relationship between these two molecules. In addition, the exact interaction between properdin and the C3 proactivator system has not been defined. *4)* West et al [49] Spitzer et al [50] and Vallota et al [51] have described a factor in the pseudoglobulin fraction of serum from patients with chronic membranoproliferative glomerulonephritis the C3 nephritic factor (C3NeF). This factor, in combination with a pseudoglobulin cofactor and magnesium, forms C3 lytic nephritic factor (C3LyNeF), which is able to cleave C3 to γ2D and β1A.

C3PA, properdin and β1A in renal disease. We have attempted to evaluate the role of the alternate complement system in various forms of glomerulonephritis by measurement of serum levels of C3PA, properdin and β1C. The various methods of protein isolation, production of antibody, protein quantitation, and the specific studies summarized here have been reported elsewhere [52]. The serum concentration of β1A, properdin and C3PA were carried out by modification of the immunodiffusion assay described by Mancini in patients with chronic membranoproliferative glomerulonephritis (CMPGN), systemic lupus erythematosus (SLE), acute poststreptococcal glomerulonephritis (AGN) and other renal diseases. Evidence derived from immunopathologic studies and complement component analysis has suggested that the alternate complement system may be involved, in part, in CMPGN [41].

Static values of properdin, C3PA and β1A represent a number of different influences and may not reliably portray the dynamic changes occurring *in vivo*. It seems clear, however, that significantly decreased values of properdin are seen only when β1A is reduced—especially in AGN but also in CMPGN (Fig. 4). In normal and SLE sera no correlation was seen between levels of β1A and properdin— in contradistinction to the positive correlation seen in sera from patients with AGN, CMPGN and other renal diseases.

Just the opposite situation was observed when C3PA data were evaluated: a positive correlation between levels of β1A and C3PA was observed in sera of normal and SLE patients but not in AGN or CMPGN. In addition, the levels of C3PA were most significantly reduced in hypocomplementemic patients with SLE. Significant decreases were also seen in hypocomplementemic AGN and CMPGN, and normocomplementemic SLE and CMPGN. (Fig. 5).

The conclusion that C3PA appears to be more prominently involved in SLE and properdin in AGN is perhaps an oversimplification of a complex situation. Demonstration of a more cathodal electrophoretic migration of properdin in some patients with CMPGN and SLE emphasizes the limitations of static serum values in evaluating any biologic system [52].
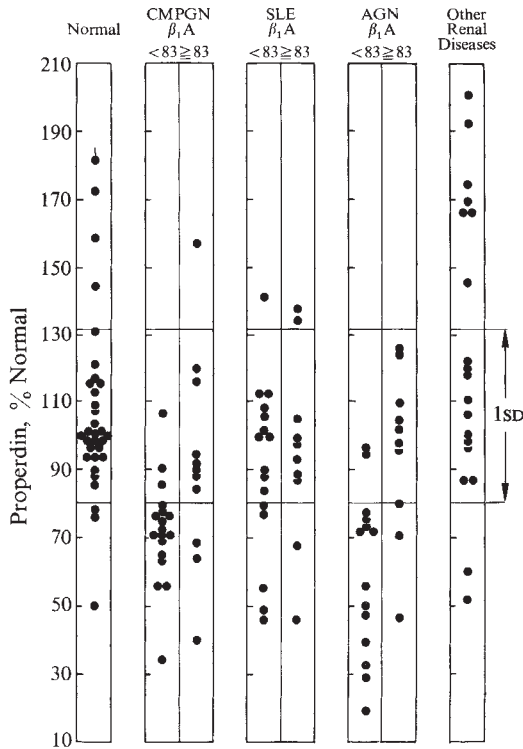
Fig. 4. *Levels of properdin in patients with chronic membranoproliferative glomerulonephritis (CMPGN), systemic lupus erythematosus (SLE), acute poststreptococcal glomerulonephritis (AGN) and other renal diseases.* There is a significant decrease in properdin ($P<0.01$) only in patients with CMPGN and AGN with reduced serum levels of $\beta1A$. (Data derived from [52].)
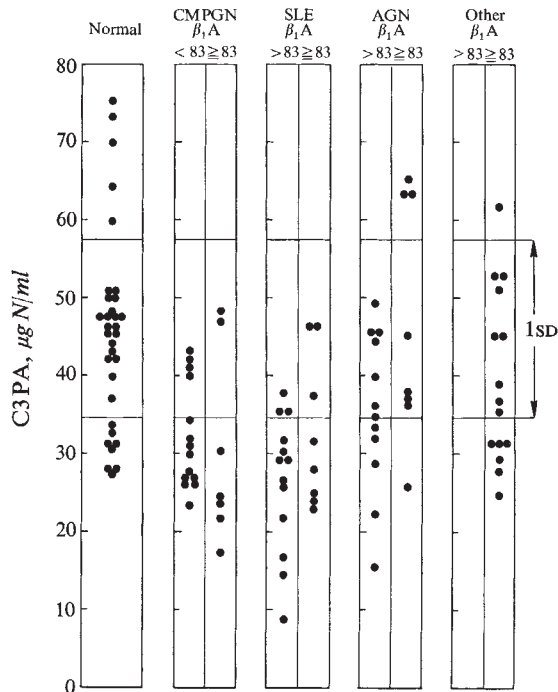

