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Ultrastructural Immunohistochemical Localization of Polyclonal IgG, C3, and Amyloid P Component on the Congo Red-negative Amyloid-like Fibrils of Fibrillary Glomerulopathy

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Renal biopsies from seven patients with Congo red-negative amyloid-like fibrillary glomerulopathy (FGP) were examined by protein A gold immunoelectron microscopy. Ultrastructurally, the fibrils in all cases exhibited positive immunostaining for IgG, both Ig light chains, C3, and amyloid P component (AP), but did not show positive immunostaining for glomerular basement membrane (GBM)-associated proteins (collagen type IV and heparan-sulfate proteoglycans) or microfibril-associated proteins (fibronectin and fibrillin). In a triple-label study, AP and IgG were colocalized along the same fibril, whereas the gold probes for the detection of collagen type IV were absent. The results suggest that the fibrils are comprised of polyclonal IgG and C3 that bind AP. AP was immunolocalized sparsely but regularly along the lamina rara interna of normal GBM. AP was absent in the fibrils in a case of diabetic glomerulopathy, was scattered randomly without specificity for the electron-dense deposits in the GBM of membranous glomerulopathy, and lined up regularly along the fibrils in amyloid deposits. FGP is an entity in which the fibrils bind AP but lack the β-pleated sheet structure necessary for Congo red staining that is typical of amyloid. (Am J Pathol 1992, 141:409–419)

Fibrillary glomerulopathy (FGP), characterized by the presence of amyloid-like fibrils in the glomerular basement membrane (GBM) and the mesangium, was first described by Rosenman and Eliakim in 1977.[1] Since then, more than 40 cases have been reported.[2–19] FGP differs from renal amyloidosis in several ways. The fibrils do not bind Congo red stain, they have a wider fibril diameter (mean range 18–22 nm)[16] than amyloid (8–12 nm), and they are found in the glomerulus[14] only and rarely in tubular basement membranes.[5] The patients lack evidence of disorders that are associated with organized deposits such as those that occur in cryoglobulinemia, dysproteinemia, or systemic lupus, and usually present with mixed nephritic and nephrotic features, and frequently, hypertension and hematuria.[5,14] The light microscopic pattern is heterogeneous ranging from membranous glomerulonephritis (GN), mesangiocapillary GN, or mesangial GN, often with prominent glomerular sclerosis.[14] Most reported cases demonstrate homogeneous, ribbonlike immunofluorescence staining for IgG, both light chains, and C3 along the capillary loops and the mesangium;[3,5,7,8,10,12–14,19] some are weakly positive or irregular for IgM, IgA, or C1q.[1–6,8,13–15,17,19] Less frequently, a single Ig isotype has been described.[8,10,13,14,19,20]

This study characterizes the immunohistochemical features of the fibrils in FGP at the ultrastructural level by immunoelectron microscopy via gold-labeled probes.

Materials and Methods

Diagnostic renal biopsies, obtained from five women and two men whose glomeruli exhibited noncongophilic fibrils that measured 15 to 20 nm in diameter in Epon-embedded tissue, were selected for this study. Each renal biopsy specimen was processed for standard light,

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Table 1. *Clinical Features of Patients with Fibrillary Glomerulopathy*

Pt	A/S/R	Ed/HTN	BUN/SCr (mg/dl)	C3	N. Synd	U Pr (g/d)	Hematuria	SIP/UIP/Cr
1	55/M/W	+ −	27/1.5		+	3.6	casts	
2	67/F/W	+	68/8.3		+	>3.0		
3	59/F/W	+ +	62/2.6	Nl		1.3	trace	
4	50/F/W	− +	Azotemia		+	2.5	+	
5	44/M/W	+ +	222/28			0.5	+	−/−/−
6	38/F/W	+ +	13/0.9	Nl		2.8	+	−/−/−
7	43/F/W	+ +	/1.5		+	5.5	+	−/−/−

Pt: patient; A/S/R: age/sex/race; Ed: edema; HTN: hypertension; BUN: blood urea nitrogen; SCr: serum creatinine; C3: serum C3 level; N. Synd: nephrotic syndrome; U Pr: urine protein (g/day); SIP: serum immunoelectrophoresis; UIP: urine immunoelectrophoresis; Cr: cryoglobulinemia; +: present; −: absent; tr: trace; Nl: normal; W: white. Blank means data not available.

immunofluorescence, and electron microscopy. Results of Congo red stains for the detection of amyloid were negative in all cases. For immunofluorescence study, 4-μm thick frozen sections were reacted with fluorescein-conjugated antisera to IgG, IgA, IgM (heavy chain specific), kappa and lambda chains (light chain specific), C3, and C1q. For routine electron microscopic study, tissues were fixed in 2.5% buffered glutaraldehyde, postosmicated, embedded in Epon, and stained with uranyl acetate and lead citrate.

Immunoelectron Microscopy

After completing the previously described procedures,[21] the frozen tissues, stored at −70°C in optimal-cutting-temperature (OCT) mounting medium (Tissue-Tek, Ekhart, IN), were fixed in 4% buffered paraformaldehyde and embedded in LR White resin, (Ladd Research Industries, Inc. Burlington, VT) from which ultrathin sections were obtained and immunostained.

Single Label

Rabbit primary antibodies were used at a dilution of 1:10 to examine all cases. Rabbit IgG anti-human antigens, obtained from Dako Co. (Carpinteria, CA), included the following: anti-amyloid P component (AP), anti-IgG (gamma chain specific), anti-kappa and anti-lambda (each light chain specific), anti-C3, and anti-fibronectin. Rabbit antisera to collagen type IV and heparan-sulfate proteoglycans (HSPG), previously characterized,[22] were gifts from Dr. Peter D. Yurchenco (UMDNJ—Robert Wood Johnson Medical School, Piscataway, NJ). Mouse monoclonal anti-fibrillin (diluted 1:5) was a gift from Dr. Lynn Y. Sakai[23] (Shriners Hospital for Crippled Children, Portland, OR). The gold probes (diluted 1:50) were conjugated to protein A for sections incubated in rabbit antisera and to goat anti-mouse IgG for sections incubated in mouse monoclonal antiserum (Amersham, Arlington Heights, IL).

