CHAPTER 7

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Membranous Glomerulonephritis

BACKGROUND

Definition

Membranous glomerulonephritis (MGN) is a pathologic diagnosis defined by the presence of subepithelial immune deposits that induce a spectrum of changes in the glomerular basement membrane (GBM). Diagnostic features of MGN may be seen by light microscopy and most notably include GBM extensions or "spikes" that project into the urinary space and are seen best with the periodic acid-Schiff (PAS) and Jones methenamine silver (JMS) stains. Electron microscopy (EM) and immunofluorescence are often required to diagnose MGN, especially in early disease when capillary walls appear normal by light microscopy and in late disease when GBM thickening is relatively nonspecific by light microscopy. The subtlety of the light microscopic changes in MGN and the lack of diagnostic specificity of GBM thickening underlie the uncertainty that surrounded the diagnosis of MGN during its evolution as a pathologic entity. The term MGN was initially used in 1946 to describe the findings in a subset of patients with "Ellis type II" nephrotic glomerulonephritis, although this category also included patients with lipoid nephrosis and lobular glomerulonephritis (1). MGN became a distinct entity in 1957 when David Jones (2), a renal pathologist at Syracuse University, developed the periodic acid-methenamine silver stain to demonstrate textural changes of the GBM and identified spikes as a defining feature of MGN. As a result of his contributions, the *Jones* methenamine silver stain bears his name (2). Within the subsequent 2 years, the introduction of ultrastructural and immunopathologic techniques allowed for further refinement and staging of the diagnosis of MGN (3,4), which in turn have facilitated the study of the natural history, outcome, and therapeutic responsiveness of MGN as a distinct entity (1).

Terminology and Synonyms

Synonyms for MGN include *membranous nephropathy, membranous glomerulopathy,* and, less commonly, *epimembranous nephropathy*. The term *membranous glomerulonephritis* (MGN) is most frequently used but is not without problems in that this entity lacks the inflammatory features typical of a glomerulonephritis. Nonetheless, this term continues to be preferred and can be justified based on the progressive nature of this entity, its apparent autoimmune pathogenesis, and the critical roles of antigen-antibody immune complex formation, serum complement fixation, and generation of the C5b-9 membrane attack complex (MAC).

Primary and Secondary MGN

MGN can be divided into primary and secondary forms of disease (Table 7.1). The term primary *idiopathic* MGN is frequently employed, but this term is likely nearing extinction because the majority of such cases are now understood to be mediated by an autoantibody to phospholipase A2 receptor (PLA_2R) expressed on podocytes. Thus, the term primary MGN may soon be replaced by the more pathogenetically

TABLE 7.1 Best established secondary etiologies of MGN

Therapeutic agents
Gold salts
Penicillamine
Bucillamine
Captopril
Mercury
NSAIDs
Tiopronin
Trimethadione
Malignancy
Mainly carcinomas, most commonly of lung, gastrointestinal, prostatic, or breast origin
Infection
HBV
HCV
Syphilis
Filariasis
Hydatid disease (echinococcosis)
Autoimmune rheumatologic conditions
SLE[a]
Rheumatoid arthritis[a]
Sjögren syndrome[a]
Mixed connective tissue disease[a]
Autoimmune thyroid disease (Graves disease, Hashimoto thyroiditis)
Additional conditions associated with MGN
Sarcoidosis
Allogeneic hematopoietic SCT
IgG4RD
Guillain-Barré syndrome
Chronic inflammatory demyelinating polyneuropathy

[a]Covered in Chapter 14.

specific term primary PLA_2R-associated MGN (5). While the majority of cases represent the primary disease, MGN may occur secondary to many other conditions. With some exceptions, the pathology of primary and secondary MGN is often similar or even identical; thus, the diagnosis of primary MGN requires careful exclusion of the known secondary etiologies. In a review of nine series published between 1975 and 1989, Glassock (6) found that 23% of cases of MGN were secondary with the prevalence higher (35%) in children younger than 16 years and adults older than 60 years as compared to adults from 16 to 60 years of age (20%). The most common secondary etiology of MGN is systemic lupus erythematosus (SLE; i.e., membranous lupus nephritis [LN]). Most cases of secondary MGN relate to autoimmune/collagen vascular disease, infection, neoplasia, or therapeutic agents (i.e., drug-induced MGN) (6). New associations continue to appear, and critical evaluation is necessary before accepting an etiologic relationship. The well-established secondary etiologies of MGN covered in this chapter include therapeutic agents (gold, penicillamine, mercury, captopril, and nonsteroidal anti-inflammatory drugs [NSAIDs]), malignancy, infections (hepatitis B virus [HBV], hepatitis C virus [HCV], and syphilis), and miscellaneous conditions (sarcoidosis, IgG4-related disease [IgG4RD], allogeneic transplantation, and autoimmune thyroiditis). Chapter 14 covers MGN associated with SLE and other autoimmune/collagen vascular disease. Primary MGN is the focus of this chapter, with an understanding that it is critical to exclude secondary etiologies due to their different prognostic and therapeutic implications.

PRIMARY MEMBRANOUS GLOMERULONEPHRITIS

Clinical Features

Primary MGN is seen throughout adult life, with a peak incidence in the fourth and fifth decades (7–12). MGN is less common in children and, in this age group, secondary forms of disease are more commonly seen (6,13–15). Males are more frequently afflicted in both adults (7,8,10–12,16) and children (15), and the proportion of male patients ranges from 57% to 72%, with a mean of 64%, in six large MGN databases (2,7,9,10,16). Within these databases, the mean age of presentation ranges from 40 to 62 years (7–10).

MGN is the most common cause of the nephrotic syndrome in Caucasian adults (17,18). However, focal segmental glomerulosclerosis (FSGS) is a more common cause of the nephrotic syndrome in African Americans (17,18) and, in some studies, has surpassed MGN in the overall population (17,19,20). Furthermore, when patients with primary glomerular disease who do not meet the full criteria for nephrotic syndrome are considered, MGN is less prevalent than FSGS and IgA nephropathy (IgAN) (17,19–21). The nephrotic syndrome is present at the time of presentation in approximately 75% of patients with MGN (7,9,10), although this percentage depends on the degree of screening for proteinuria in a particular patient population. In six large studies, a mean 24-hour urine protein of 6.5 g/d and a mean serum albumin of 2.5 g/dL were seen (7–10,16).

While nephrotic syndrome is the most common presentation of MGN, renal insufficiency, hematuria, and hypertension may also be seen. In six large databases from five different countries, the mean creatinine at presentation ranged from 0.9 to 1.3 mg/dL (mean of means: 1.08 mg/dL) and the mean creatinine clearance varied from 76 to 107 mL/min/1.73 m^2 (mean of means: 88 mL/min/1.73 m^2) (7–10,16). Renal insufficiency was seen in approximately 25% of patients with MGN at the time of presentation (7–10). Microscopic hematuria is present in approximately half of the patients with MGN. In contrast, gross hematuria is extremely rare, and its presence should prompt a search for an alternative etiology of gross hematuria in the kidney or elsewhere within the genitourinary tract. Similarly, hypocomplementemia is not a feature of primary MGN and, when present, secondary etiologies of MGN should be carefully excluded, in particular membranous LN (14). At the time of presentation, hypertension is present in at least half of the patients with MGN (7,9,10,16) Similar to most etiologies of the nephrotic syndrome, and unlike minimal change disease, there is a loss of selectivity of proteinuria in patients with MGN (22).

MGN has also been studied in particular age groups and ethnic populations. As previously noted, primary MGN is a

much less common etiology of nephrotic syndrome in children, accounting for only 3% of renal biopsies in a recent large pediatric biopsy series (23). Secondary forms of MGN are more common in the pediatric population (6) and most often relate to SLE (14) or infection, in particular HBV (13). At the opposite extreme, MGN is the most common etiology of nephrotic syndrome among patients above the age of 60, accounting for 32% of cases (24). This also holds true when only considering patients above the age of 80 (25). There is also significant experience with MGN in pregnant women who often experience a doubling of 24-hour urine protein, new onset of hypertension and, in some cases, renal insufficiency (26). The hypertension and worsening proteinuria often but not always reverse following parturition (26).

Pathologic Findings

Gross Pathology

Gross evaluation of the kidneys does not play a significant role in establishing the diagnosis of MGN. In the rare case where gross evaluation is possible (i.e., autopsy), the early appearance of kidneys with MGN is largely unremarkable. Similar to other patterns of glomerular disease, cases that run their course to end-stage renal failure are characterized by a contracted parenchyma with a granular surface, and these changes are more prominent in individuals with hypertension. Ehrenreich and Churg (27) described 10 autopsied cases of histologically confirmed MGN. In patients dying at the height of the nephrotic syndrome without renal insufficiency, the kidneys were large and pale with combined weights from the upper limit of normal (300 g) to 450 g or more.

Light Microscopy

Glomeruli

The GBM is the principal site of pathology in MGN. Within a biopsy, the GBM changes are homogeneous, typically showing little variation among glomeruli. However, the pathology is dynamic, and as it evolves, the appearance of the GBM varies over time in each individual and between different patients. The resulting pathologic spectrum of glomerular capillary wall changes can be seen by light microscopy but is best understood and staged at the ultrastructural level (27). The light microscopic findings in MGN may be subtle, especially in early cases, and even with optimally stained thin sections, diagnostic changes may not be obvious by light microscopy alone. In these cases, immunofluorescence and EM readily establish the diagnosis.

In MGN, the glomeruli range in size from normal to enlarged and often appear normocellular. In the earliest stage of MGN, the GBMs appear normal in thickness and contour, resulting in no detectable abnormalities at the light microscopic level. More commonly, early cases will exhibit good preservation of the glomerular architecture, but the glomeruli appear stiff and inflated (Fig. 7.1), giving them an exaggerated appearance of normality. Even at this early stage, the podocytes typically appear swollen with enlarged cell bodies. As the disease progresses, the glomerular capillary walls appear thicker and more rigid than normal in PAS-stained histologic sections (Figs. 7.2 and 7.3), and the GBM becomes intensely eosinophilic and refractile in hematoxylin and eosin–stained sections (Fig. 7.4).

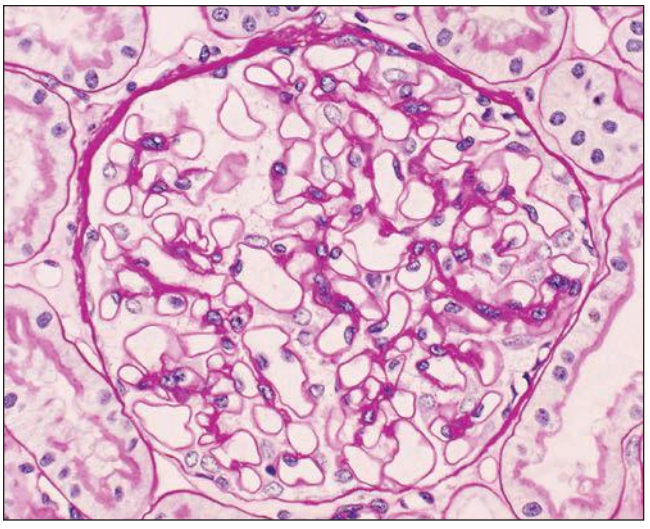


FIGURE 7.1 Histopathology of early MGN (stage I). The glomerulus exhibits no apparent abnormalities by light microscopy. The glomerular basement membrane appears thin and delicate, without evidence of thickening or spike formation. (PAS, ×200.)

Eventually, thickening of the GBM, increased mesangial matrix, and accumulation of immune deposits give the glomerulus a solid appearance, and in advanced cases, segmental scarring and global glomerulosclerosis develop. Even when renal insufficiency develops, unscarred glomeruli maintain their characteristic appearance.

The spectrum of GBM changes seen in MGN is best demonstrated by the use of special stains. Although hematoxylin and eosin stain can show overall capillary wall thickening, it is

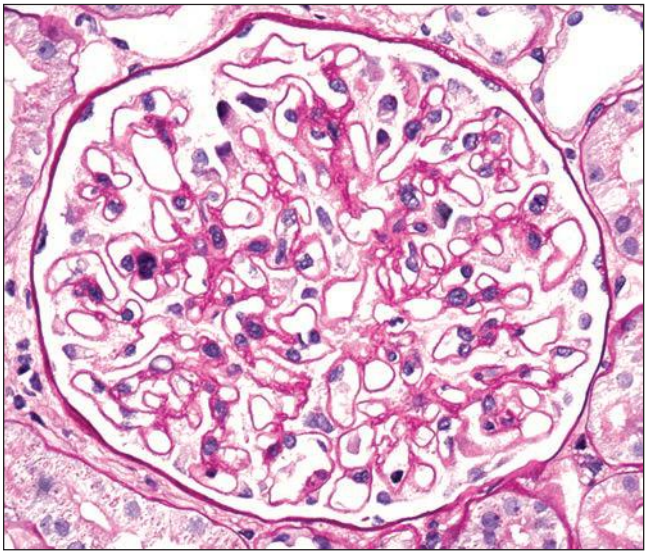


FIGURE 7.2 Histopathology of MGN with mild glomerular basement membrane (GBM) thickening (stage II). The GBM exhibits mild diffuse thickening with spike formation. Diffuse swelling of visceral epithelial cells is noted. (PAS, ×400.)

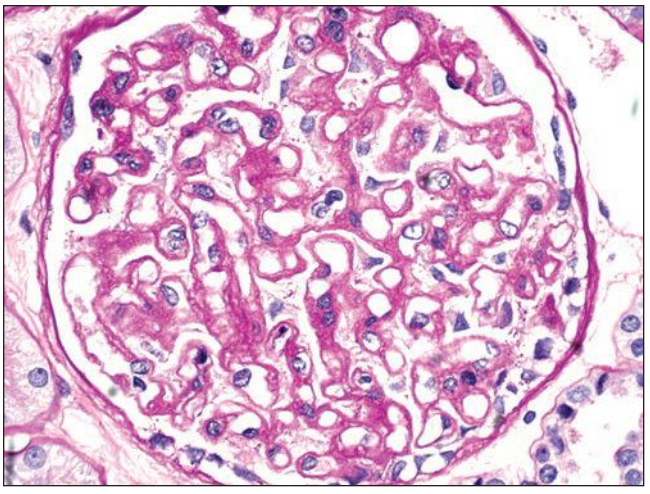


FIGURE 7.3 Histopathology of GBM thickening in MGN. There is marked global thickening of the glomerular basement membrane, which has a vacuolated appearance. (PAS, ×400.)