Fig. 5. *Levels of C3PA in the same group of patients described in Fig. 1.* SLE and CMPGN groups with low or normal levels of $\beta1A$ and hypocomplementemic AGN had significantly reduced values of C3PA. (Data derived from [52].)

Idiopathic nephrotic syndrome (INS)

This syndrome has certain unique characteristics that separate it from other forms of nephrotic syndrome associated with glomerulonephritis. These differences are outlined in Table 3. The clinical and pathologic findings have been described in detail in the excellent reviews of White, Glasgow and Mills [53] and Habib and Kleinknecht [54] and Churg, Habib and White [55].

The precise etiology of INS is unknown. Evidence that immunological mechanisms play a role have been largely circumstantial and have depended upon relationships to certain events that imply an immunological mechanism, namely, recurrent disease associated with respiratory infections, the rare association with exposure to toxins such as bee stings, the occurrence of allergic manifestations such as hay fever and pollen hypersensitivity with episodes of the syndrome [56] and the response to cyclophosphamide therapy which has been shown to prolong the duration of remissions in children with frequently relapsing idiopathic nephrotic syndrome [57–58].

Complement. Reduced serum levels of whole complement activity have been detected in some patients with relapsing

Table 3. Comparison of various forms of immune-related glomerulonephritis and idiopathic nephrotic syndrome

	Glomerulonephritis	Idiopathic nephrotic syndrome
Clinical features of nephrotic syndrome	May be present. Depends on amount of proteinuria	Almost always present
Frequency	Major form of nephrotic syndrome in adults	Major form in children
Light microscopy	Proliferation and/or glomerular basement membrane (GBM) thickening	Normal or minimal abnormalities; mesangial proliferation
Immunofluorescent microscopy	Prominent deposits of immunoglobulin and complement (e. g., $\beta1C$) along the GBM and mesangium	No GBM-oriented deposits; glomeruli negative or show focal stalk or mesangial deposits
Electron microscopy	Electron dense deposits present; GBM may be thick; foot process fusion; increased mesangial matrix	Foot process fusion
Serum complement ($\beta1C$ or C3)	Normal or low	Normal
Urine protein selectivity	Normal or low	High
Response to prednisone	Only in lupus erythematosus-	Complete in two to four weeks in over 95% patients

nephrotic syndrome [59]. However, this observation has not been consistently confirmed and because of the associated biochemical changes induced by the nephrotic state, measurements of whole complement activity are open to question. Numerous studies have demonstrated normal serum values for $\beta1C/\beta1A$ as well as for C4 [60–64]. Lewis, Carpenter and Schur [64] described a decrease in C1q in one-third of patients with this disease, a finding that likely reflects the metabolic effects of the nephrotic syndrome rather than an immune process.

Ngu, Barratt and Soothill [61] demonstrated a significant increase in the titer of immunoconglutinin—autoantibody to hidden antigenic determinants of C3 and C4—during episodes of INS, even though the levels of whole complement and $\beta1C$ were essentially normal. The exact significance of this observation is unknown, although elevations in titer reflect immunological reactions and have been observed in acute poststreptococcal glomerulonephritis and viral infections.

C3PA, properdin and $\beta1C$ in INS. Measurements of C3PA, properdin and $\beta1C$ in eight children with steroid-responsive INS at the time of relapse when not receiving corticosteroid therapy revealed the following values (mean and range): $\beta1C$—180 mg/100 ml (154 to 219); C3PA—24 µg N/ml (23 to 33); properdin 139 mg/100 ml (92 to 198) (normal values, mean $\pm$ SD: $\beta1C$ 165$\pm$41 mg%; C3PA 46$\pm$12 µg N/ml; properdin 107$\pm$17 mg%). The values for $\beta1C$ and properdin are normal or slightly elevated, whereas the levels of C3PA are significantly depressed. The low values of C3PA may reflect urinary loss, since the molecular weight is 80,000. In addition, immunofluorescent studies of renal tissue using antiserum to C3PA have not revealed significant glomerular fluorescence in any disease, although proximal tubules frequently demonstrate this protein. Although it has been shown that reduced serum values of $\beta1C$ are not caused by urinary loss, such may not be the situation with C3PA.