Positive controls that were run in parallel for each of the staining reactions included four similarly processed diagnostic biopsies, i.e., membranous GN for IgG and C3, secondary amyloidosis (AA) and light-chain amyloidosis (AL) for AP, and AL kappa and AL lambda for light chains. Additional tissue controls for AP immunostaining included normal glomeruli obtained from a nephrectomy specimen, and renal biopsy specimens from one case of diabetic nodular glomerulosclerosis (DM) and one case of membranous GN. Negative controls included parallel sections incubated in 1:10 dilutions of the appropriate nonimmune serum, i.e., nonimmune rabbit serum (NRS) instead of rabbit primary antibody and nonimmune mouse serum instead of mouse primary antibody. The specificity and reactivity of each antibody was tested by immunofluorescence on frozen sections of known posi-

Table 2. *Light and Immunofluorescence Microscopic Features in Fibrillary Glomerulopathy*

	Light microscopy			Immunofluorescence						
Pt	Morphology	GS	VS	G	A	M	K	λ	C3	Clg
1	MesCapGN	10%	−	+	−	−	+	+	+	
2	Cresc GN	22%	+	+	−	tr	+	+	+	
3	Mes GN	48%	+	+	−	−	+	+	+	
4	Mes GN	0%	−	+	tr	tr	+	+	+	tr
5	MesCapGN	12%	−	+	−	tr	+	+	+	tr
6	Memb GN	34%	+	+	−	tr	+	+	+	+
7	Mes GN	35%	+	+	−	tr	+	+	+	+

Pt: patient; GS: glomerular sclerosis; VS: vascular sclerosis; MesCap GN: mesangiocapillary GN; CrescGN: crescentic GN; Mes GN: mesangial proliferative GN; MembGN: membranous GN; G: IgG; A: IgA; M: IgM; K: kappa light chain; λ: lambda light chain. Blanks: data not available.

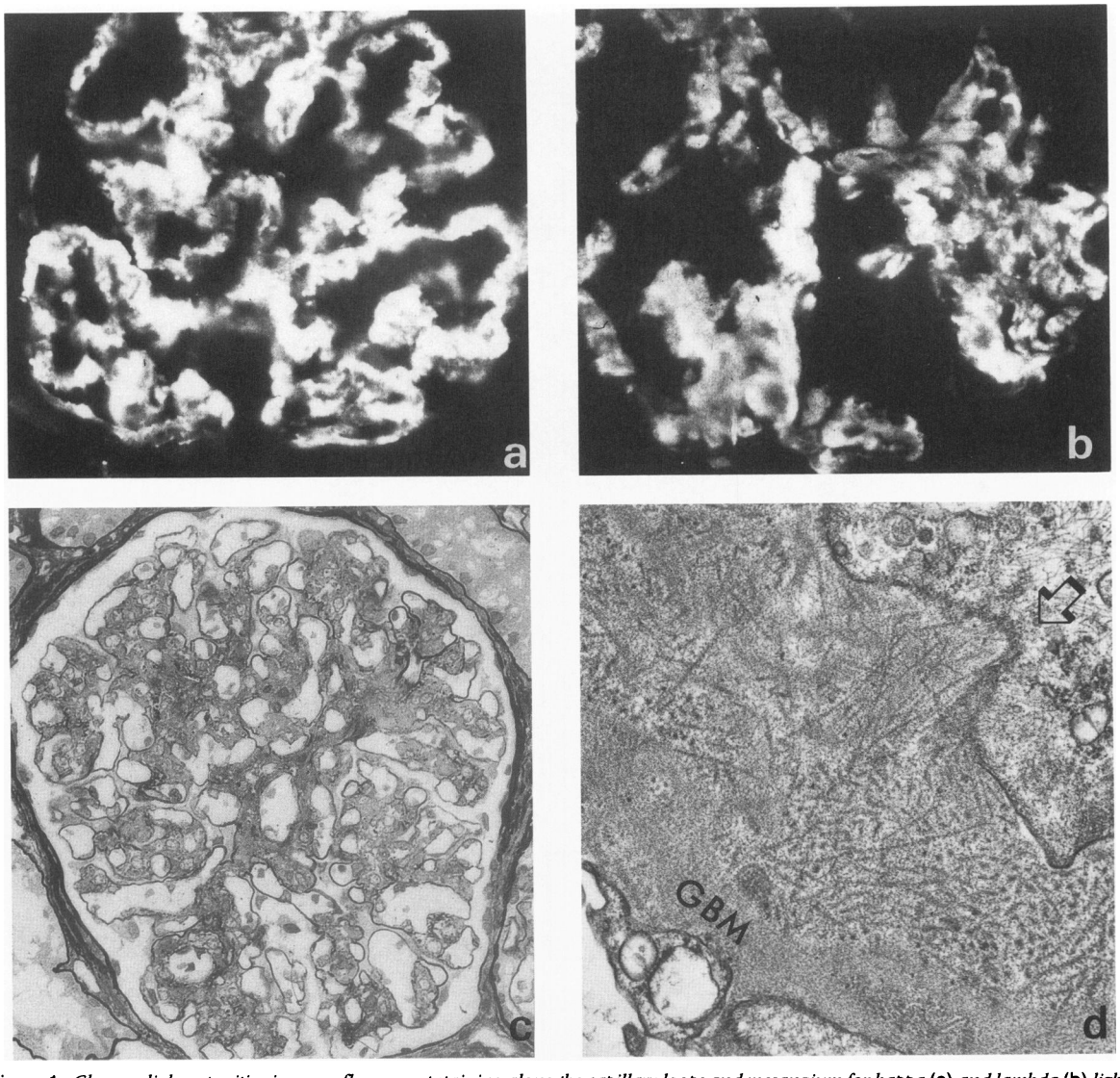

Figure 1. *Glomeruli show positive immunofluorescent staining along the capillary loops and mesangium for kappa* (a) *and lambda* (b) *light chain. (×850);* (c) *glomerulus, stained with periodic acid-silver methenamine, counterstained with hematoxylin and eosin, demonstrates the mesangial expansion by increased cells, delicate matrix, and eosinophilic silver-negative material (×560);* (d) *electron micrograph of a thickened segment of glomerular basement membrane (GBM) illustrates the randomly arranged fibrils creating a spicular deformity (arrow). Fibrils in longitudinal views are straight and measure 15–20 nm in diameter; in cross-section they appear as solid dots. (uranyl acetate and lead citrate, ×28,000).*

tive tissue, and on the tissue to be studied by immunoelectron microscopy.