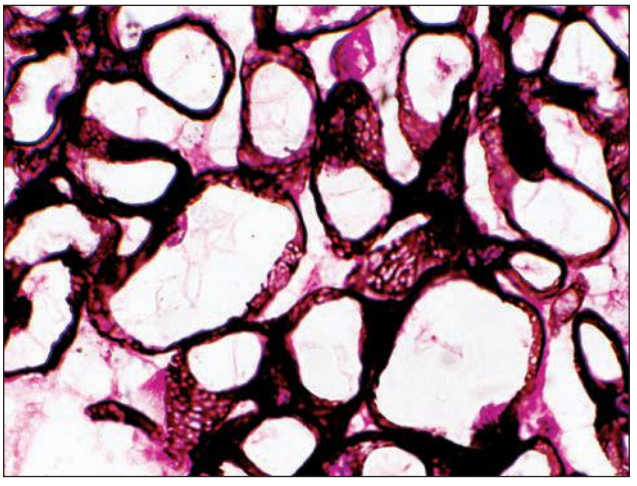


FIGURE 7.5 Histopathology of stage I MGN. In stage I MGN, the JMS stain may demonstrate small holes or depressions in the GBM. (JMS, ×600.)

not an optimal stain for demonstration of GBM pathology because it does not distinguish well between the cell cytoplasm, immune deposits, and extracellular matrix. The GBM changes in MGN are best appreciated using the JMS stain (27) but are also well visualized with the PAS stain. By light microscopy, the earliest change in MGN is mottling of and small depressions in the GBM seen in en face sections stained with JMS (Fig. 7.5). This appearance is subtle and results from alterations in the GBM caused by the subepithelial deposits. More commonly, the JMS stain will reveal further developed changes of MGN represented by small projections (spikes) of silver-positive material (Fig. 7.6) composed of type IV collagen and noncollagenous extracellular matrix proteins, including laminin, heparan sulfate proteoglycan, and vitronectin (28–30). Initially, the spikes may be small and segmental, and a careful search under oil immersion is necessary to demonstrate them. Cases such as this, with only focal spikes, may represent either an earlier or a milder form of the disease (15), but immune deposits in cases with segmental spikes usually are more diffusely distributed than indicated by the light microscopic changes. As the lesion progresses, the spikes become larger, thicker, and diffuse (Fig. 7.7). Eventually, the GBM becomes more prominently expanded by a thick band of argyrophilic material containing abundant nonargyrophilic "holes" and imparting a vacuolated appearance (Fig. 7.8). The "holes" represent a normal-thickness GBM beneath the deposits surrounded by a heaped-up matrix around the deposits. In many cases, combinations of these various abnormalities including spikes, holes, and complex thickening of the GBM are present simultaneously in the same biopsy. The nonargyrophilic material deposited within the GBM and on its epithelial side stains red with the trichrome stain, while the surrounding GBM stains blue or green depending on the method used (Fig 7.9). The deposits

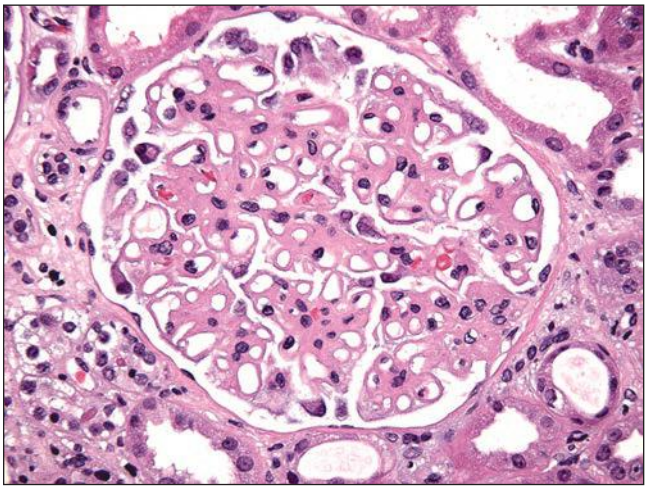


FIGURE 7.4 Histopathology of MGN. With the hematoxylin and eosin stain, the GBM has a thick and rigid appearance in this example of stage III MGN. Mild diffuse mesangial sclerosis is present. (H&E, ×400.)

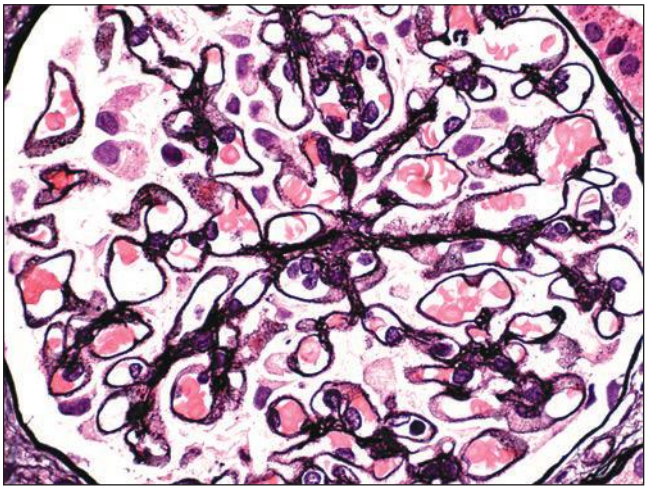


FIGURE 7.6 Histopathology of early stage II MGN. In early stage II MGN, the JMS stain demonstrates short GBM spikes. (JMS, ×400.)

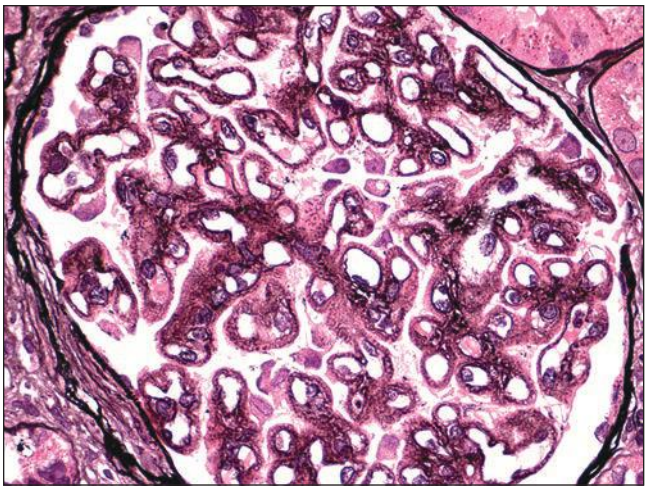


FIGURE 7.7 Histopathology of stage II MGN. In this better developed example of stage II MGN, the JMS stain exhibits more prominent GBM spike formation with intervening silver-negative subepithelial deposits (JMS, ×400.)

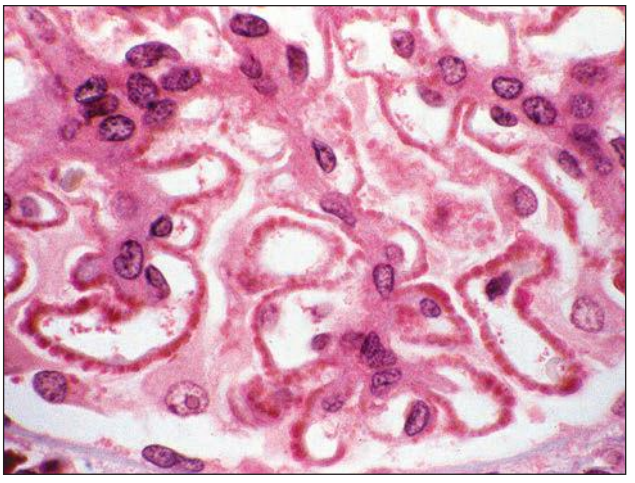


FIGURE 7.9 Light microscopy of subepithelial deposits in MGN. The Masson trichrome stain demonstrates fuchsinophilic deposits along the subepithelial aspect of the glomerular basement membrane. (Masson trichrome stain, ×600.)

also stain blue in toluidine blue–stained 1-μm sections of plastic-embedded tissue. However, both the trichrome and toluidine blue demonstration of deposits are inconsistent, and these stains may be negative even in obvious cases of MGN. Thus, the more consistent histologic changes in MGN are thickening and remodeling of the GBM itself, seen best with the JMS and, to a lesser extent, PAS stains.

Endocapillary proliferation, GBM duplication, mesangial hypercellularity, fibrinoid necrosis, and crescent formation are uncommon features of primary MGN. When present, these findings suggest either a secondary form of MGN or the concurrence of MGN and an additional glomerular disease process. Thus, the presence of such atypical findings requires careful evaluation for a systemic disease and appropriate serologies before concluding that the patient has primary MGN. Each of these findings is considered separately in this section or the sections that follow.

The glomeruli in primary MGN typically are enlarged (31) and exhibit an increase in total glomerular area and mesangial volume, including the number of mesangial cells (28,31). In routine histologic sections, mesangial hypercellularity is a subtle finding, and well-defined mesangial hypercellularity is uncommon (Fig. 7.10). When present, the finding of mesangial hypercellularity may suggest a secondary form of MGN related to SLE or HBV infection (32,33) or the possibility

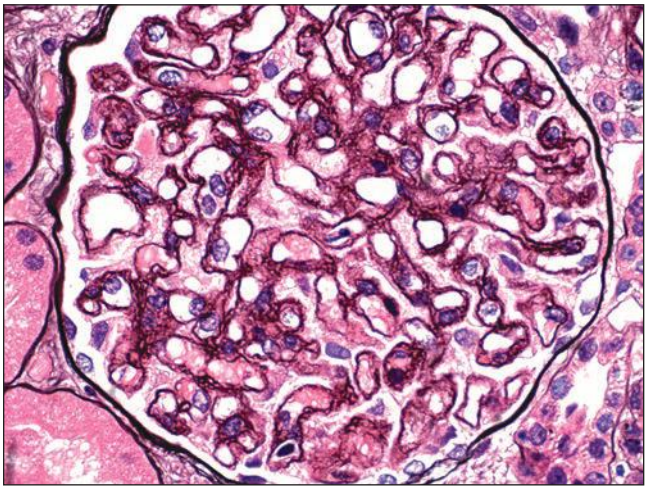


FIGURE 7.8 Histopathology of stage III MGN. In stage III MGN, the JMS stain reveals a globally vacuolated glomerular basement membrane (GBM) due to the presence of GBM spikes and overlying neomembrane formation. (JMS, ×400.)

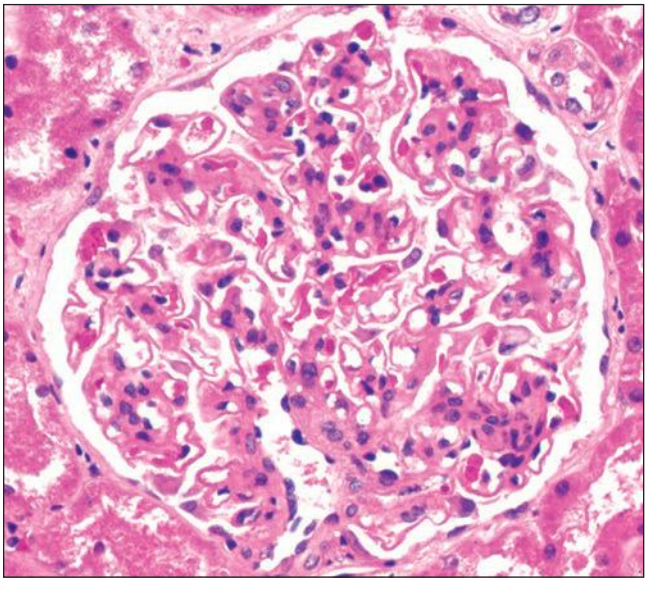


FIGURE 7.10 Mesangial hypercellularity in MGN. In this example of MGN, glomerular basement membrane thickening is accompanied by diffuse mesangial hypercellularity with up to 12 cells per mesangial area. (H&E, ×400.)

of coexistent IgAN (34,35). A secondary form of MGN (or coexistent IgAN) is particularly likely when the mesangial hypercellularity is accompanied by mesangial immune deposits (32–36).

While mesangial hypercellularity can be seen in primary MGN, endocapillary proliferation and GBM duplication are generally considered to be incompatible with the diagnosis of primary MGN. GBM duplication, which is typically accompanied by glomerular lobulation and described as a "membranoproliferative" feature, can coexist with findings of MGN. This constellation of mixed membranous and membranoproliferative changes is most commonly encountered in the setting of LN (i.e., class IV and V), in patients with HBV or HCV infection, or as the idiopathic entity of membranoproliferative glomerulonephritis (MPGN) type 3, Burkholder subtype (37). The combination of mixed membranous and endocapillary proliferative changes is less common but similarly should raise the possibility of changes related to SLE, HBV, or HCV. In one study, the finding of an increased number of inflammatory cells within the glomeruli, in the absence of endocapillary proliferation or membranoproliferative features, favored a secondary form of MGN related to malignancy over primary MGN (38).

Lesions of FSGS are present in approximately 20% of renal biopsies with primary MGN (range 13% to 42%) (39–42) (Fig. 7.11). As compared to biopsies with MGN in the absence of FSGS, the finding of FSGS lesions with MGN (FSGS-MGN) is associated with a greater degree of proteinuria (39,42) and renal insufficiency (39–42) and a higher incidence of hematuria (39–42) and hypertension (39,40,42). Histologically, the lesions of FSGS form discrete segmental scars associated with hyaline and/or lipid insudation, adhesions to Bowman capsule, and swelling of overlying epithelial cells, resembling changes in FSGS not otherwise specified (NOS) or occasionally the glomerular tip lesion variant (43). FSGS-MGN is associated with a greater degree of tubulointerstitial scarring (39–42) and a higher stage of MGN (40,41). Most importantly, in the setting of MGN, the finding of FSGS is associated with a worse prognosis and can be viewed as a marker of chronicity and a negative prognostic indicator (39,41,42). Of note, rare cases exist in which the clinical and pathologic findings in FSGS-MGN suggest two separate and distinct glomerular disease processes, MGN and primary FSGS (44).

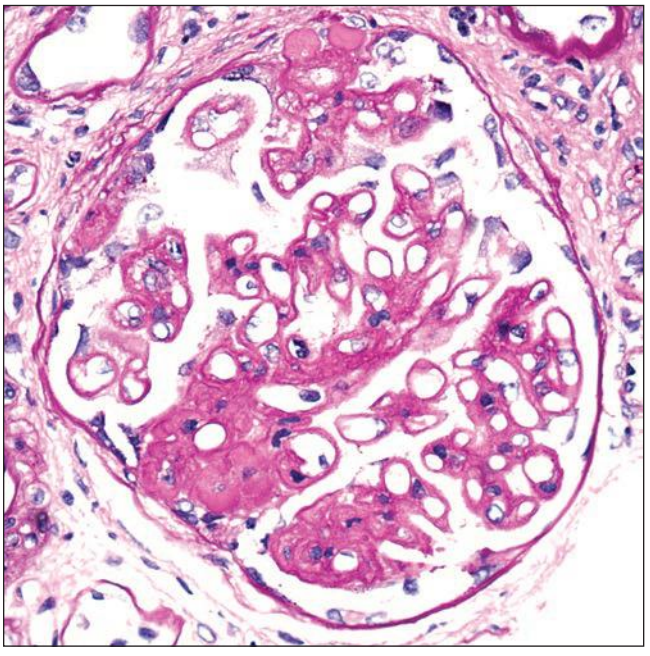


FIGURE 7.11 Focal segmental glomerulosclerosis in MGN. Findings of MGN are accompanied by two discrete lesions of segmental sclerosis with capsular adhesion. (PAS, ×400.)

Tubules and Interstitium

A spectrum of tubular and interstitial changes may be encountered in patients with MGN. Similar to other etiologies of nephrotic syndrome, proximal tubules often contain protein and lipid resorption droplets. Tubules may exhibit acute tubular injury characterized by luminal ectasia, cytoplasmic simplification and vacuolization, irregular luminal contours, loss of brush border, prominent nucleoli, and mitotic or apoptotic figures. These acute degenerative changes may result from severe, unremitting proteinuria or may relate to alternative factors such as drug-induced injury, ischemia, or prerenal hemodynamic changes resulting from intravascular volume depletion. As the glomerular scarring progresses, tubular atrophy and interstitial fibrosis ensue, and the extent of these findings correlates with decreased renal survival (8,28,45,46) (Fig. 7.12). This tubulointerstitial scarring likely results in large part from glomerulosclerosis, reduced efferent arteriolar blood flow, and resultant post–glomerular ischemia. In some instances, the degree of tubular atrophy and interstitial fibrosis significantly exceeds the extent of glomerulosclerosis (45). The pathogenesis of the tubulointerstitial scarring in this setting is incompletely understood. Although cell-mediated immunity may play a role, the absence of extraglomerular immune deposits argues against an immune complex mechanism. Magil (45) examined the extent of tubulointerstitial disease in MGN patients with no or mild vascular disease and fewer than 10% obsolescent glomeruli and found that the degree of tubulointerstitial scarring correlated

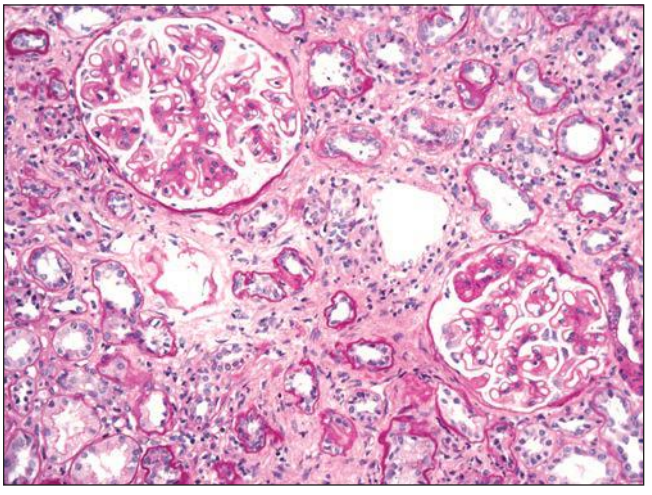


FIGURE 7.12 Interstitial fibrosis and tubular atrophy in MGN. In this example of MGN, the majority of tubules appear atrophic and are accompanied by diffuse interstitial fibrosis. (PAS, ×200.)

with the 24-hour urine protein excretion, serum albumin, and the percent of glomeruli with visceral epithelial cell protein resorption droplets, leading him to conclude that proteinuria per se played a role in the development of tubulointerstitial injury. A discussion of the role of proteinuria in the pathogenesis of tubular atrophy and interstitial fibrosis is included in the section on Etiology and Pathogenesis.