Immunopathologic studies. Immunopathologic studies have been carried out on renal tissue from children with INS and have demonstrated either no glomerular deposits of IgG or $\beta1C$ or the presence of focal and local deposition in the axial region and mesangial stalk [65]. Similar findings have been observed by Habib and Kleinknecht [54], who also observed the presence of IgM in areas of focal sclerosis. The recent demonstration of IgE in glomeruli in the form of "comma" deposits in patients with INS by Gerber and Paronetta were especially interesting in view of the occasional association with allergic states [66].

We have recently described immunopathologic studies in INS using antisera against a number of different proteins including IgE [67]. The results of these studies, summarized in Table 4, fail to demonstrate IgE in the glomeruli of 19 patients with INS (Fig. 6). The reason for the differences between these results and those of Gerber and Paronetta are unknown, although it is possible that IgE plays some

Table 4. Immunopathologic studies in idiopathic nephrotic syndrome

Morphologic diagnosis	Steroid-responsive[a]	Significantly positive glomerular fluorescence using antisera to:[b]		
		IgG, IgA, IgE, fibrin, albumin, properdin, C3PA	IgM[c]	$\beta1C$[c]
Minimal lesion	8/9	0/9	8/9	9/9
Mesangial proliferation	3/3	0/3	3/3	3/3
Focal sclerosis	1/7	0/7	6/7	6/7
Normal controls (Transplant donors)		0/6	2/6	2/6

[a] The demoninator indicates the total number of patients in each group and the numerator denotes the number who ultimately were shown to be steroid-responsive.
Three patients with minimal lesions and three with focal sclerosis were receiving steroid therapy at the time of kidney biopsy; the rest were untreated.
[b] The denominator indicates the number in each group evaluated and the numerator the number with significantly positive glomerular fluorescence.
[c] IgM and $\beta1C$ were focally present in the mesangial stalk; no GBM-oriented deposits were present (modified from [67]).

role in atopic patients with nephrotic syndrome even though it is not uniformly detected in glomeruli.

The presence of axial and mesangial deposits of IgM and $\beta1C$ in some glomeruli in a focal distribution cannot be explained with certainty. The appearance of mesangial deposits has been described late in the course of patients with congenital nephrotic syndrome in whom tissue obtained shortly after birth failed to reveal the presence of immune deposits [68]. A similar finding has been demonstrated in rats with aminonucleoside nephrosis, a form of experimental nephrotic syndrome in which immune mechanisms are not known to play a role [69]. In addition, a unique relationship between mesangial function and glomerular capillary permeability has been demonstrated by Mauer et al [70] in aminonucleoside nephrosis in rats. A five- to tenfold increase in the mesangial uptake of intravenously administered aggregated IgG (^{125}I) has been observed in animals with proteinuria. The reason for this increased entrapment is unknown, although an important interaction may exist between mesangial function and events occurring at the filtering surface of the capillary. We have also observed immunoglobulin and especially $\beta1C$ in the glomerular stalk and afferent arterioles in normal kidney tissue (e.g., transplant donor).