All of the seven biopsy sections were examined by single label on separate grids with all or some of the antibodies (Table 3). Two of the biopsy specimens were examined by double or triple label to determine whether colocalization of labels on the same fibrils occurred.

One-surface Double Label

Sections from patient #1 were sequentially incubated with anti-IgG labeled with 5-nm gold, and then with anti-AP labeled with 10-nm gold. Sections were also immunostained in the reverse order, with anti-AP labeled with 5-nm gold probes, followed by anti-IgG labeled with 10-nm gold. Free protein A aqueous solution at a concentration of 0.05 mg/ml (Sigma Chemical Co, St. Louis, MO) was used according to Amersham's instruction to prevent cross reaction between two different sized probes.

Two-surface Double Label

Sections from patient #1 were incubated with anti-AP and labeled with 20-nm gold on one surface, and then incubated with anti-IgG labeled with 10-nm gold on the other surface of the section.

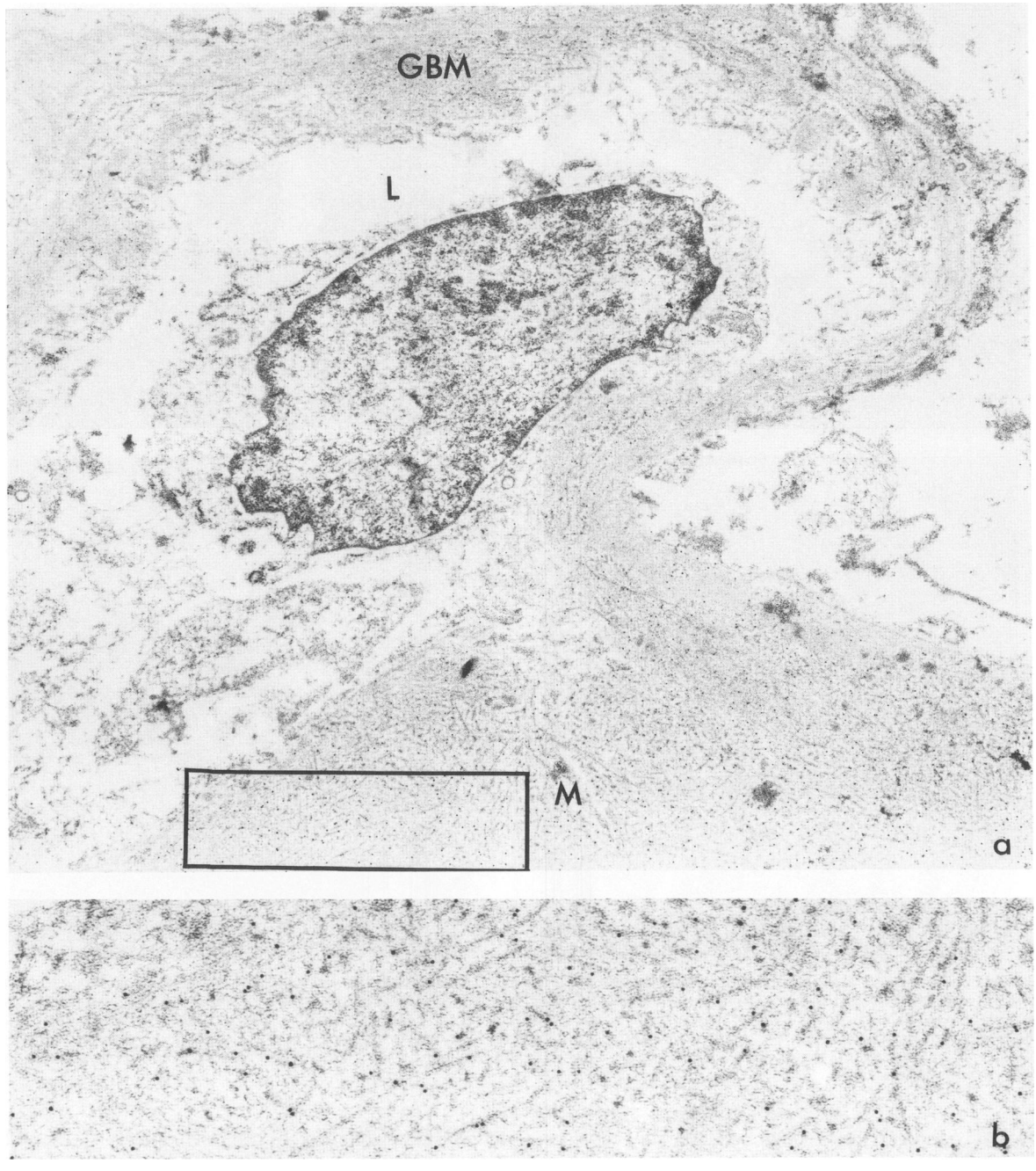

Figure 2. a: *Single-label protein A-gold (10 nm) immunoelectron micrograph of a glomerulus shows numerous gold probes labeling amyloid P component (AP) in the mesangium (M) and along the glomerular basement membrane (GBM).* **b:** *Area within the rectangle, enlarged, demonstrates the localization of AP along the fibrils (uranyl acetate and lead citrate;* **a,** *×16,800;* **b,** *×52,500); L: capillary lumen.*

Triple Label

Sections from patient #6 were incubated on drops of solutions in the following sequence: 1% bovine serum albumin at 25°C for 2 hours; anti-type IV collagen at 4°C overnight; sequentially washed on 9 drops of buffer; 5-nm protein A gold at 25°C for 2 hours. The same sequence was repeated on the same surface of the section for the second label (anti-IgG, 10-nm protein A gold) and for the third label (anti-AP, 15-nm protein A gold). Free protein A solution was used between different labels to prevent cross reaction.