Interstitial inflammation is commonly seen in MGN, is usually mild, and is typically most prominent in areas of tubular atrophy and interstitial fibrosis. The interstitial infiltrates are mainly composed of monocytes and T cells with a predominance of $CD4^+$ T cells, suggesting a pathogenic role for cell-mediated immunity (47). Interstitial foam cells are seen in approximately 16% of biopsies with MGN and originate from macrophages (48) (Fig. 7.13). The finding of interstitial foam cells does not correlate with proteinuria or hyperlipidemia (48). In rare instances, the degree of interstitial inflammation is out of proportion to the degree of tubulointerstitial scarring and is accompanied by tubulitis and interstitial eosinophils, leading to a diagnosis of coexistent acute interstitial nephritis (AIN). Potential secondary etiologies of both AIN and MGN include SLE, Sjögren syndrome, sarcoidosis, and treatment with NSAIDs (49,50).

Blood Vessels

Arteriosclerosis and arteriolosclerosis are commonly present in renal biopsies with MGN and are often a reflection of the patient's age and the presence of systemic hypertension. That said, these vascular lesions have also been shown to correlate with decreased renal survival (8). Occasionally, fibrin thrombi may be seen in blood vessels or glomeruli in biopsies with MGN, where their presence should increase the suspicion for the possibility of renal vein thrombosis (RVT). Additional findings that may suggest RVT include prominent congestion of glomerular or interstitial capillaries and a disproportionate degree of interstitial edema (51). Vascular inflammation is not a feature of MGN and, when present, should raise the possibility of a systemic vasculitis.

Immunopathology

Immunopathologic studies have shown that histologic changes seen in the GBM by light and electron microscopy in MGN are due to deposits of immunoglobulin and complement components. These immune deposits are best demonstrated by immunofluorescence and correspond to the ultrastructural finding of electron-dense deposits that lie between GBM spikes. The typical immunofluorescence finding in MGN is global deposits of immune reactants that follow the contour of the GBM (Fig. 7.14). Since the deposits lie at the subepithelial aspect of the GBM and project toward the urinary space, they typically have a granular appearance and appear relatively discrete and uniform. In contrast, a minority of cases are characterized by small, confluent deposits that produce a pseudolinear appearance (Fig. 7.15). In rare instances, the deposits are sparse and only segmentally distributed; this mainly occurs very early in the course of disease or in a resolving phase, although rare cases of segmental MGN have been described (52). Mesangial deposits are present in less than 10% of cases of primary MGN (53) but are important to identify as their presence favors a secondary form of disease. Mesangial deposits can be difficult to differentiate by immunofluorescence from subepithelial deposits that follow the GBM reflection around mesangial areas (33).

The principal and invariable component of the subepithelial immune deposits in primary MGN is IgG (Fig. 7.16), with a composition that includes both kappa and lambda light chains. Staining for complement component C3 is also usually present, seen in 85% of cases in one large series (33). Staining for IgM, IgA, and C1q is present in 47%, 16%, and 23% of cases, respectively (33). The intensity of staining for IgG is greatest in virtually all cases, and staining for IgM, IgA, and C1q is typically of no more than 1+ intensity (scale +/–, 1+ to 3+). The intensity of staining for C3 is more variable and typically less than that of IgG; few cases may have equivalent staining to IgG. There are rare cases of MGN in which the deposits are monoclonal and exhibit light chain restriction and IgG subclass restriction, most commonly IgG1-kappa (54,55).

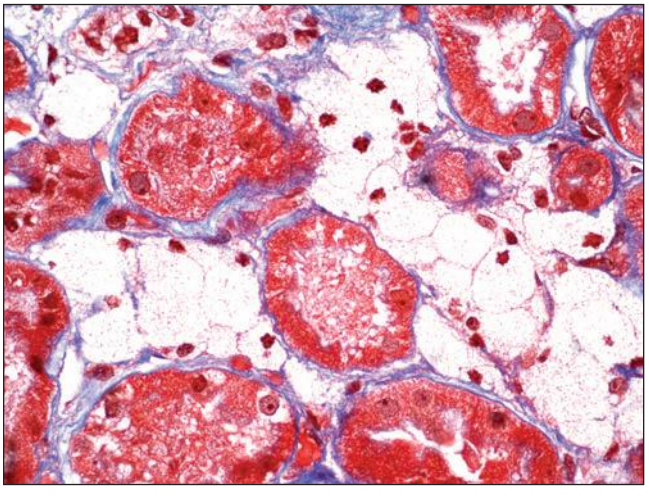


FIGURE 7.13 Interstitial foam cells in MGN. Interstitial foam cells expand the interstitium between tubules. (Trichrome stain, ×600.)

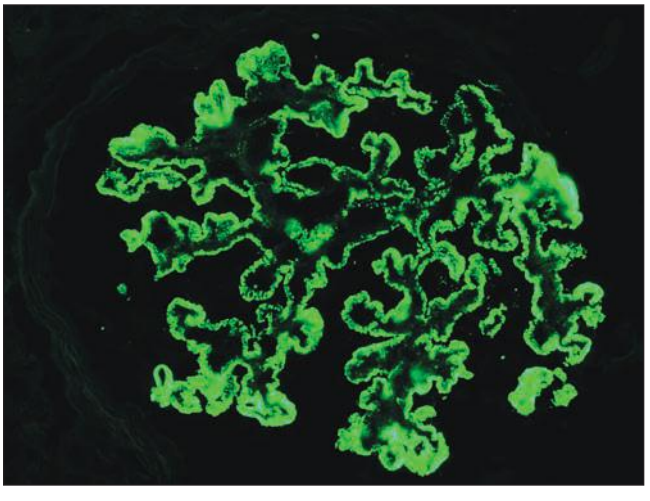


FIGURE 7.14 Immunofluorescence staining in MGN. Staining for IgG reveals intense, granular global subepithelial positivity involving the glomerular capillary walls. (×400.)

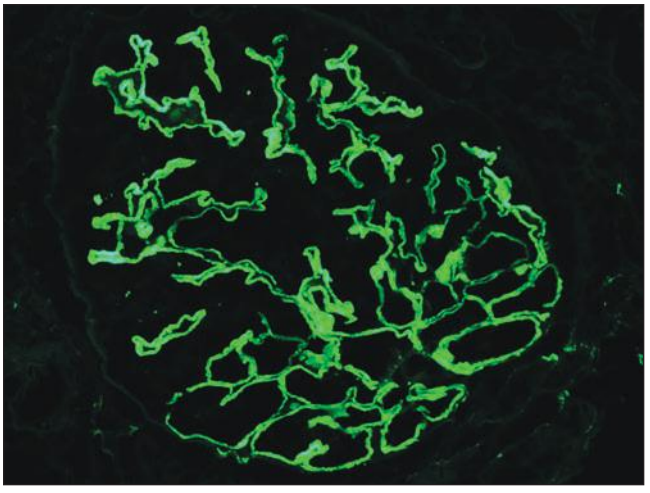


FIGURE 7.15 Immunofluorescence staining for IgG in early MGN. In early MGN, the subepithelial deposits may appear small and confluent, imparting a pseudolinear appearance. (IgG, ×400.)

Not surprisingly, these cases can be associated with hematologic malignancy (54,55).

Immunopathologic findings are often helpful in distinguishing primary MGN from membranous LN and, to a lesser extent, other secondary forms of disease (33). In comparison to primary MGN, membranous LN is characterized by a greater prevalence of positive staining for IgM (62% vs. 47%), IgA (38% vs. 16%), C3 (95% vs. 85%), C1q (67% vs. 23%), and, in particular, intense, ≥2+ staining for C1q (67% vs. 11%) (33). Combined staining for IgG, IgM, and IgA carries a sensitivity of 29% and a specificity of 87% for the diagnosis of membranous LN versus primary MGN, while intense, ≥2+ staining for C1q has a sensitivity of 67% and a specificity of 88% (33). The classic description and hallmark of membranous LN is "full house" staining for immunoglobulins and complement, an expression derived from the game of poker, which refers to the presence of *three of a kind* (three immunoglobulins: IgG, IgM, and IgA) and *two of a kind* (complement components: C3 and C1q). Importantly, many of these findings can also be seen in other secondary forms of MGN. For instance, staining for IgG, IgM, IgA, C3, and C1 are each individually present in greater than 50% of biopsies with MGN secondary to HBV infection (32).

There are four distinct subclasses of IgG (IgG1, IgG2, IgG3, and IgG4), which nonetheless exhibit 95% homology with one another (56). The numbering of the subclasses reflects their relative prevalence in human serum, with IgG1 representing 66% of circulating IgG and IgG4 comprising only 4%. The small differences in amino acid sequence have significant functional consequences. For instance, IgG3 has the greatest ability to activate complement, the highest affinity for Fc receptors on phagocytic cells, and a significantly shorter serum half-life than the remaining three subclasses (7 vs. 21 days) (56). IgG1 also effectively fixes complement and binds to phagocytic cells. IgG4, the least prevalent subclass of IgG, is the only subclass that does not significantly activate complement (56). IgG4 has the unique property of weak disulfide bonds between the two heavy chains, allowing for dissociation into ½ IgG4 molecules composed of a single light and heavy chain and then reassembly with alternative ½ IgG4 molecules to form a heterobivalent IgG4 with two distinct specificities (57). Because the resultant IgG is bispecific, cross-linking of antigens is extremely unlikely, leading to the belief that IgG4 may serve to down-regulate the immune response (56,57). IgG4 is thought to play an important role in multiple disease processes, including IgG4RD and, more notably, MGN.

The predominant IgG subclass in the subepithelial deposits of primary MGN is IgG4 (58–63) (Table 7.2). While this is a well-established finding, the reasons remain somewhat unclear. IgG4 is not significantly increased in the serum of patients with MGN (61–63). The IgG4 immune response is thought to require prolonged antigenic exposure (57) and involves T-helper (Th)2 cell–mediated B-cell stimulation (64). It is possible that the IgG4 in MGN represents a protective response against cross-linking of antigens by other subtypes of

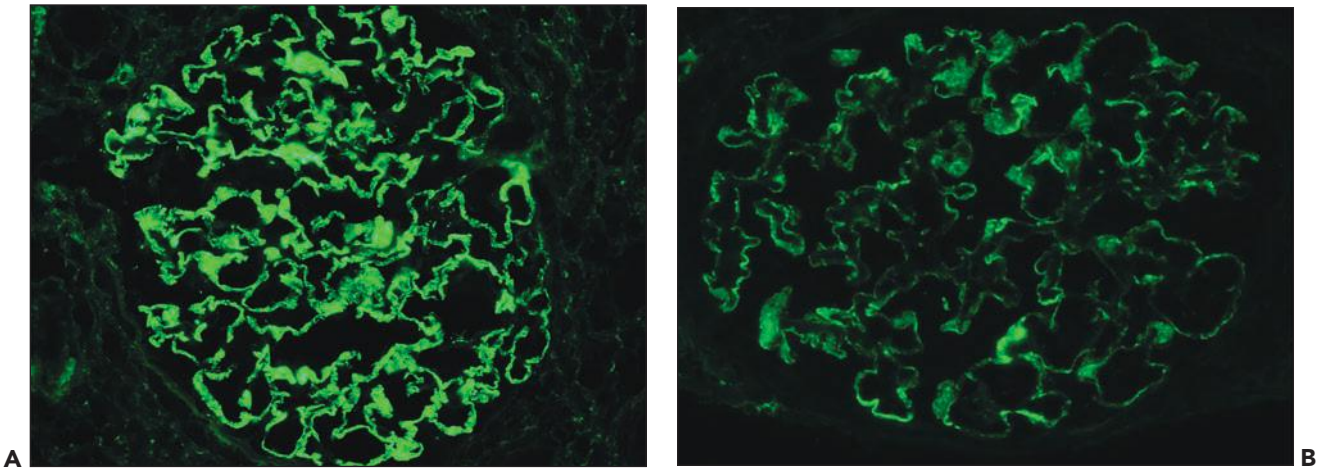


FIGURE 7.16 Comparative immunofluorescence findings in MGN. A: Staining for IgG reveals intense granular global positivity involving the glomerular basement membranes. **B:** In the same biopsy, a similar distribution but less intense staining for C3 is present along the GBM. (**A** and **B:** ×400.)

TABLE 7.2 Staining for IgG subtypes in primary and secondary forms of MGN

	No. of patients	IgG1	IgG2	IgG3	IgG4
Primary MGN (58–63)	108	1+ to 2+	1+	+/–	2+ to 3+
Recurrent MGN in the allograft (67)	7	2+	2+	1+	3+
Membranous LN (59,60,62,63,69)	54	2+ to 3+	2+	2+ to 3+	1+
De novo MGN in the allograft (63)	16	3+	2+	–	1+
MGN secondary to malignancy (58)	10	3+	2+	1+	2+
MGN secondary to mercury exposure (68)	11	3+	NA	+/–	1+

Degree of positivity reflects all studies referenced and reflects both frequency and intensity of positivity.

Scoring graded on a scale of –, +/–, 1+, 2+, and 3+.

NA = not available.

IgG, for instance IgG1 (64). This possibility is supported by the observation that C3 is present in the subepithelial deposits in 85% of cases of MGN (33), a finding that cannot be explained by the presence of IgG4 alone, unless it is capable of activating complement through the lectin pathway (64,65). A recent study reconfirmed the dominance of IgG4 in primary MGN but noted that IgG1 predominated in early, stage I disease, suggesting that an IgG subclass switch occurs early in the course of primary MGN (66).

While IgG4 is the predominant subclass in the subepithelial deposits of primary MGN, IgG1 is also present in the majority of cases and is often accompanied by small amounts of IgG2 and IgG3 (58–63) (see Table 7.2). Not surprisingly, IgG4 is also the dominant subclass when MGN recurs in the allograft (67). In contrast, IgG1 tends to predominate in MGN secondary to malignancy (58) or mercury exposure (68) and in de novo MGN in the renal allograft (63). In membranous LN, IgG1, IgG2, or IgG3 may predominate and all three typically stain more intensely than IgG4, although IgG4 is present in the majority of cases (59,60,62,63,69). Staining for IgG subtypes has been proposed as a modality to differentiate primary and secondary forms of MGN. In our experience, this approach is of somewhat limited utility due to the extensive overlap in staining patterns seen in Table 7.1 as well as the significant subjectivity in grading of positivity. Nonetheless, this approach is likely to be helpful when the main diagnostic considerations are primary MGN and membranous LN. Fortunately, staining for the PLA_2R has emerged as a far more effective strategy to differentiate primary and secondary forms of disease (70–73).

Given that primary MGN is causally linked to the development of anti-PLA_2R antibodies and that renal expression of the PLA_2R is limited to podocytes, it is not surprising that extraglomerular deposits are extremely uncommon in primary MGN. For instance, in two series involving 142 and 26 patients with primary MGN, extraglomerular deposits were not identified in any patient (33,74). In contrast, the finding of extraglomerular deposits favors a secondary form of the disease. In particular, extraglomerular deposits involving tubular basement membranes (TBMs) are present in 30% to 50% of cases of membranous LN (33) and are often accompanied by interstitial and vessel wall deposits (Fig. 7.17). We have reported a series of three patients with MGN and prominent Bowman capsular and TBM deposits in which a secondary etiology was not identified (75).