The regular absence of immunoglobulin, complement components and electron dense deposits along the glomerular capillary filter make it unlikely that either an antigen-antibody complex mechanism or antiGBM antibody is operative in INS. The failure to demonstrate glomerular-bound IgE would place some question on the role of reaginic antibody in all patients with INS.
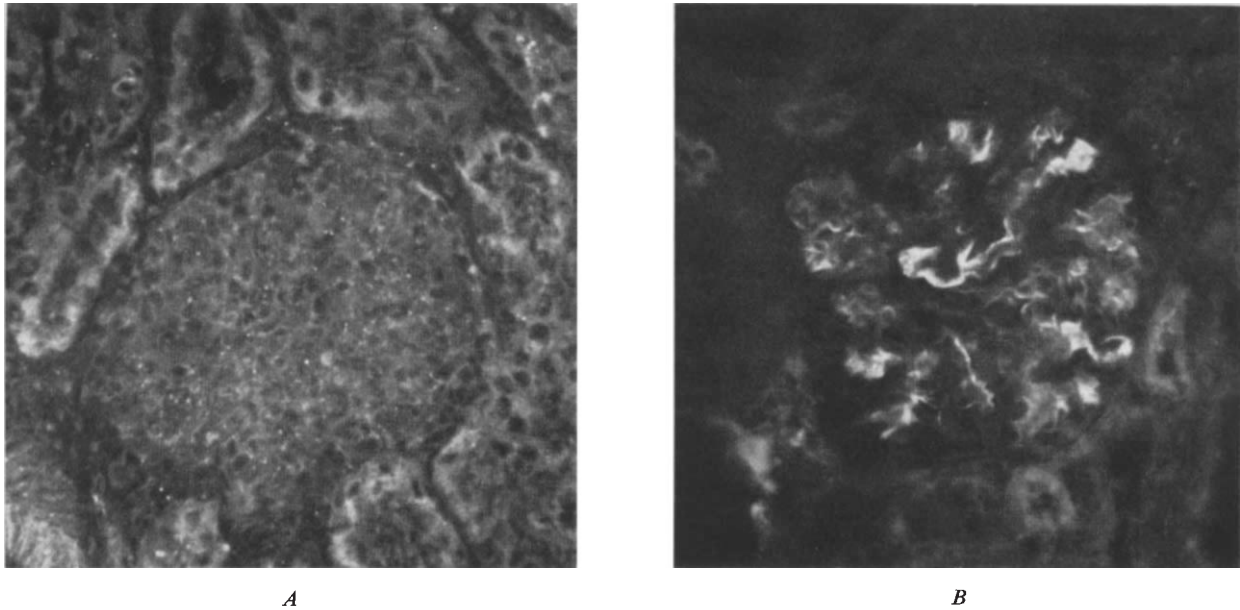
A   B

Fig. 6. *Immunopathologic studies on kidney tissue from patients with idiopathic nephrotic syndrome (INS). A) No evidence for glomerular deposition of IgE in tissue from a patient with steroid-responsive nephrotic syndrome.* A similar picture was seen utilizing antisera to IgG, IgA, fibrin, albumin, properdin and C3PA. *B) Focal deposition of IgM is shown in this glomerulus from a child with steroid-responsive INS.* The exact locus cannot be determined with certainty, although the IgM is probably present within the mesangium.
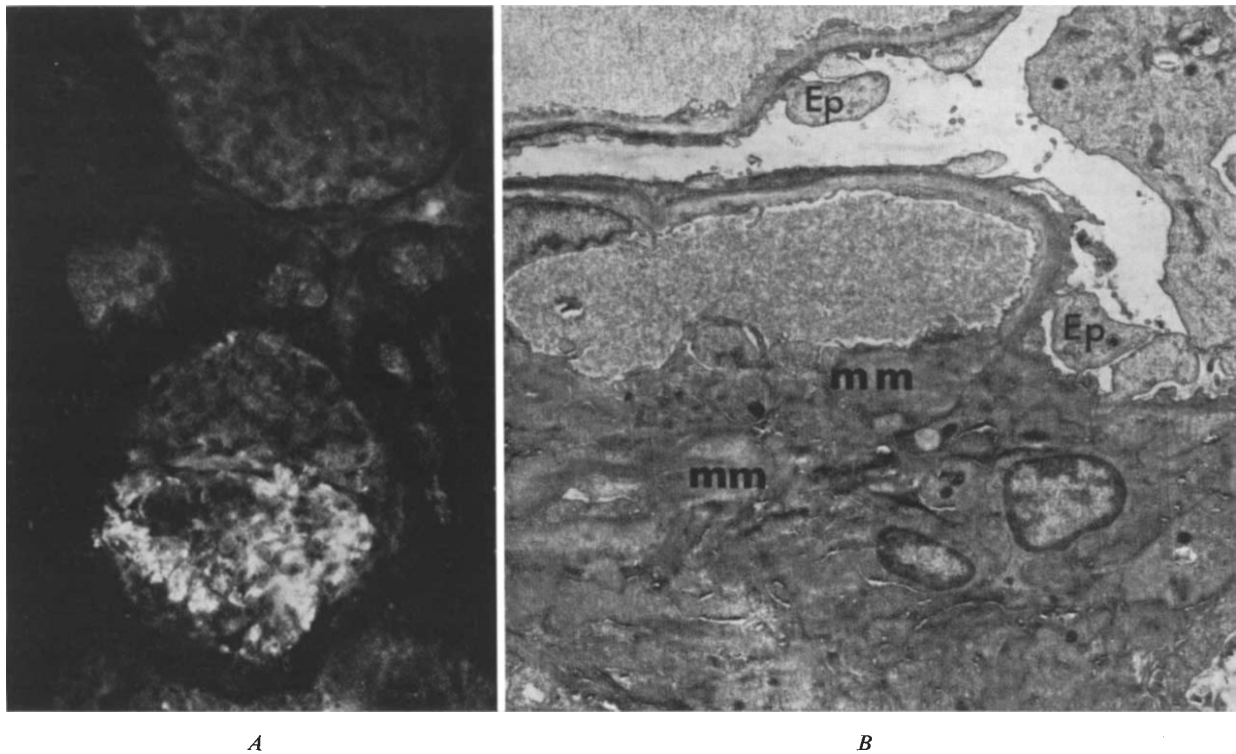