The immunolabeled sections were stained with uranyl acetate and lead citrate and then examined at 60 KV with a Zeiss 10 A electron microscope (Carl Zeiss, Inc., Thornwood, NY).

Results

The clinical features and light and immunofluorescence observations are summarized in Tables 1 and 2. The ages of the patients ranged from 38 to 67 years with a mean age of 50 years. Hypertension, proteinuria (range, 0.5–5.5 g/day), hematuria, and renal functional impairment were common findings. None of the patients had clinical evidence of systemic lupus, paraproteinemia, or cryoglobulinemia.

The light microscopic features were heterogeneous and included mesangiocapillary GN, mesangial GN, crescentic GN, and membranous GN (Table 2). All except one biopsy specimen had glomerulosclerosis involving 10–48% of glomeruli. All were negative for amyloid in Congo red and crystal violet stains.

Immunofluorescence microscopy revealed homogeneous ribbonlike staining along the capillary loops and mesangium for IgG, both light chains (Figure 1a, b) and C3 in all, and trace or negative staining for IgA and IgM. In four biopsies examined, mild-to-moderate staining occurred for C1q in a similar pattern. There was no staining of extraglomerular sites.

Ultrastructurally, all of the cases exhibited the accumulation of similar straight, nonbranching fibrils of indeterminate length in the mesangium and irregularly along the GBM, sometimes creating spicular deformities (Figure 1d). Unlike amyloid, there was no twisting of the fibrils. The fibrils in Epon-embedded sections that were fixed in glutaraldehyde and osmicated (Figure 1d) uniformly appeared larger (17–20 mm) than fibrils in the tissue embedded in LR White that had been previously frozen (Figure 2–6) then fixed in paraformaldehyde but not osmicated (12–15 nm). In cross section, the fibrils were solid dots (Figure 1d). Some electron-dense granular material surrounded clusters of fibrils or was found in membranes elsewhere.

Immunoelectron Microscopic Study

Single Label

The results listed in Table 3 demonstrate that the fibrils of FGP were immunolabeled for AP, IgG, both light chains, and C3. The fibrils were immunolabeled for AP (Figure 2) and both light chains in all of seven cases, and showed positive labeling for IgG and C3 in all of five tested (Figure 3). In contrast, the fibrils were not labeled with antibodies to collagen type IV, HSPG, fibronectin, or fibrillin in any of those examined (Figure 4).

Double Label

In the one-surface sequential double-label study, the fibrils in glomeruli of patient #1 were labeled by anti-AP marked by 5-nm gold, followed by anti-IgG marked by 10-nm gold, or in the reverse order, anti-IgG marked by 5-nm gold, followed by anti-AP marked by 10-nm gold (Figure 5a). In the two-surface double-label study of patient #1, the fibrils were labeled by anti-AP bound to 20-nm gold on one surface of the section and anti-IgG bound to 10-nm gold on the other surface (Figure 5c).

Triple Label

As shown in Figure 5 (b, d, e, f), the fibrils of patient #6 were labeled by gold probes of two different sizes, the larger 15-nm one immunolabeled AP and the smaller 10-nm one immunolabeled IgG. The smallest gold probe, 5 nm, for labeling collagen type IV, was absent on the fibrils, consistent with the results using single labels.

Immunolocalization of AP in Tissue Controls

AP was immunolocalized sparsely but regularly along the lamina rara interna of normal GBM (Figure 6a), absent on the microfibrils in the mesangial nodules of DM (Figure 6b), scattered diffusely in the GBM without propensity for the electron-dense deposits of MGN (Figure 6c), and lined up regularly along the fibrils in AA amyloidosis (Figure 6d).

Discussion

FGP, characterized by the Congo red-negative amyloid-like fibrils in glomeruli, is a clinicopathologic entity of un-

Table 3. *Composite of Immunostaining of Fibrils in Fibrillary Glomerulopathy by Single-label Immunoelectron Microscopy*

Pt	NRS	AP	IgG	K	λ	C3	COLL	HSPG	FBNT	FBLN
1	−	+	+	+	+	+				
2	−	+	+	+	+	+	−	−	−	−
3	−	+	+	+	+	+	−	−	−	−
4 (E)	−	+/−		+	+					
5	−	+	+	+	+	+	−	−	−	−
6	−	+	+	+	+	+	−	−	−	
7	−	+		+	+			−	−	−

(E): immunostaining performed on osmicated Epon-embedded tissue only. Pt: patient; NRS: nonimmune rabbit serum; AP: anti-amyloid P component; IgG: anti-IgG; K, anti-kappa; λ, anti-lambda; C3, anti-C3; COLL, anti-collagen type IV; HSPG, anti-heparan sulfate proteoglycans; FBNT, anti-fibronectin; FBLN, anti-fibrillin.

certain etiology and pathogenesis with a poor prognosis.[14] In previous studies, questions regarding the nature of the fibrils considered whether fibrils represent deposits of proteins from circulation, modified by polymerization to form fibrils, or whether they represent proliferation of endogenous membrane fibrils in response to injury.[5,6]

Immunofluorescence studies in cases of FGP frequently have demonstrated staining of the GBM and the mesangium for polyclonal Igs and complement[3,5,7,8,10,12–14,19] as we too have observed in the present study of seven cases, suggesting that the fibrils are immune deposits. To determine whether the fibrils themselves or deposits between the fibrils are labeled by antibodies, immunoelectron microscopy was used to precisely localize the immune reactants. The ultrastructural localization of IgG, kappa and lambda light chains,