There are reports of children with anti-TBM nephritis and concurrent MGN. This entity is mainly seen in male children between the age of 2 months and 10 years (76,77), and an X-linked pattern of inheritance has been reported in two families with four affected male offspring (78). Clinical presentation typically includes proteinuria, renal insufficiency, and Fanconi syndrome, and serum studies may document the presence of anti-TBM antibodies. In additional to findings of MGN, pathologic evaluation reveals tubulointerstitial nephritis (TIN) with linear staining of TBMs for IgG, kappa, and lambda by immunofluorescence, and EM often demonstrates electron-dense deposits within TBMs. Indirect immunofluorescence applying the patient's serum to normal kidney reveals linear staining of TBMs and may be used to confirm the diagnosis. The anti-TBM antibodies seen in this condition cross react with the TBM of multiple animal species (79). By Western blot, the antibodies react with a 58-kDa noncollagenous glycoprotein component of TBMs (79) that exhibits 30% homology with human preprocathepsin B (80) and interacts directly with type IV collagen and laminin, suggesting a role in tubular epithelial cell adhesion to TBMs (81). The 58-kDa

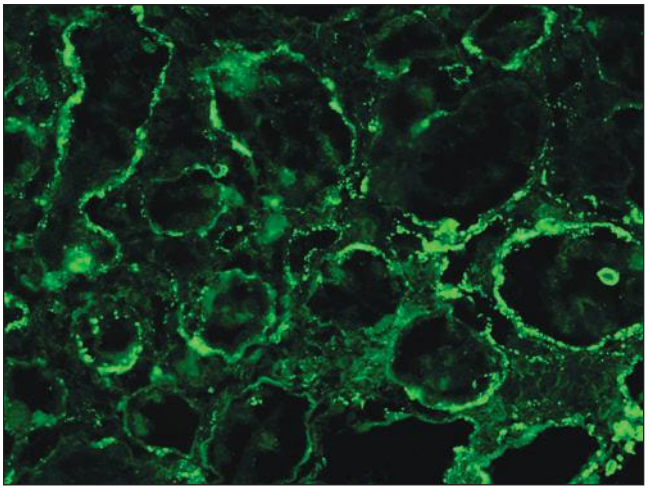


FIGURE 7.17 Tubular basement membrane deposits in MGN. In this patient with MGN, immunofluorescence reveals granular immune deposits within tubular basement membranes. The patient was subsequently found to have systemic lupus erythematosus. (IgG, ×400.)

anti-TIN antigen has not been shown to be expressed in podocytes, although possible cross-reactivity of anti-TBM antibody with a podocyte antigen has been proposed (77). Prognosis for this condition is poor, with frequent progression to end-stage renal disease (ESRD).

A small subset of patients with MGN exhibit mesangial deposits that, in contrast to the subepithelial deposits, stain intensely for IgA with minimal to absent staining for IgG. These cases represent MGN with coexistent mesangial IgAN (34,35,82) (Fig. 7.18). Patients with combined MGN and IgAN are typically adults who present with proteinuria and hematuria. Given the separate and distinctive pathogenesis of these two disease entities and rarity of this combination, a unified mechanism of disease is unlikely. Combined MGN and IgAN appear to be common in patients with hepatitis B infection, in patients with Asian ethnicity, and in the allograft, where IgAN recurs in a large percentage of cases and MGN is among the most frequent de novo form of glomerular disease (34).

Electron Microscopic Findings

EM plays a central role in establishing the diagnosis of MGN, as it demonstrates both the immune complex deposits identified by immunofluorescence and the GBM "spikes" seen best by light microscopy. EM also is needed to accurately determine the stage of MGN.

MGN is defined by the presence of *subepithelial* deposits that form on the outer aspect of the GBM, beneath the podocyte. The deposits appear to sit on the GBM and are accompanied by a spectrum of GBM changes ranging from intervening projections of the extracellular matrix ("spikes") to areas where the GBM projections surround and encase the deposits, creating the appearance of a newly formed, overlying "neomembrane." The deposits can range from electron dense to pale and electron lucent, consistent with focal resorption. In the absence of neomembrane formation, the deposits are in direct contact with and may indent the cytoplasm of the overlying podocytes. Podocytes exhibit a spectrum of reactive changes including condensation of actin filaments, increased cytoplasmic organellar content, lipid and protein resorption droplets, microvillous transformation, and foot process effacement. Animal models have shown that at a molecular level, podocytes exhibit loss of nephrin expression, dissolution of the actin cytoskeleton, and loss of slit diaphragm integrity (reviewed in (83)).

The range of ultrastructural findings seen in MGN led Ehrenreich and Churg (27) in 1968 to propose a morphologic classification that describes a pathologic sequence of subepithelial immune deposit formation, reactive GBM changes, and, in some cases, subsequent resorption of deposits and GBM repair (Fig. 7.19). This classic publication describes four sequential stages of MGN that provide general information about the relative age of the glomerular lesions.

Stage I MGN is characterized by subepithelial electron-dense deposits that are typically small, sparsely distributed, and by definition devoid of significant intervening GBM spike formation, although small depressions in the GBM may be noted (27) (Fig. 7.20). In the majority of cases, no significant abnormalities are identified by light microscopy with the exception of cases in which focal depressions of the GBM may be noted with the JMS stain or fuchsinophilic deposits are apparent with the trichrome stain. The diagnosis of stage 1 MGN is easily established by immunofluorescence and EM. Given that stage 1 represents the earliest changes of MGN, it is not surprising that, unlike the other stages, the deposits may be only segmentally distributed. Scanning EM of acellular glomeruli shows shallow depressions on the epithelial side of the GBM (84) (Fig. 7.21).

Stage II MGN is characterized by subepithelial electron-dense deposits that appear larger than the deposits in stage 1 and by definition are surrounded by intervening projections of the GBM, referred to as GBM "spikes" (27) (Fig. 7.22). By light microscopy, there is global thickening of the GBM. GBM spikes are best visualized with the JMS stain but are also apparent with the PAS stain. Similar to stage 1, the

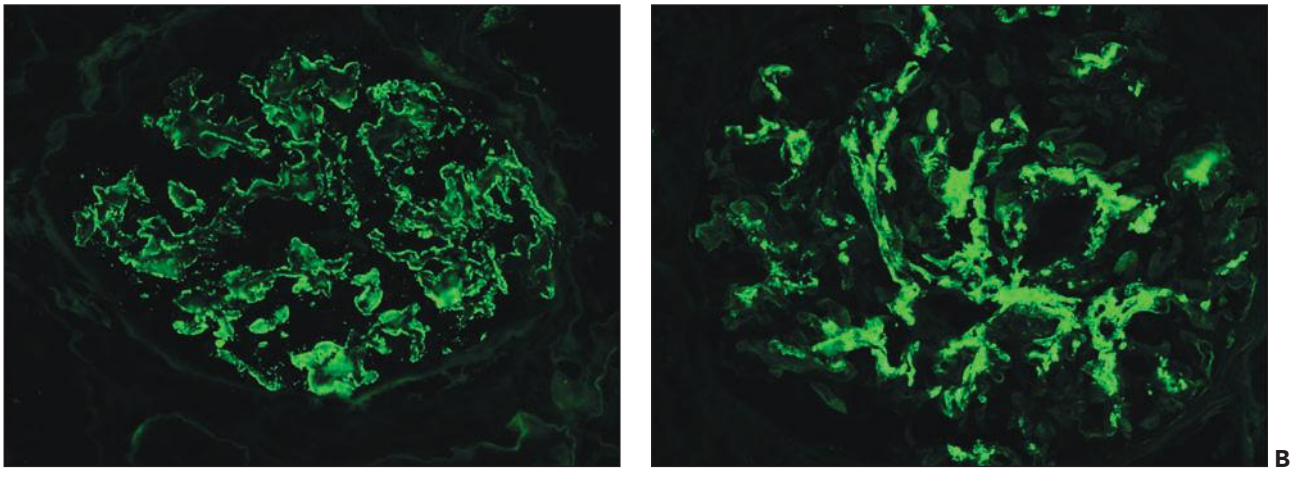


FIGURE 7.18 MGN with IgA nephropathy. A: Staining for IgG reveals granular global glomerular capillary wall positivity in a subepithelial distribution. **B:** Staining for IgA in the same biopsy reveals abundant mesangial deposits that are confined to the mesangium and do not appear to involve the peripheral capillary walls. (**A** and **B:** ×400.)

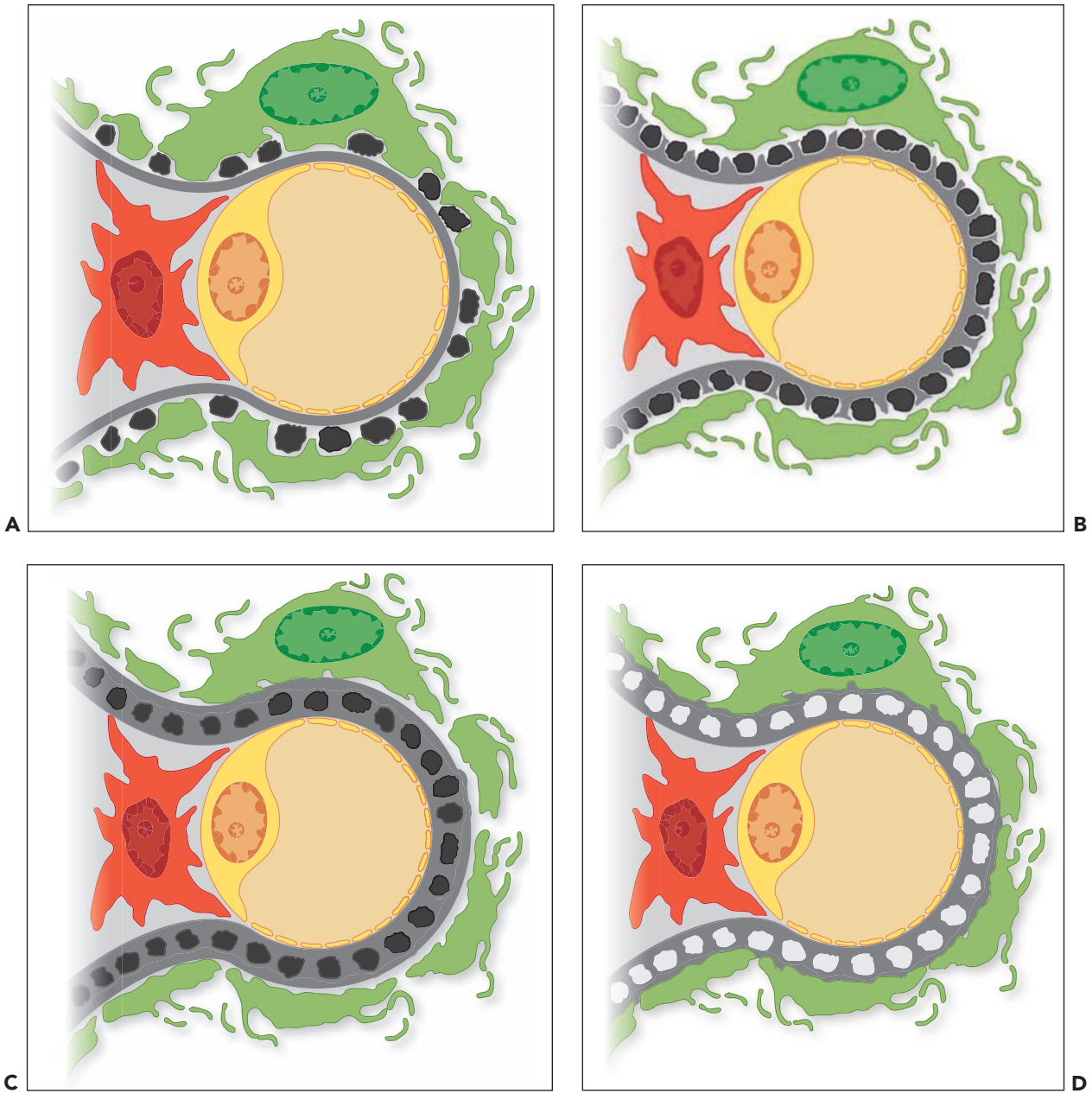


FIGURE 7.19 Depiction of the four stages of MGN as described by Ehrenreich and Churg. A: Stage I MGN is characterized by interspersed subepithelial deposits without intervening GBM spike formation. **B:** In stage II MGN, the subepithelial deposits are more numerous and more closely approximated with intervening GBM spikes. **C:** In stage III MGN, the GBM spikes extend over and encircle the deposits, incorporating them into the glomerular capillary walls. **D:** In stage IV MGN, the deposits lie within a mottled, irregularly thickened GBM and appear electron lucent, consistent with resorption. The irregular thickness of the GBM is consistent with extracellular matrix remodeling.

deposits typically stain intensely by immunofluorescence. The three-dimensional appearance of the deposits can be partially appreciated by scanning EM of acellular glomeruli, where the elongated deposits are surrounded by a complex anastomosing network of basement membrane projections (84) (Fig. 7.23).

In *stage III* MGN, a new layer of GBM is laid down over the subepithelial deposits and connects the GBM spikes (27). As a result, the deposits appear to sink into the GBM (85) and are often described as having an intramembranous appearance, lying beneath a neomembrane (Fig. 7.24). In stage III, the deposits can be electron dense, similar to stages I and II, or may exhibit diminished electron density, indicating that they are undergoing resorption and incorporation into the GBM. The intensity of immunofluorescence staining is variable in stage III, as less intense staining is seen in cases in which the

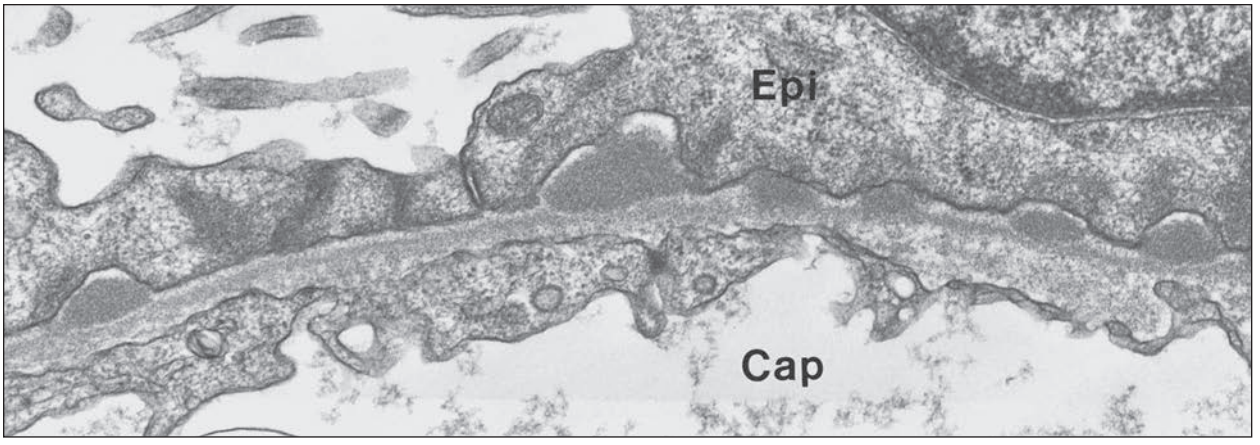


FIGURE 7.20 Electron micrograph of stage I MGN. In stage I MGN, there are small, interspersed subepithelial deposits without significant GBM spike formation. (×20,000.)

deposits have a more electron-lucent appearance. By light microscopy, GBM thickening is most pronounced in stage III, and the JMS stain typically shows a complex, vacuolated GBM, while the deposits usually are not visible with the trichrome stain. Although the staining intensity may be reduced, the deposits are usually demonstrable by immunofluorescence. The findings of pure stage III MGN suggest a single generation of deposits, presumably formed over a similar time period. In contrast, most cases of stage III MGN have a mixed appearance with fresh deposits layered over older intramembranous deposits, suggesting a dynamic process of ongoing deposit formation, incorporation, and resorption. In such cases, it may be possible to assign a dominant stage based on the major pattern present. In many cases, two stages coexist, making it most appropriate to designate both stages (such as mixed stage II to III) (Fig. 7.25). By scanning EM, the complex network of GBM projections seen in stage II MGN is replaced by bridged segments of the neomembrane in stage III that have a relatively smooth appearance (84) (Fig. 7.26).