A   B

Fig. 7. *A) Tissue from a patient with steroid-resistant nephrotic syndrome, demonstrating focal and local deposition of β1C in an area of glomerular sclerosis.* Note the negative staining glomerulus above. *B) Electron micrograph of a segment of a glomerulus from a patient with steroid-resistant nephrotic syndrome and focal glomerular sclerosis.* The epithelial cell (Ep) foot processes are fused along the normal-appearing GBM. The mesangial matrix (mm) is increased in quantity and seen as GBM-like material between processes of the mesangial cell (× 7500).

The relationship between nil or minimal lesion nephrotic syndrome and that associated with focal sclerosis is unknown. Immunopathologic studies reveal little differences between these two groups of patients with the exception that areas of focal sclerosis are often associated with nondescript deposition of immunoglobulins (Fig. 7). Whether or not these syndromes represent two different diseases or a variable expression of the same pathogenetic process is unknown. Complete steroid responsiveness of patients with minimal lesion compared with the virtual steroid-resistance of patients with glomerular sclerosis suggests at least some important biological differences. We have recently had a unique opportunity to observe four patients with steroid-resistant nephrotic syndrome associated with gradual glomerular sclerosis and ultimate renal failure. All four were subjected to homotransplantation, and recurrence of nephrotic syndrome has been documented in three of these patients, suggesting that nonrenal factors are important in the genesis of the disease [71].

It has not been possible to prove with certainty that immunological mechanisms play no role in the pathogenesis of INS. It seems clear, however, that attempts to identify a specific immune mechanism analogous to antigen-antibody complex disease or antiGBM nephritis have been unsuccessful. It has been recognized for some time that nephrotic syndrome may occur in association with Hodgkin's disease. There is no evidence, in most instances, that this represents an antigen-antibody complex disease as postulated for the renal disease associated with other malignancies [31]. There is good evidence, however, on the basis of light, fluorescent and electron microscopy, that the renal disease is similar to or the same as INS [72]. This provocative observation may indicate that a lymphoreticular cellular mechanism may in some way play a role in glomerular permeability to protein.

Summary

Available evidence suggests that the nephrotic syndrome is caused by increased permeability of the glomerular capillary filter to protein. This evidence is derived from morphologic and immunopathologic studies in human and experimental renal disease and from micropuncture and electron microscopic studies using enzyme markers. Evidence that immunological mechanisms play a major role in certain forms of nephrotic syndrome are derived from immunopathologic observations, by analogy to certain forms of experimental renal disease and by alterations in serum complement and complement component levels. This group of diseases includes a variety of forms of glomerulonephritis which are presumed to be antigen-antibody-complex–mediated as well as the less frequent forms of antiGBM nephritis. Evidence that the alternate complement system may be involved in certain forms of immune-related glomerulonephritis includes the demonstration of properdin and C3 in the glomerular deposits of all patients with membranoproliferative glomerulonephritis and acute poststreptococcal nephritis, the demonstration of a decrease in the level of properdin in both of these diseases associated with a reduction of levels of serum β1A, the demonstration of a positive correlation between levels of β1A and C3PA in SLE patients associated with a significant depression in the level of C3PA and a demonstration of a more cathodal electrophoretic migration of properdin in some patients with chronic membranoproliferative glomerulonephritis and lupus erythematosus.

Evidences that immunological mechanisms play a role in idiopathic nephrotic syndrome have been largely circumstantial and include the frequent recurrence of the disease associated with respiratory infection, the infrequent association with certain toxins and hypersensitivity states, the response to cyclophosphamide therapy and the demonstration of increase in the serum level of immunoconglutinin. Serum levels of complement and β1A have generally been within normal limits. Immunopathologic studies have generally revealed either the absence of significant immune deposits or the presence of stalk or mesangial deposits of IgM or β1C; it is possible that this is a consequence of proteinuria and not a cause of it, although the matter has not been settled. We have found no evidence for IgE within the glomeruli of patients with this syndrome. Measurement of alternate complement pathway components has revealed a significant decrease in the level of C3PA—which may be due to urinary loss of this protein although this has not been proved. There is thus no conclusive proof that this form of nephrotic syndrome is immunologically mediated.

Acknowledgements

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