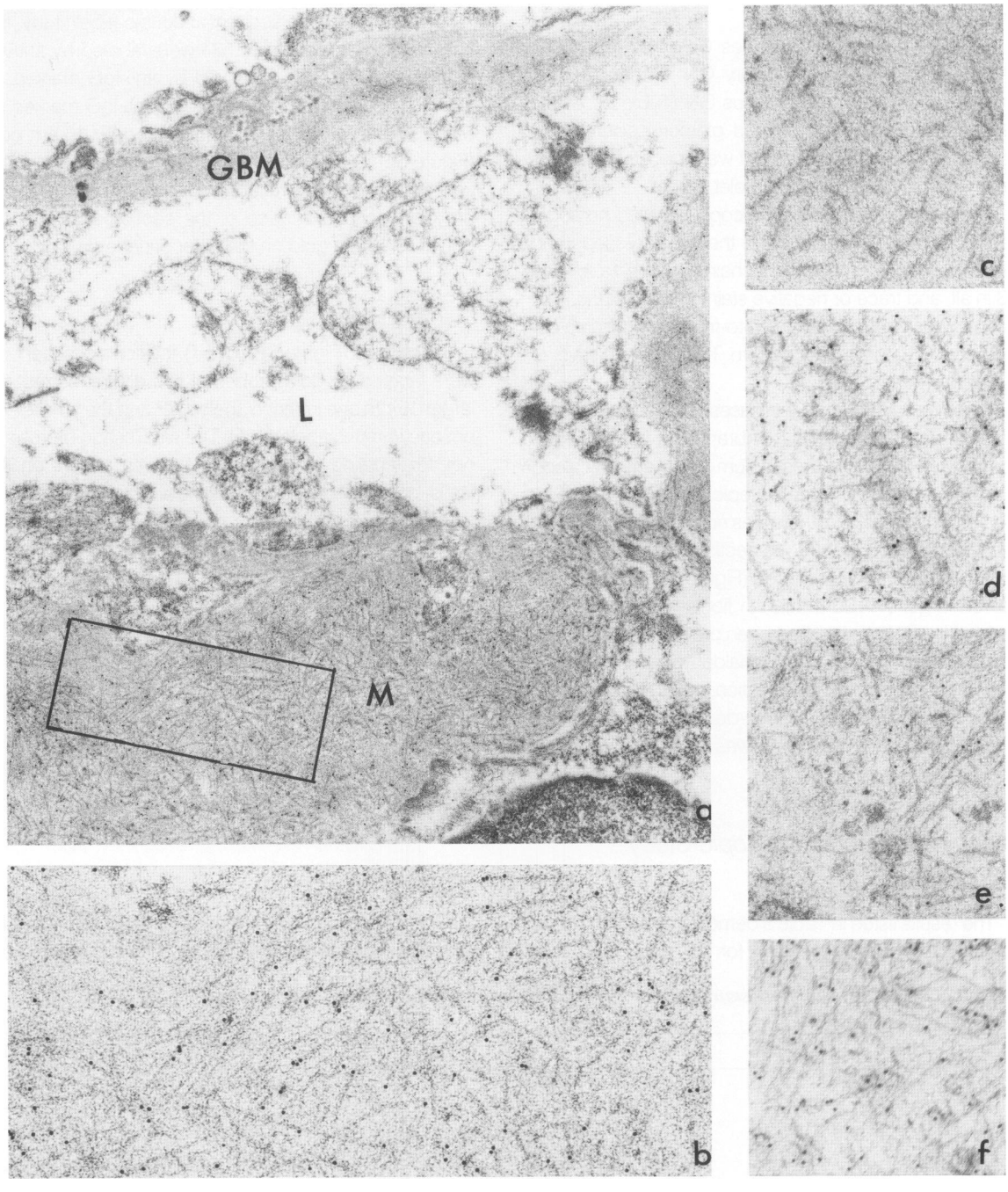

Figure 3. **a**: *Single-label protein A-gold (10 nm) depicts many gold particles labeling anti IgG bound to fibrils in the mesangium (M) and glomerular basement membrane (GBM).* **b**: *Area within the rectangle, enlarged, shows gold probes along fibrils.* **c**: *Nonimmune rabbit serum control shows unlabeled fibrils.* **d–f**: *demonstrates the detection of kappa light chain* (**d**), *lambda light chain* (**e**), *and the third component of complement* (**f**) *along fibrils (uranyl acetate and lead citrate,* **a**, ×*17,600;* **b–f**, ×*52,500).*

and C3 specifically along the fibrils that we observed, together with the immunofluorescence observations, allows the speculation that the fibrils are immune deposits that have undergone fibrillogenesis, but lack the β-pleated sheet configuration necessary for Congo-red binding that defines amyloid.