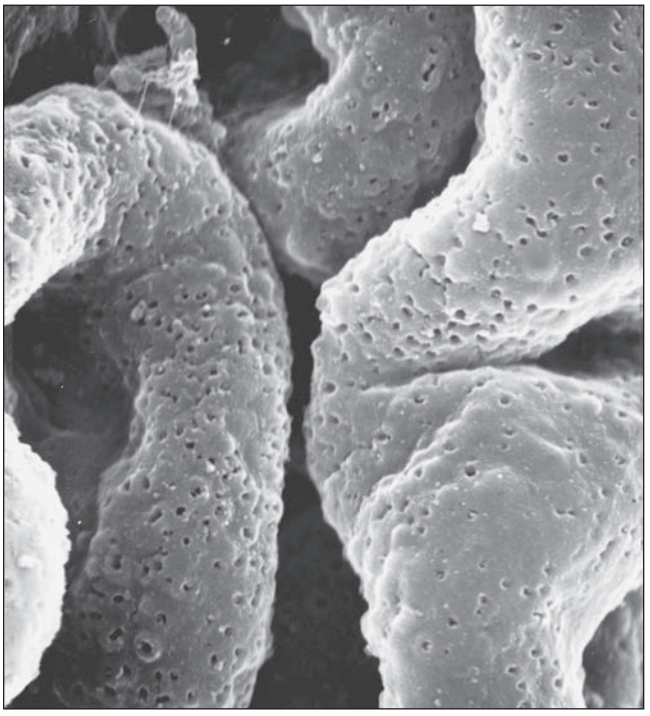


FIGURE 7.21 Scanning electron micrograph of an acellular glomerulus from a patient with stage I MGN. The cells were removed from the tissue by sequential treatment with detergents and deoxyribonuclease. The GBM contains scattered shallow pits representing the sites of immune complex deposits removed in the preparation of the tissue. (×5,000.) (Courtesy of Dr. Stephen M. Bonsib.)

In *stage IV* MGN, the subepithelial deposits lie within the GBM and no longer have an electron-dense appearance (27). In contrast, the deposits either are electron lucent or have a similar electron density to the surrounding GBM owing to remodeling of the extracellular matrix. These findings are irregularly distributed, leading to a GBM that ranges from markedly expanded to more normal in thickness. In some cases, the main finding is a layer of intramembranous vaguely electron-lucent material that may more closely approximate the subendothelial than the subepithelial aspect of the GBM (Fig. 7.27). By light microscopy, the GBM appears thickened and GBM vacuolations may be appreciated with the JMS and PAS stains. Ehrenreich and Churg also described a stage V of MGN characterized by capillary collapse, sclerosis, capsular adhesions, and crescents. In current clinical practice, these stage V changes, which unlike the previous stages are not based mainly on EM findings, are largely viewed as part of MGN stage IV. In stage IV (and stage V), immunofluorescence staining for IgG is typically of low intensity and can be absent, making the diagnosis of MGN difficult. In these instances, the finding of focal areas more typical of MGN II or III is of great assistance in establishing the diagnosis.

Although it represents a significant advance in our understanding of the morphogenesis of MGN, the Ehrenreich and Churg (27) classification of MGN into four stages of disease

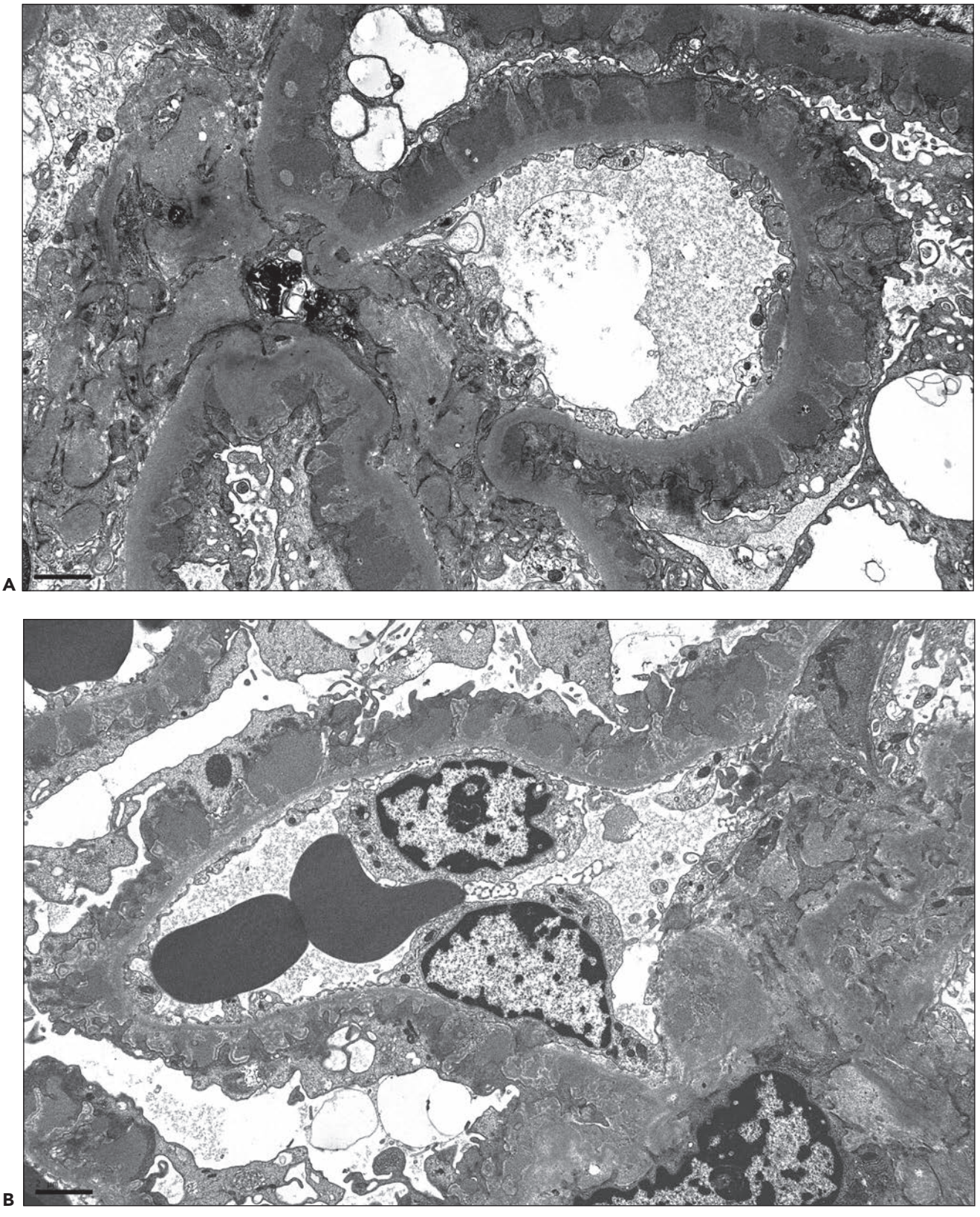


FIGURE 7.22 Electron micrograph of stage II MGN. Images **(A)** and **(B)** show the typical findings of stage II MGN, including global subepithelial electron-dense deposits separated by intervening GBM spikes. (**A** and **B:** ×6000.)

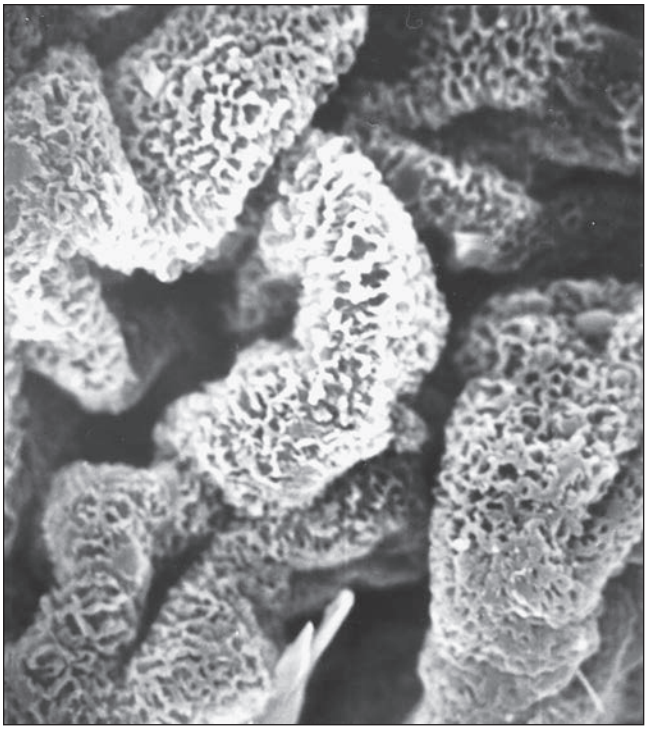


FIGURE 7.23 Scanning electron micrograph of an acellular glomerulus prepared as described in Figure 7.21 from a patient with stage II MGN. The projections of basement membrane material are seen as a complex anastomosing network on the outer surface of the GBM. (×4,000.) (Courtesy of Dr. Stephen M. Bonsib.)

has certain limitations. First, the staging system provides insight into the evolution of disease but should not imply that all cases necessarily progress from stage I to stage IV. Second, it is often difficult to classify a case of MGN into a discrete stage because multiple stages may overlap, particularly when a fresh generation of deposits develops over an older layer of intramembranous deposits (85,86). Third, the morphologic stages do not correlate well with the level of proteinuria, renal function, or outcome. Fourth, progression from one stage to another can be associated with clinical improvement or worsening of disease. For example, transition from stage II to III to IV may be seen in the setting of resolution of clinical disease, while a patient may progress to advanced renal failure with biopsy findings of only stage II to III. Finally, clinical remission may be associated with no change in the appearance of the deposits, evolution to stage IV, or, less commonly, complete resolution with restoration of a normal glomerular architecture (27,87–90).

Subepithelial deposit formation in MGN is a dynamic and potentially reversible process. The limitations of the Ehrenreich and Churg classification stem from the fact that the four stages are likely accurate for a single generation of deposits but do not address the complexity of ongoing and simultaneous deposit formation, incorporation into the GBM, and in many cases, resorption of the deposits, leading to GBM remodeling and potential healing. The clinical and pathologic resolution of disease is likely most dependent upon diminishing the rate of antibody production and deposit formation. Stated differently, outcomes are likely dependent on creating an imbalance such that the rate of healing and remodeling outpaces the rate of deposit formation. Along these lines, it has been suggested that the degree of thickening of the GBM indicates a more prolonged disease course (85), and the finding of homogeneous, synchronous deposits (i.e., deposits of a single stage) has been shown to have a significantly better prognosis than heterogeneous deposits (i.e., multiples phases of deposits) (91) (Fig. 7.28). Along the same lines, another method to prognosticate in MGN may be to measure the percentage of deposits that have an electron-lucent appearance, indicating at least partial resorption; in our experience, cases with a preponderance of electron-lucent deposits tend to have lesser degrees of proteinuria and are often in a state of at least partial remission. Future studies may be helpful to address this issue.

While the subepithelial deposits are globally distributed in the majority of cases of MGN, there are multiple reports of *segmental MGN* (52,92–95) (Fig. 7.29). The term "segmental MGN" should be reserved for cases with a segmental distribution of the deposits by light microscopy, immunofluorescence, and EM. The pathogenetic significance of segmental MGN, as compared to the more commonly encountered global lesion, is not well understood. It is likely that some of the cases, in particular those that exhibit stage I changes, represent an early manifestation of the usual form of (global) MGN, and it has been proposed that other cases may represent a resolving phase of MGN (92). Obana et al. (93) compared 27 children with global MGN to 11 children with segmental MGN and found that the segmental lesion was associated with a higher incidence of C1q positivity by immunofluorescence and mesangial deposits by EM but a similar clinical presentation and outcome. Interestingly, only 3 of the 11 patients with segmental MGN had stage I changes, and 2 patients underwent repeat biopsy at 3 years and were found again to have segmental deposits, arguing in favor of segmental MGN being a distinctive variant of MGN rather than an early manifestation of global MGN (93). Based on the limited information available, segmental MGN is most commonly reported in children (92–94). There are reports of segmental MGN in adults and, in most cases, the findings are superimposed on another pattern of glomerular injury. Bertani et al. (52) described four adult cases of segmental MGN, all of which coexisted with other glomerular lesions including minimal change disease (two patients), diabetic glomerulosclerosis, and hereditary nephritis. In a recent report on MGN with antineutrophil cytoplasmic antibodies (ANCA)-associated necrotizing and crescentic glomerulonephritis, the membranous changes were only segmentally distributed in 6 of 13 cases (95).

The electron-dense deposits in primary MGN are usually amorphous and finely granular, with notable exceptions (96–101). Kowalewska et al. (97) described 14 patients with a variant of MGN in which the subepithelial deposits exhibit a unique, microspherical substructure with a mean diameter of 85 nm (Fig. 7.30). Although these structures are the approximate size of nuclear pores, the authors were unable to identify nuclear pore antigens as a source for the spherules. Clinical presentation and outcomes were similar to other cases of primary MGN with the exception of associations with autoimmune diseases (SLE or Sjögren syndrome) in two patients. There are

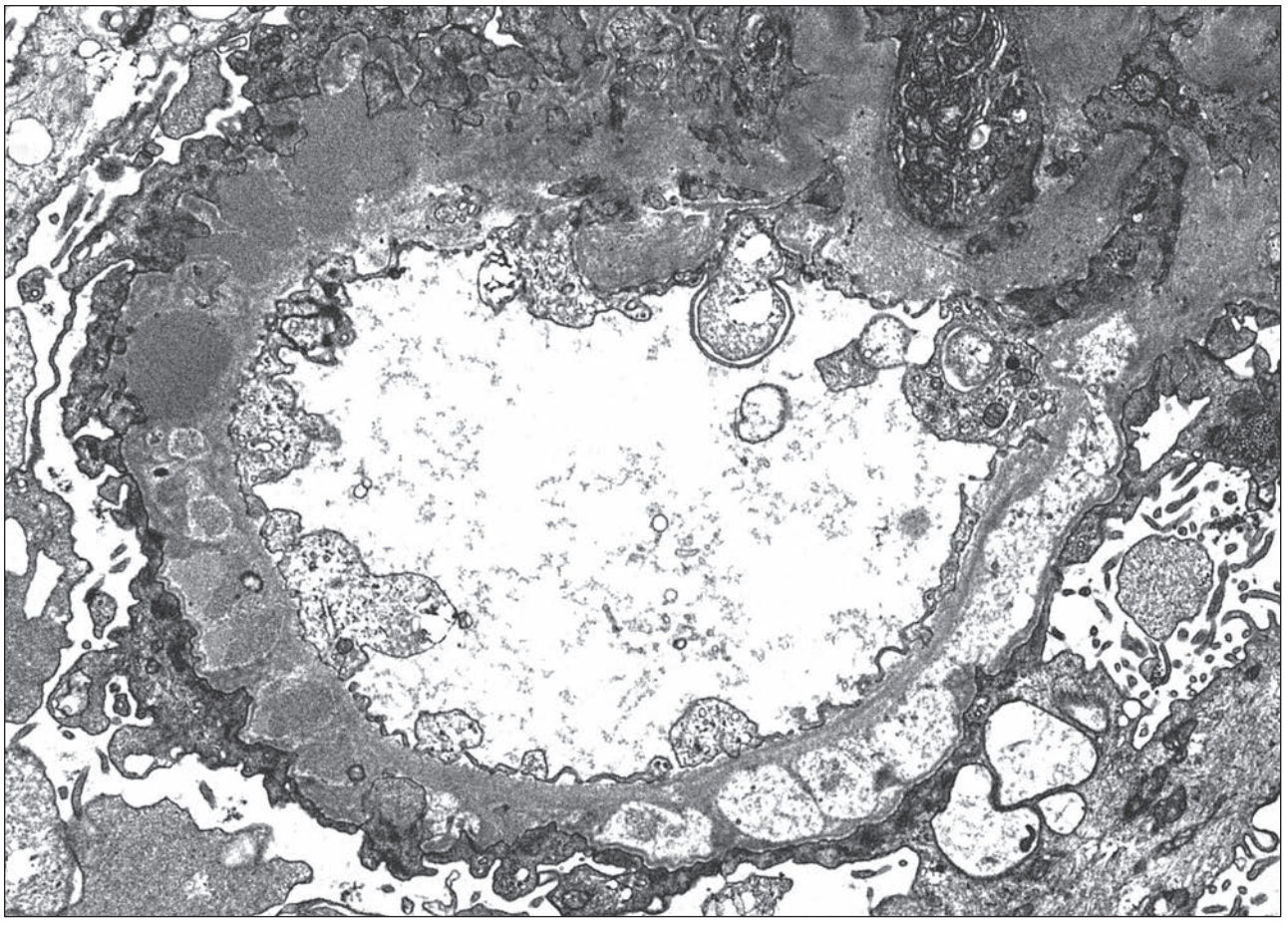


FIGURE 7.24 Electron micrograph of stage III MGN. In this example of stage III MGN, the subepithelial deposits are separated by intervening GBM spikes and accompanied by overlying neomembrane formation. Some of the deposits appear electron lucent consistent with partial resorption. (×6000.)

reports of cases in which light microscopy and immunofluorescence strongly suggest the diagnosis of MGN, but EM reveals deposits that exhibit a fibrillar or microtubular substructure (96,98–101). Based on their ultrastructural appearance, these cases are best considered as examples of fibrillary glomerulonephritis and immunotactoid glomerulopathy, respectively, and should not be considered as variants of MGN (96,98–101). Podocyte infolding glomerulopathy is a recently described entity that resembles MGN by light microscopy and may or may not exhibit granular positivity for IgG by immunofluorescence (102–104). In contrast to MGN, EM reveals podocyte infolding with microspherical and microtubular structures within the GBM. The majority of cases of protein infolding glomerulopathy have occurred in Japan, and many of the patients have evidence of SLE (102–104). Although the morphogenesis of this lesion is unknown, the irregular outer contours of the GBM suggest that podocyte cytoplasmic fragments and cell membranes may become trapped in the course of deposit resorption and matrix remodeling. Finally, organized electron-dense deposits can be seen in membranous LN, and occasional cases of apparently primary MGN have unexplained organized deposits.