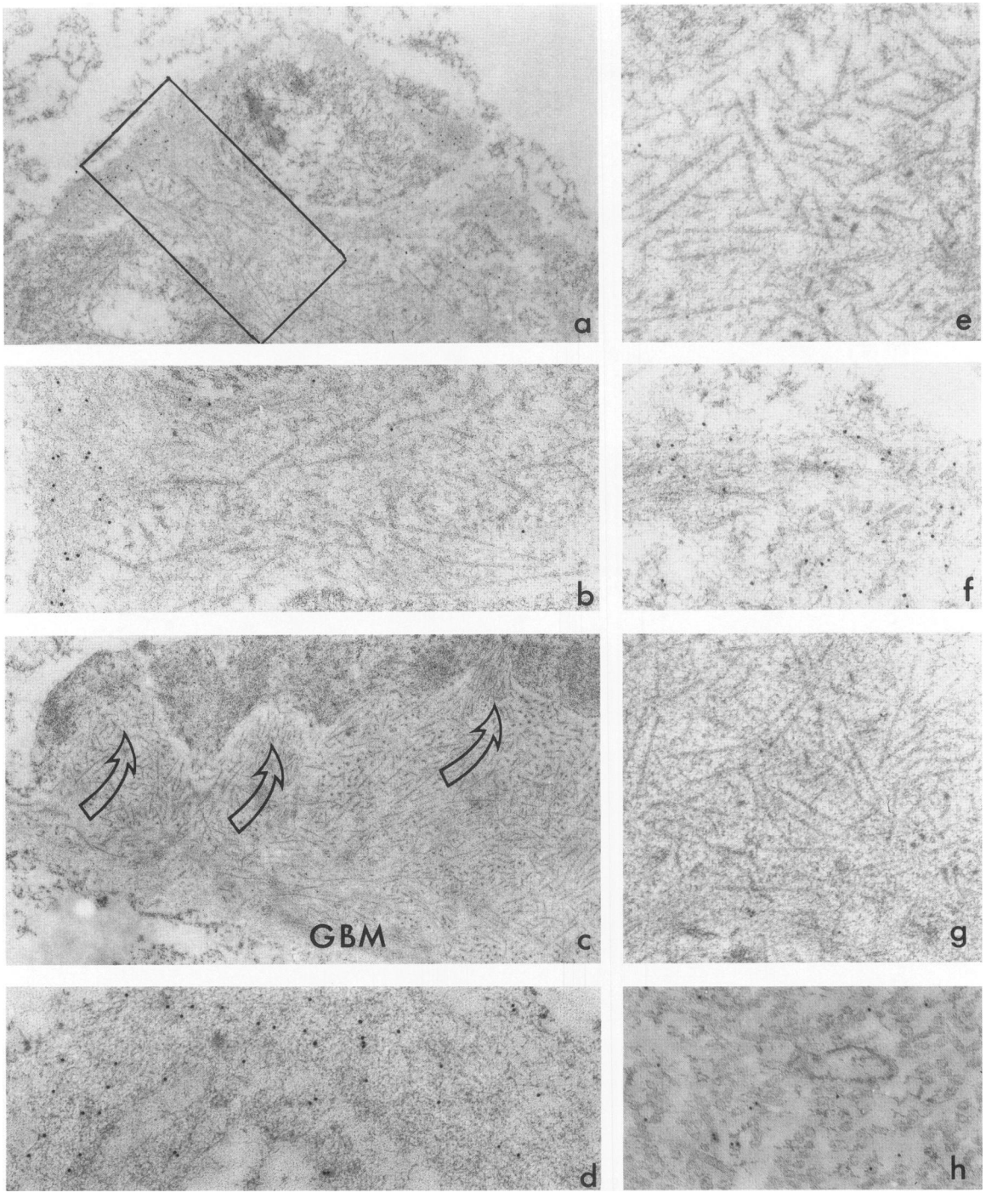

Figure 4. *Single-label protein A-gold (10 nm) micrograph of fibrils examined for the GBM antigens in* (a) *through* (d), *and microfibril-associated antigens in* (e) *through* (h); (a) *a collection of fibrils demonstrates no labeling for collagen type IV;* (b) *area within the rectangle, at higher magnification, shows the localization of gold probes in the GBM matrix at the left edge of the fibrils, but no labeling of the fibrils themselves;* (c) *a segment of the GBM with spicular deformity (arrows) shows no labeling of fibrils for HSPG; dense dots are fibrils in cross-section;* (d) *positive immunolabel for HSPG is shown in the GBM elsewhere in the section;* (e) *fibrils are negative for fibronectin, while the connective tissue at the Bowman's capsule shows immunolabel for fibronectin in* (f); (g) *fibrils show no labeling for fibrillin while positive labeling is in the interstitium* (h) *(uranyl acetate and lead citrate,* a, *×18,800;* c, *×13,300;* b, d–g: *×52,500).*