Mesangial electron-dense deposits are uncommon in primary MGN (33,105) and, when present, a secondary form of MGN should be carefully excluded (Fig. 7.31). Follow-up is necessary in MGN patients with mesangial deposits because SLE may manifest after a latent period of several years (14,33). Shearn et al. (105) found mesangial deposits in 9 of 107 cases (8.5%) of MGN in which SLE was not detected during a mean follow-up period of 9.8 years. In a series of 53 children with primary MGN followed for a mean of 53 months who did not have evidence of SLE or HBV, the Southwest Pediatric Nephrology Study Group (SPNSG) (14) reported an incidence of mesangial deposits of 31%, which is significantly higher than has been reported in adults. Jennette et al. (33) found mesangial deposits in 11% of 142 patients with primary MGN compared with 96% of 28 patients with membranous LN. Lai et al. (32) found mesangial deposits in 20 of 26 (76.9%) patients with membranous LN and 11 of 22 (50%) patients with MGN secondary to HBV infection. In addition to SLE and HBV infection, mesangial deposits have been described rarely in patients with MGN related to metastatic carcinoma and following treatment with penicillamine (36).

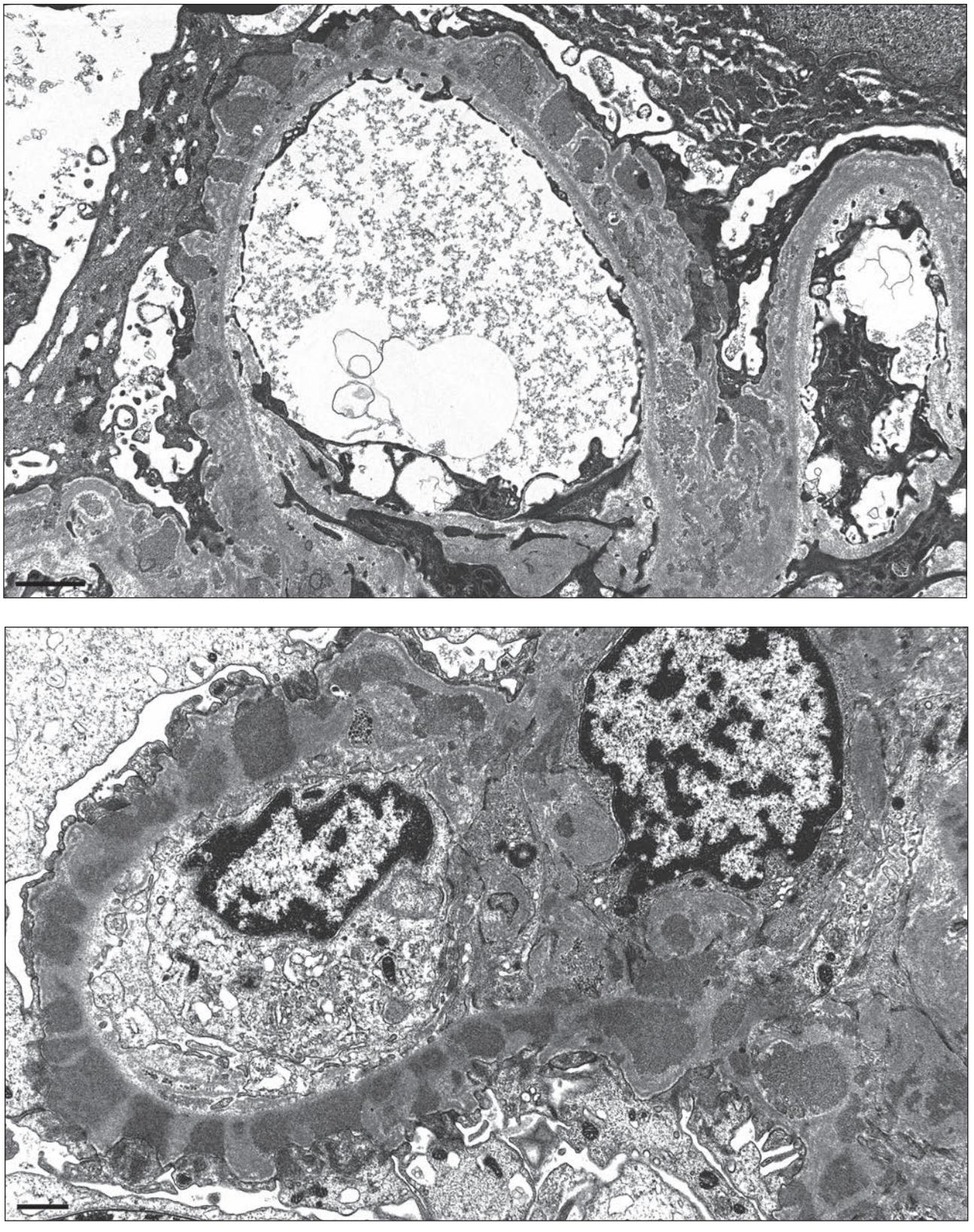


FIGURE 7.25 Electron micrographs of MGN stage II to III. In these two examples of stage II to III MGN, there are global subepithelial deposits, global intervening GBM spikes, and segmental overlying neomembrane formation. Thus, a mixture of stage II and stage III changes is present. (**A:** ×8000; **B:** ×10,000.)

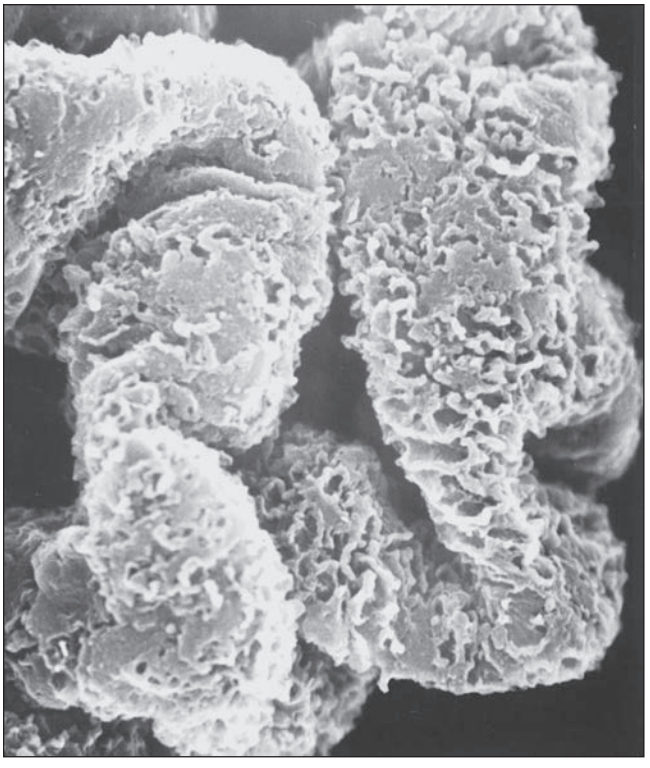


FIGURE 7.26 Scanning electron micrograph of an acellular glomerulus prepared as described in Figure 7.21 from a patient with stage III MGN. The anastomosing ridges of basement membrane material that surround and project above the electron-dense deposits (removed in this material by processing) show areas where they bridge over the deposits and form smooth plaques on the external surface of the GBM. (×5000.) (Courtesy of Dr. Stephen M. Bonsib.)

Subendothelial and extraglomerular deposits are also rarely encountered in the setting of MGN and, when present, a secondary form of disease is strongly favored (Fig. 7.32). Jennette et al. (33) described subendothelial deposits in 61% of 28 patients with membranous LN but only 3% of 142 patients with primary MGN. Similarly, TBM deposits were identified in 32% of 28 patients with membranous LN versus none of the 142 patients with primary MGN (33) (see Fig. 7.17). The SPNSG found subendothelial deposits in 9 of 9 children with membranous LN, as compared to 13% of 45 children with primary MGN (14). Lai et al. (32) found subendothelial deposits in 21 of 26 (80.8%) patients with membranous LN and 15 of 22 (68.2%) patients with MGN secondary to HBV infection. Another ultrastructural finding that favors a secondary form of MGN is endothelial tubuloreticular inclusions (Fig. 7.33), which are identified in 32% to 73% of cases of membranous LN (19,89) and 13.4% of cases of MGN secondary to HBV infection (32) but were absent in all 142 patients with primary MGN in at least one series (33).

Combined Membranous and Crescentic GN

The subepithelial deposits and associated GBM changes that characterize MGN do not typically result in GBM rupture or crescent formation. Nonetheless, crescents are encountered in a small percentage of cases of MGN and, when present, should raise the possibility of concurrent SLE, anti-GBM disease, or systemic vasculitis and should lead to a serologic workup that includes testing for antinuclear antibodies, anti-GBM antibodies, and ANCA (Fig. 7.34). The topic of mixed membranous and proliferative/crescentic forms of LN is covered in Chapter 14.

The first case of combined membranous and crescentic GN due to the presence of anti-GBM antibodies was reported by Klassen et al. in 1974 (106). In 1984, Pettersson et al. (107) reviewed 11 similar cases and observed that the relationship between MGN and anti-GBM disease fell into three temporal patterns: anti-GBM disease followed by MGN, MGN followed by anti-GBM disease, and patients in whom MGN and anti-GBM disease were simultaneously detected. The topic of MGN and anti-GBM disease has been the subject of more recent reviews (108,109). At present, there are 28 reports of this dual glomerulopathy (108) including 5 patients in whom MGN preceded the development of anti-GBM disease, 5 patients who initially presented with anti-GBM disease and subsequently developed MGN, and 18 patients who were simultaneously diagnosed with both entities. Based upon scant data, patients with anti-GBM disease before MGN tend to be younger and have a better prognosis than those with MGN before anti-GBM disease (108). Among the 28 patients, clinical recovery was noted in 11 patients, including 4 with anti-GBM disease before MGN and 7 who were simultaneously diagnosed.

The pathogenesis of MGN with anti-GBM disease is obscure. It has been proposed that MGN may damaged the GBM and expose cryptic epitopes that incite anti-GBM antibody formation (106), and the converse mechanism may be operative in cases of MGN that follow Goodpasture syndrome, in which the anti-GBM antibodies may incite an immune response to a podocyte or planted antigen. Interestingly, exposure to mercuric chloride in Brown Norway rats leads to a biphasic immune response with initial development of anti-GBM antibodies and subsequent development of proteinuria and MGN (110). The diagnosis of MGN with anti-GBM disease may be challenging because the granular subepithelial deposits of MGN may obscure the linear anti-GBM antibody staining. As a result, testing for anti-GBM antibodies should be performed in all patients with MGN and significant crescent formation.

The first case of membranous and crescentic GN related to ANCA seropositivity was reported in 1993 in a patient with Wegener granulomatosis (111). In 1997, Tse et al. (112) reported 10 cases of "vasculitic GN" in patients with MGN. All 10 biopsies revealed MGN with cellular and/or fibrous crescents. ANCA serologies were positive in only four of the nine patients who were tested, raising the question of whether the crescents can be attributed to a vasculitic mechanism in the absence of ANCA seropositivity. MGN and "vasculitic GN" were simultaneously diagnosed in nine patients, while one had MGN with a subsequent crescentic transformation (112). The authors of this study reviewed the relevant literature at the time and found 10 similar cases, although only one had documented ANCA seropositivity (111).

In 2009, Nasr et al. (95) described 14 cases of MGN with ANCA-associated necrotizing and crescentic GN.

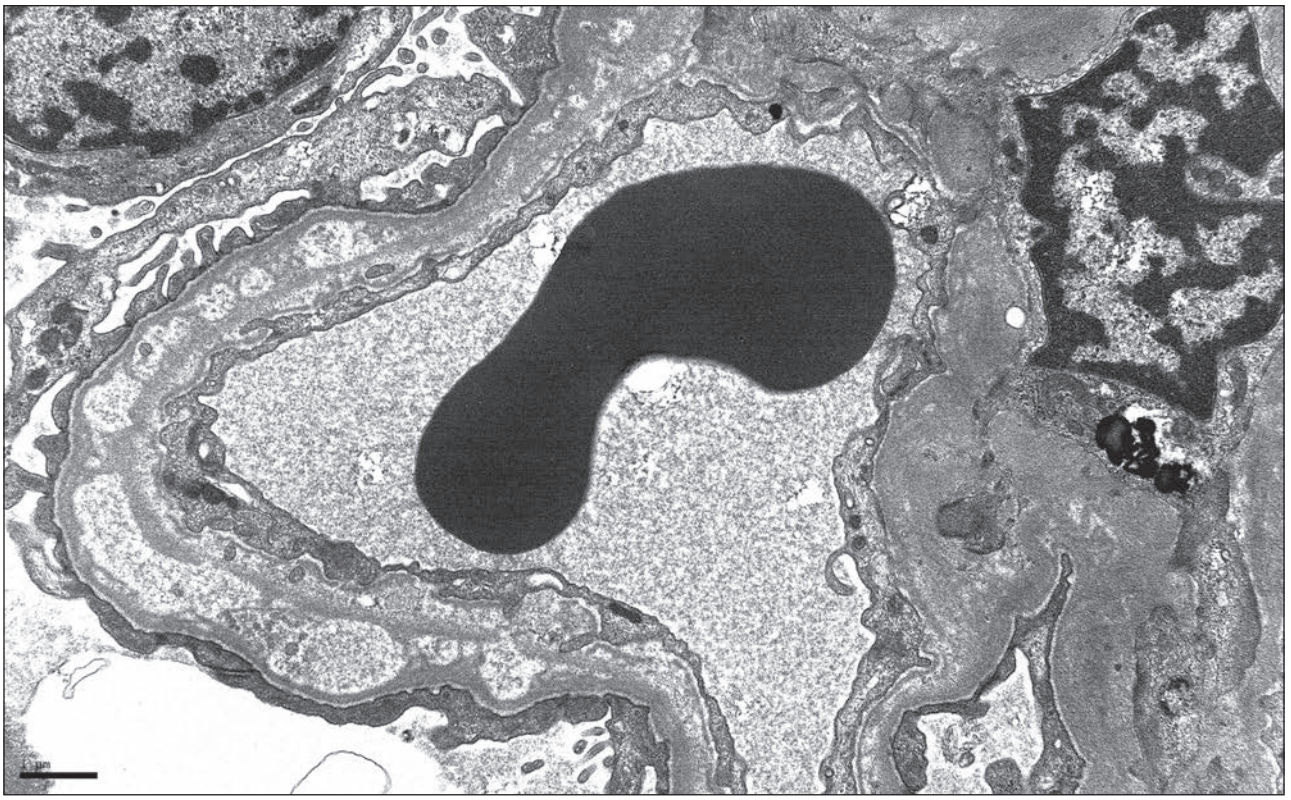


FIGURE 7.27 Electron micrograph of stage IV MGN. In this example of stage IV MGN, there is global remodeling of the glomerular basement membrane which contains intramembranous lucencies consistent with resorbed deposits. (×6000.)

ANCA serology was positive by indirect immunofluorescence or ELISA in all cases and was identified as P-ANCA with specificity for myeloperoxidase (MPO) in most cases. The cohort consisted with 8 men and 6 women with a mean age of 59 years. The mean serum creatinine was 4.4 mg/dL, and 12 of 14 patients presented with acute kidney injury (AKI). The mean 24-hour urine protein was 6.5 g/d, all of the patients had evidence of hematuria, and six had extrarenal manifestations of vasculitis (95). The diagnosis of MGN and ANCA-associated GN were established simultaneously in 13 patients, while one had been previously diagnosed with MGN. On pathologic evaluation, the findings of MGN were typically stage I or II and were only segmentally distributed in six cases. Twelve of thirteen patients with available follow-up were treated with steroids and cyclophosphamide; among these patients, 7 had stabilization or improvement in renal function, 1 had worsening renal function, and 4 progressed to ESRD (95).

Rare cases of MGN with crescents are seen in the absence of ANA, ANCA, or anti-GBM antibody seropositivity. Crescentic transformation should be considered in the differential diagnosis of the patient with MGN who develops a rapid decline in renal function with a nephritic urine sediment.

Etiology and Pathogenesis

The finding of subepithelial immune deposits defines MGN and raises the age-old question of whether circulating immunoglobulins traverse the GBM to bind to antigens that are inherent to the glomerulus and expressed on the podocyte surface or to circulating antigens that have become "planted" in the subepithelial region. Prevailing data suggest that both are correct depending on the etiology; primary MGN appears to represent an autoimmune response to endogenous antigens expressed on the podocyte cell membrane, whereas "planted" antigens likely mediate secondary forms of disease.

Great insights into MGN came from the 1959 landmark work of Heymann and Hackel (113), who immunized Sprague-Dawley rats with a crude preparation of the fractionated renal cortex (FX1a) containing the brush border of proximal tubules and produced an experimental model of MGN in which subepithelial deposit formation preceded the onset of nephrotic syndrome (114). Injection with fractionated liver, muscle, or lung did not produce the same effect, leading the authors to conclude that an "autosensitization mechanism" was central to the pathogenesis of this not yet named pattern of glomerular injury that was associated with nephrotic syndrome. It was shown subsequently that the subepithelial deposits in this model of *active* Heymann nephritis were composed of antigens and antibodies (115) and that passive transfer of heterologous antibodies produced in another species, such as sheep, to naive rats created a more rapid and therefore manipulable model, known as *passive* Heymann nephritis (PHN) (116).

A period followed in which there was an intense search for the antigenic target of the anti-rat kidney tubular antibody that is the central to the pathogenesis of PHN (117). In 1978, it became apparent that the FX1a antigen was

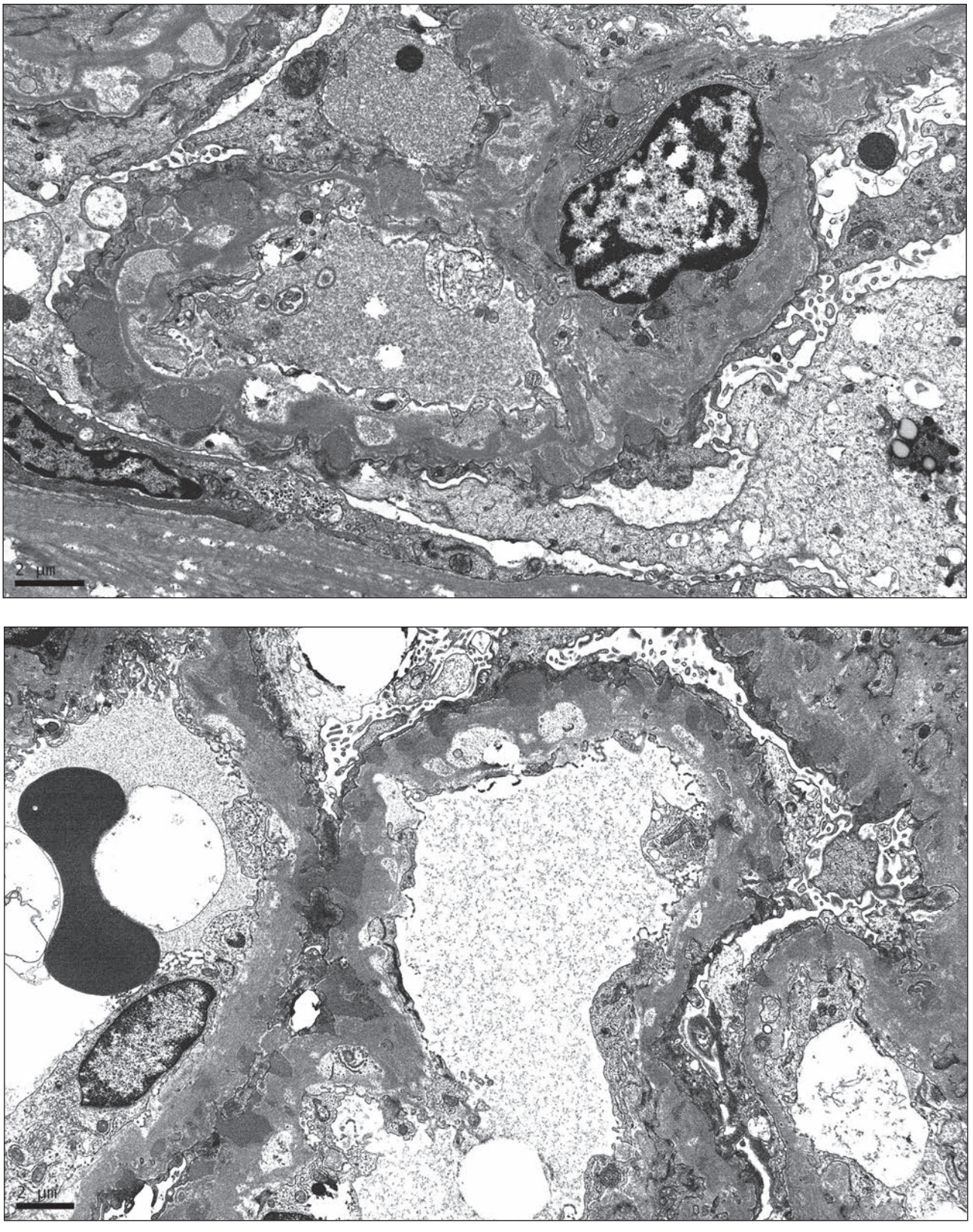


FIGURE 7.28 Heterogeneous deposits in MGN. In these two examples of MGN with heterogeneous deposits, the glomerular basement membrane is expanded by multiple generations of deposits. The deeper layer of intramembranous deposits appears electron lucent consistent with ongoing resorption. The outer layer of newly formed deposits appears electron dense. (**A**: ×8000; **B**: ×6000.)

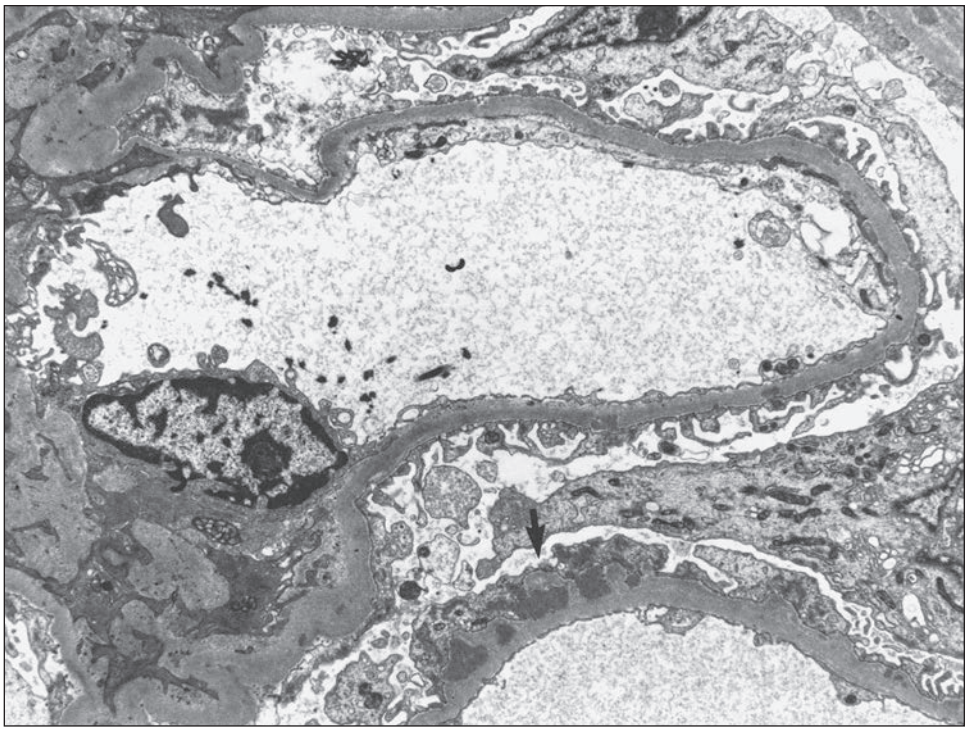


FIGURE 7.29 Electron micrograph of segmental MGN. In segmental MGN, there are segmental subepithelial deposits with intervening GBM spikes (*arrow*). The adjacent glomerular capillary exhibits only a rare, minute deposit. (×8000.)

localized to the subepithelial aspect of the GBM and that the Heymann nephritis model resulted from in situ antigen-antibody complex formation involving an endogenous antigen, rather than circulating immune complexes containing tubular proteins that deposited in the subepithelial region (118,119). In a series of elegant experiments published in 1982, Kerjaschki and Farquhar determined that glycoprotein 330 (gp330) expressed on the proximal tubular brush border was the critical component of FX1a that induced PHN. Specifically, injection of isolated gp330 was able to induce PHN, while injection of FX1a depleted of gp330 did not produce this model (120). As a result, gp330, also referred to as megalin, was identified as the target antigen in Heymann nephritis.

Megalin/gp330 is expressed in the proximal tubular brush border of the rat, as well as the clathrin-coated pits at the base of the podocyte foot processes (120,121). Rats immunized with gp330 derived from proximal tubules produce antibody that cross-reacts with gp330 expressed on podocyte foot processes, leading to capping and shedding of antigen-antibody complexes into the subepithelial space. Megalin/gp330 is a large transmembrane glycoprotein that is a member of the low-density lipoprotein (LDL) receptor gene family and serves as an endocytic receptor for many ligands including apolipoproteins E and B (122,123). In the setting of PHN, antimegalin antibodies block the uptake of these apolipoproteins (124), leading to lipoprotein accumulation, lipid peroxidation, and adduct formation on matrix proteins of the GBM, a sequence of events that contributes to the development of proteinuria (125).

Human and rat megalin exhibit 77% amino acid sequence homology (122) and play a similar role in protein trafficking within the proximal tubule. The critical distinction is that megalin/gp330 is not expressed by human podocytes and is not present in the subepithelial deposits of primary MGN in man. Therefore, while megalin/gp330 is the "Heymann antigen" in the rat model, it is not the *human* Heymann antigen. The main historical significance of PHN is that it is a valuable experimental model for studying the molecular and cellular mechanisms of glomerular injury in MGN and pointed to the podocyte as a potential source of the target antigen in human disease (126).

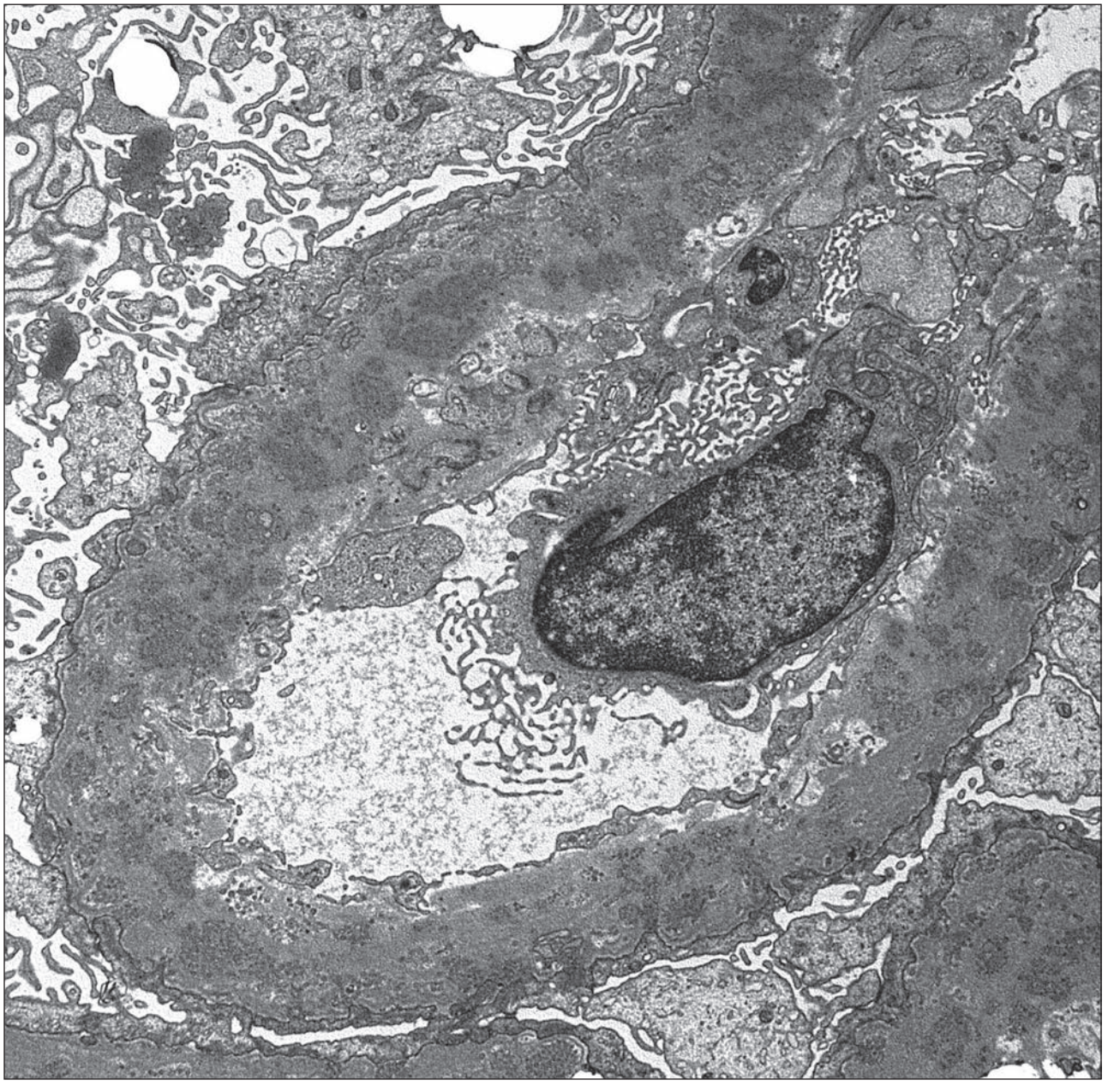
The PHN model has elucidated the role of serum complement in the pathogenesis of MGN (126–135). In 1980, Salant et al. (132) treated rats with cobra venom factor to deplete C3 complement levels prior to injecting anti-FX1a; the rats developed pathologic changes of PHN, including anti-FX1a antibodies within the subepithelial deposits, but did not develop significant proteinuria. Subsequent studies showed a similar effect of C6 depletion (127), and isolated perfused rat kidneys with PHN develop pathologic changes but no proteinuria in the setting of C8-deficient plasma; with restoration of C8 levels, proteinuria develops (129). These studies demonstrated that proteinuria is complement dependent, with C5b-C9, the MAC, playing a central role. In MGN, MAC inserts into the cell membrane of podocytes, producing sublytic injury and inducing multiple cellular responses including synthesis of reactive oxygen species and proteases that degrade and disrupt the GBM, podocyte cytoskeletal alterations including nephrin-actin dissociation and loss of slit diaphragm integrity (133,135), up-regulation of transforming growth factor–β (TGF-β), and podocyte apoptosis and detachment (130). MAC formation also has been implicated in the tubulointerstitial changes that accompany the unremitting proteinuria in progressive MGN (136).