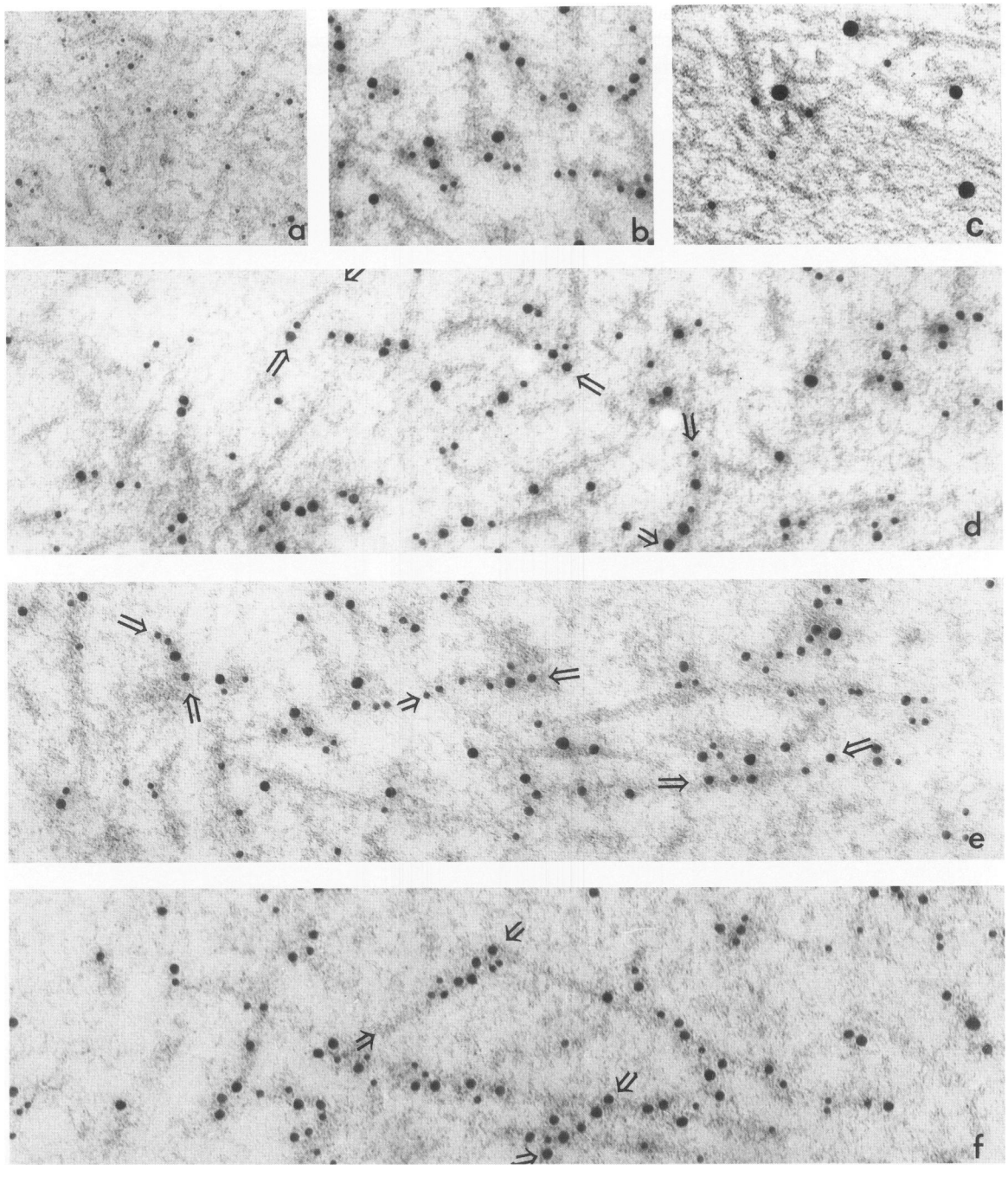

Figure 5. *Protein A-gold immunoelectron micrographs in studies of glomeruli from patient #1 using double labels* **(a,c)** *and from patient #6 using triple labels* **(b,d–f)**; **(a)** *colocalization of AP (10 nm) and IgG (5 nm) on the fibrils in the one-surface double-label study;* **(c)** *colocalization of AP (20 nm) and IgG (10 nm) in the two-surface double-label study;* **(b, d–f)**: *colocalization of AP (15 nm) and IgG (10 nm) on the same fibrils (arrows) in the triple-label study but absence of the 5-nm gold probes for detection of collagen type IV (uranyl acetate and lead citrate, ×110,525).*

Although most immune deposits are ultrastructurally homogeneous and granular and lack an organized substructure, deposits such as those seen in mixed IgG-IgM cryoglobulinemic GN or paraproteinemia may exhibit crystalline or fibrillar configurations ultrastructurally.[26,27] As shown in cryoglobulinemia, similar crystalline configurations in both the serum cryoprecipitates and glomeruli are evidence that the cryoproteins deposit in glomeruli from the circulation.[26,27] Similarly, a monoclonal Ig detected in the serum as well as in glomeruli, for example, in

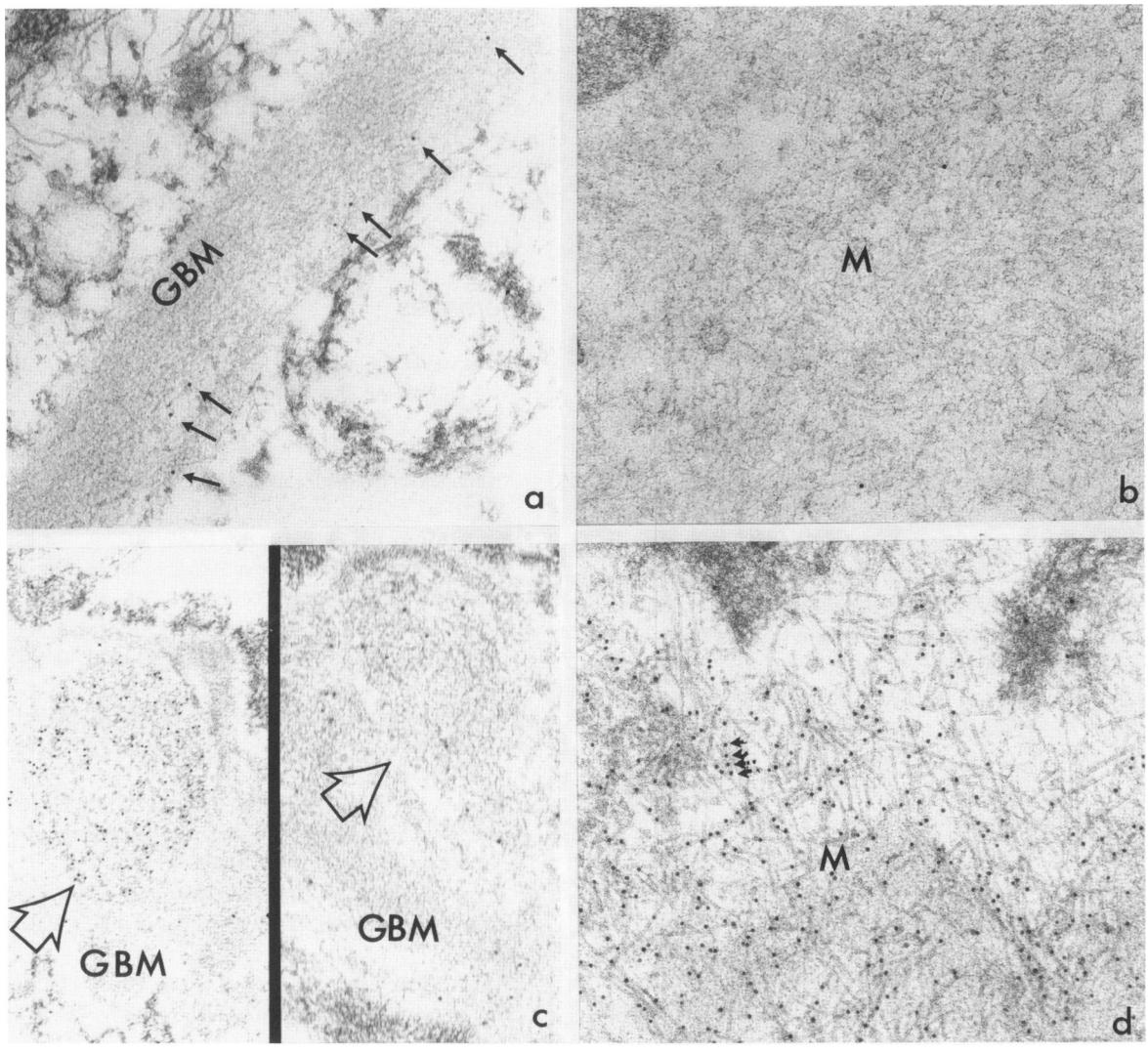

Figure 6. *Protein A-gold immunoelectron micrographs of AP distribution in glomeruli of controls, labeled by 10-nm gold probes;* **(a)** *normal glomerular basement membrane (GBM) demonstrates sparse but regular labeling of AP (arrows) along the lamina rara interna;* **(b)** *diabetic glomerulopathy shows no immunostaining for AP in the delicate fibrils of the mesangium (M);* **(c)** *membranous glomerulopathy with subepithelial immune deposits (large arrows) shows the immunolabel for AP in the right panel and for IgG in the left panel. Gold probes detecting AP are diffusely distributed in the GBM; in contrast, the gold probes detecting IgG are selectively localized in the electron dense deposit;* **(d)** *AA amyloidosis exhibits dense and regularly arranged gold probes along fibrils immunolabeled for AP (arrows) (uranyl acetate and lead citrate, ×52,500).*

light chain amyloid, is evidence that the fibril protein is deposited in glomeruli from the serum. In the case of FGP, with a few exceptions[4–9,12–14,19] serum cryoglobulins and monoclonal proteins have not been reported to assume that the fibrils are modified immune complexes or paraproteins from the circulation. This was true also in three of our patients (Table 3).

An alternative possibility, that the fibrils are reactive basement membrane proteins, prompted our use of antibodies to GBM-associated antigens[28] and microfibril-associated proteins[23,24] to see if the fibrils are antigenically related. Other investigators have described fibrils (cords) in basement membranes of normal glomeruli.[25,28] Therefore, the fibrils in FGP may represent an abnormal proliferative response of normal GBM structures. Immunostaining of normal glomeruli has demonstrated type IV collagen, laminin, HSPG, entactin, and fibronectin in the basal lamina, presumably integrated to form a meshwork of fibrils in the membrane.[28] However, in the present study none of the antibodies to type IV collagen, HSPG, fibronectin, or fibrillin labeled the fibrils (Table 3). Although we did not use antibodies to all of the known GBM antigens, our panel included several that are known to bind to normal membrane fibrils.[28] Although our observations do not support the view that the fibrils in FGP are reactive membrane proteins, we cannot exclude the

possibility that the fibrils are neonantigens that are immunogenic. In this case, an autoimmune reaction with binding of immune reactants to the fibrils by mechanisms similar to what occurs, for example, in anti-GBM disease, would be consistent with our observations.

An unexpected and interesting finding was the observed binding of AP immunolabels to the fibrils of FGP (Figures 2, 5) in a manner similar to that seen in amyloid.[21] AP is a glycoprotein normally found in the serum,[29] in GBM,[30,31] in the ciliary zonule fibers,[32] and in all types of amyloid thus far examined.[34,35] Its biologic function is unknown. Whether AP binds to amyloid fibrils already formed[36] or plays a role in fibrillogenesis is presently unknown. Similar questions may be posed regarding the role of AP in the fibrils in FGP. Since connective tissue AP is found immunohistochemically in fibrils located in the lamina rara interna of the GBM,[30,31] its presence in the fibrils of FGP might be expected if they are in fact intrinsic GBM structures. However, the observed large difference in the density of AP immunolabels found in the fibrils in the GBM and the mesangium (Figure 2) as compared with that of normal GBM (Figure 6a) leads us to speculate that the fibril-bound AP might be serum-derived. Since human AP molecules rapidly autoaggregate and stack vertically into 9-nm wide microtubules *in vitro*,[37,38] AP may play a role in the fibrillogenesis *in vivo*. HSPG as well as other basement membrane components have been shown histochemically and immunohistochemically to be associated ultrastructurally with amyloid fibrils,[39,40] but they were not detected along the fibrils in FGP that we have examined thus far (Table 3), demonstrating another difference between the fibrils of amyloid and FGP.

Fibrils have been described in the subendothelial spaces of the GBM and in the mesangium of normal glomeruli,[41,42] as well as in diabetic nephropathy[42,43] and rejected renal allografts.[44] Microfibrils, 12-nm thick, in subendothelial sites of the GBM are described in other glomerular diseases including focal segmental glomerulosclerosis, preeclamptic toxemia, hemolytic uremic syndrome, malignant hypertension, and mesangiocapillary GN, leading to the conclusion that glomerular fibrils are morphologically similar to connective tissue microfibrils, suggesting that such fibrils occur in locations subject to stress.[25]

Some investigators have considered FGP synonymous with "immunotactoid glomerulopathy," a term introduced to describe glomerular diseases with aggregates of Ig deposits having a crystalline or tactoidal structure. As defined, the term properly includes immune complexes and monoclonal proteins as seen in mixed cryoglobulinemia and dysproteinemias.[16–19] The sizes, ranging from 10 to 49 nm, and the morphologic structures of tactoids described are varied and some are associated with dysproteinemias.[16–19] In contrast, the fibrils included in the present study and in many of those described by others, called FGP, are uniform in size and appearance, and thus far few have had proven dysproteinemia. Until the nature of the fibrils in FGP is clarified and criteria for the diagnosis of FGP are established, the term FGP should be applied to our cases and others that are similar.

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