MAC formation in MGN involves the classic and alternative complement pathways (128). IgG4, the predominant subtype of IgG present in the subepithelial deposits of MGN, has minimal ability to fix complement. This observation underscores the importance of alternative complement pathway activation

in the formation of MAC. In the normal state, complement regulatory proteins (CRPs) are synthesized by podocytes and inhibit local alternative complement pathway activation. In the setting of MGN, there is diminished CRP function, leading to alternative pathway activation and MAC formation. In support of this concept, complement receptor 1–related protein (Crry), the rodent analog to membrane cofactor protein, is a CRP that is present in FX1a, and antibodies against Crry are present in the subepithelial deposits of PHN (131,134). Depletion of anti-Crry antibodies ameliorates proteinuria in PHN without disrupting subepithelial deposit formation (134).

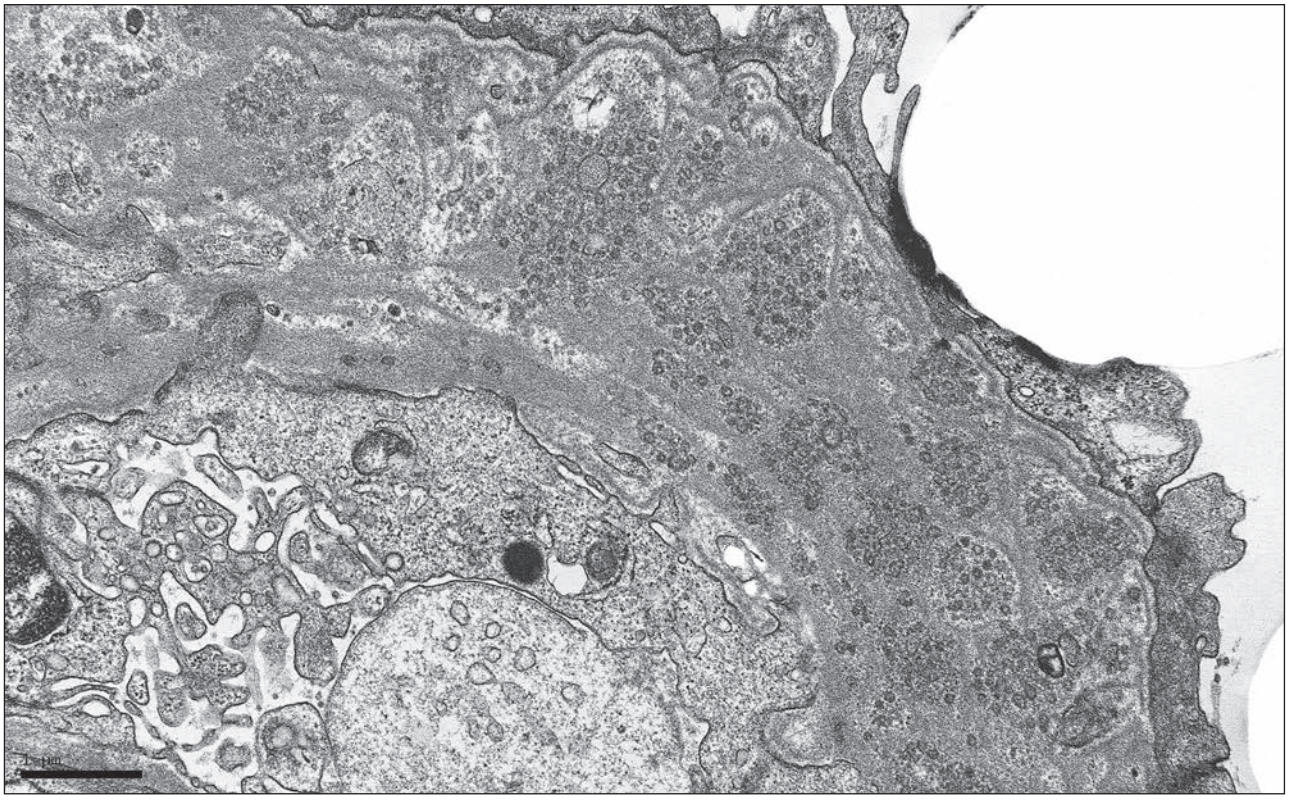
Neutral Endopeptidase as a Human Target Antigen

A significant advance in our insight into the pathogenesis of MGN occurred in 2002 when Debiec et al. (137) identified the first human analogue of the Heymann antigen. A full-term male infant was born with oligoanuric renal failure and massive nephrotic syndrome with biopsy findings of MGN, undoubtedly the result of transplacental transfer of maternal antibodies. Two months prior to this pregnancy, the mother had had a miscarriage. Multiple serum samples from the mother and infant were available for study. By indirect immunofluorescence on normal human kidney, the



A

FIGURE 7.30 MGN with microspherular deposits. In a small subset of patients with MGN, the subepithelial deposits have a microspherular appearance, which can be appreciated at low magnification **(A)**, but is best seen at high magnification **(B)**. (**A**: ×5000; **B**: ×20,000.)



B

FIGURE 7.30 (*Continued*)

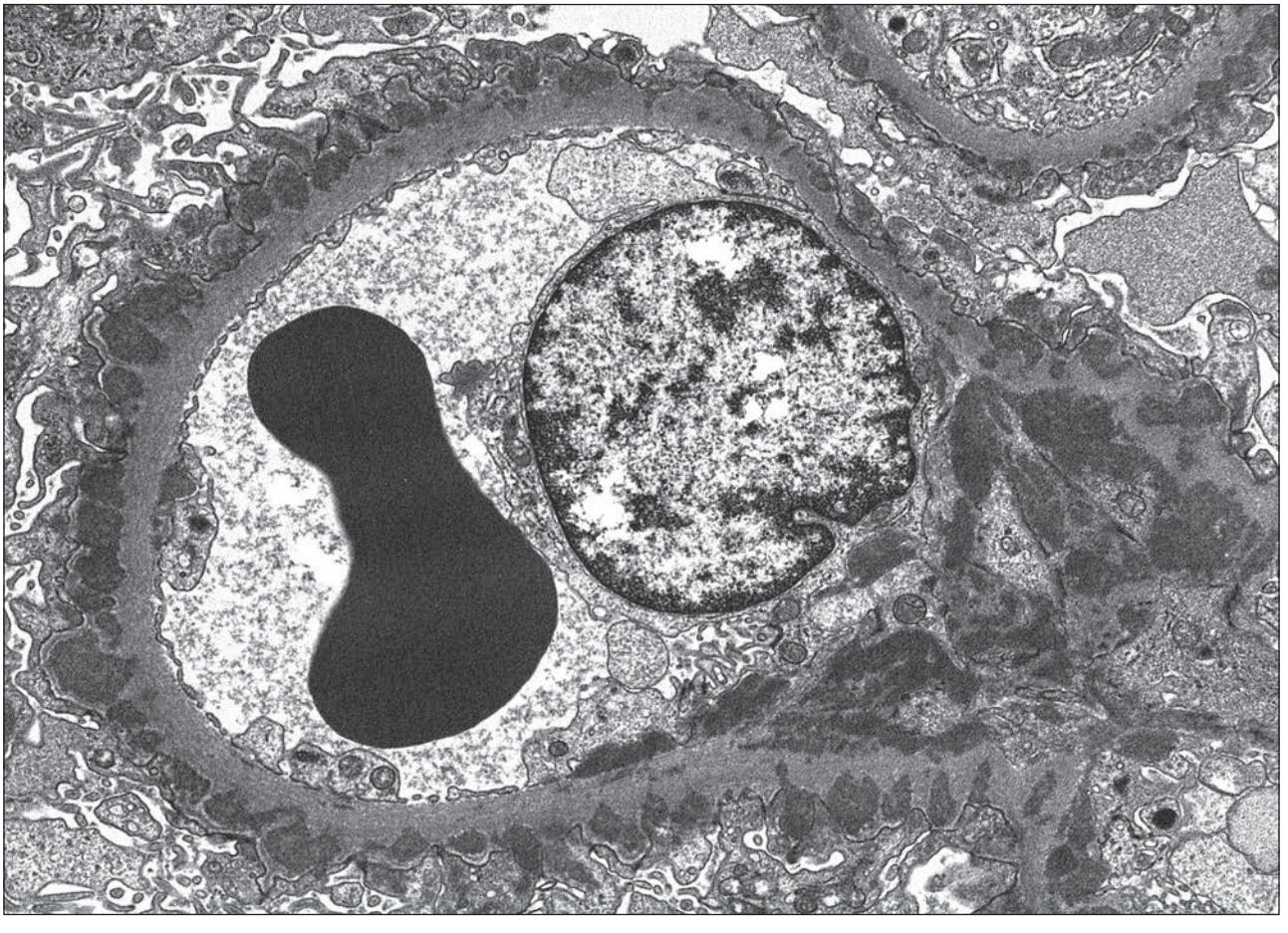


FIGURE 7.31 **Mesangial deposits in MGN.** In this example of MGN, electron-dense deposits are seen within the mesangial matrix and focally extend into the subendothelial region. The patient was later found to have systemic lupus erythematosus. (×6000.)

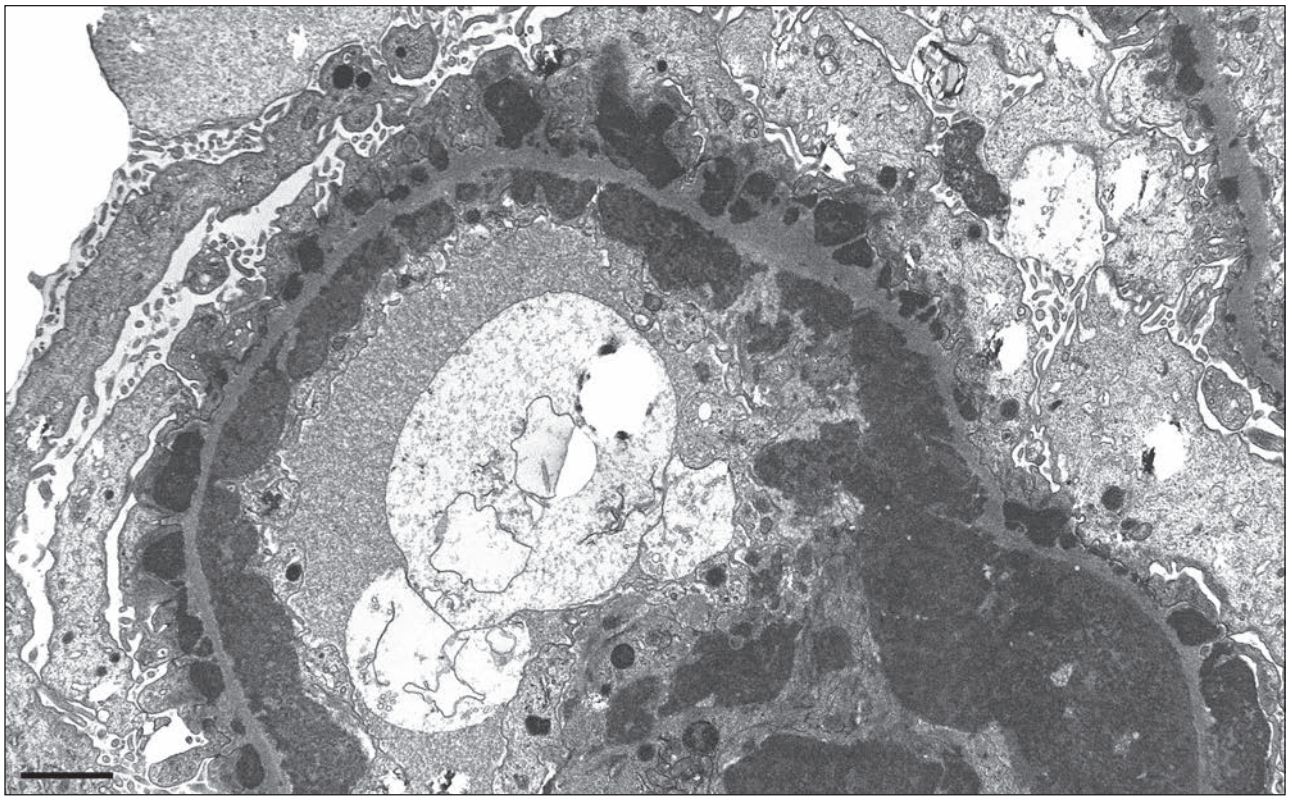


FIGURE 7.32 Subendothelial deposits in MGN. Prominent global subendothelial deposits are seen in this example of MGN. On subsequent evaluation, the patient was found to have systemic lupus erythematosus. (×8000.)

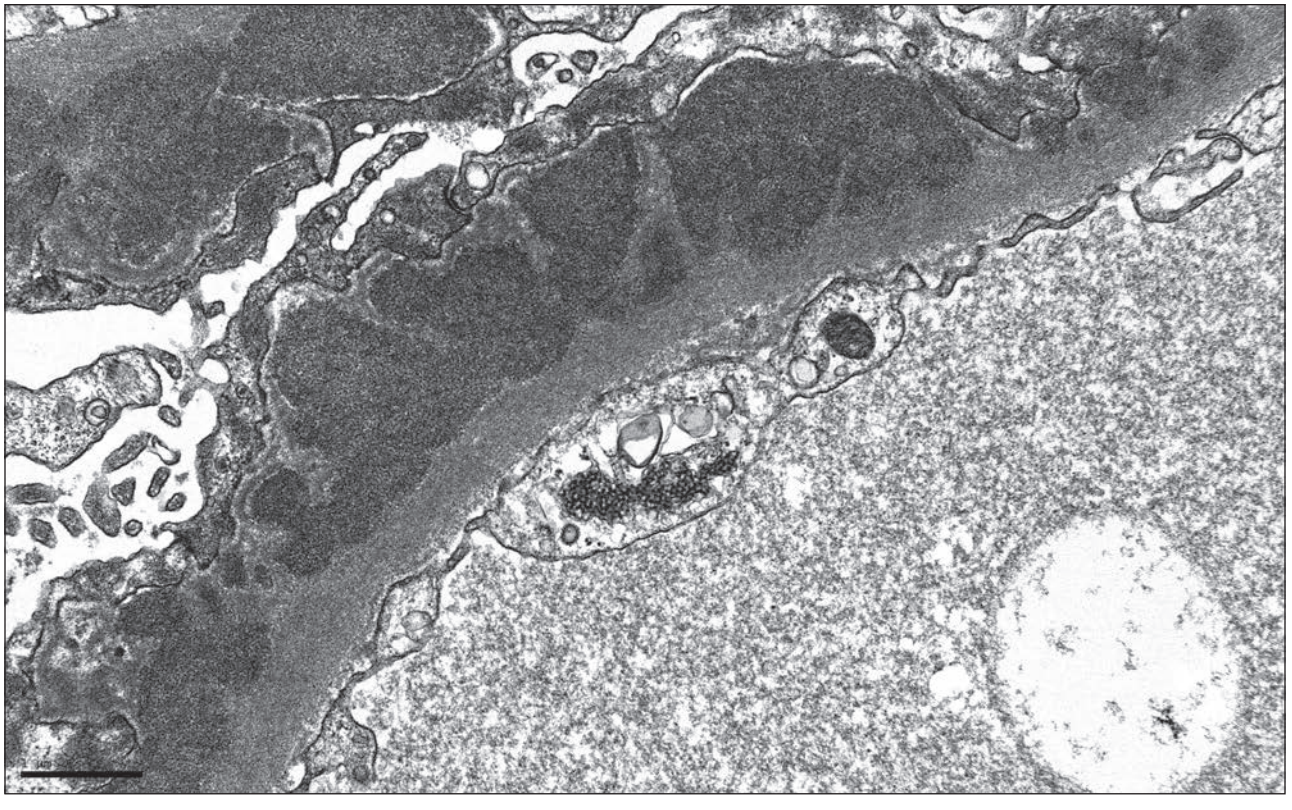


FIGURE 7.33 Endothelial tubuloreticular inclusions in MGN. The finding of an endothelial tubuloreticular inclusion in a patient with MGN should prompt evaluation for possible SLE or HIV infection. (×20,000.)

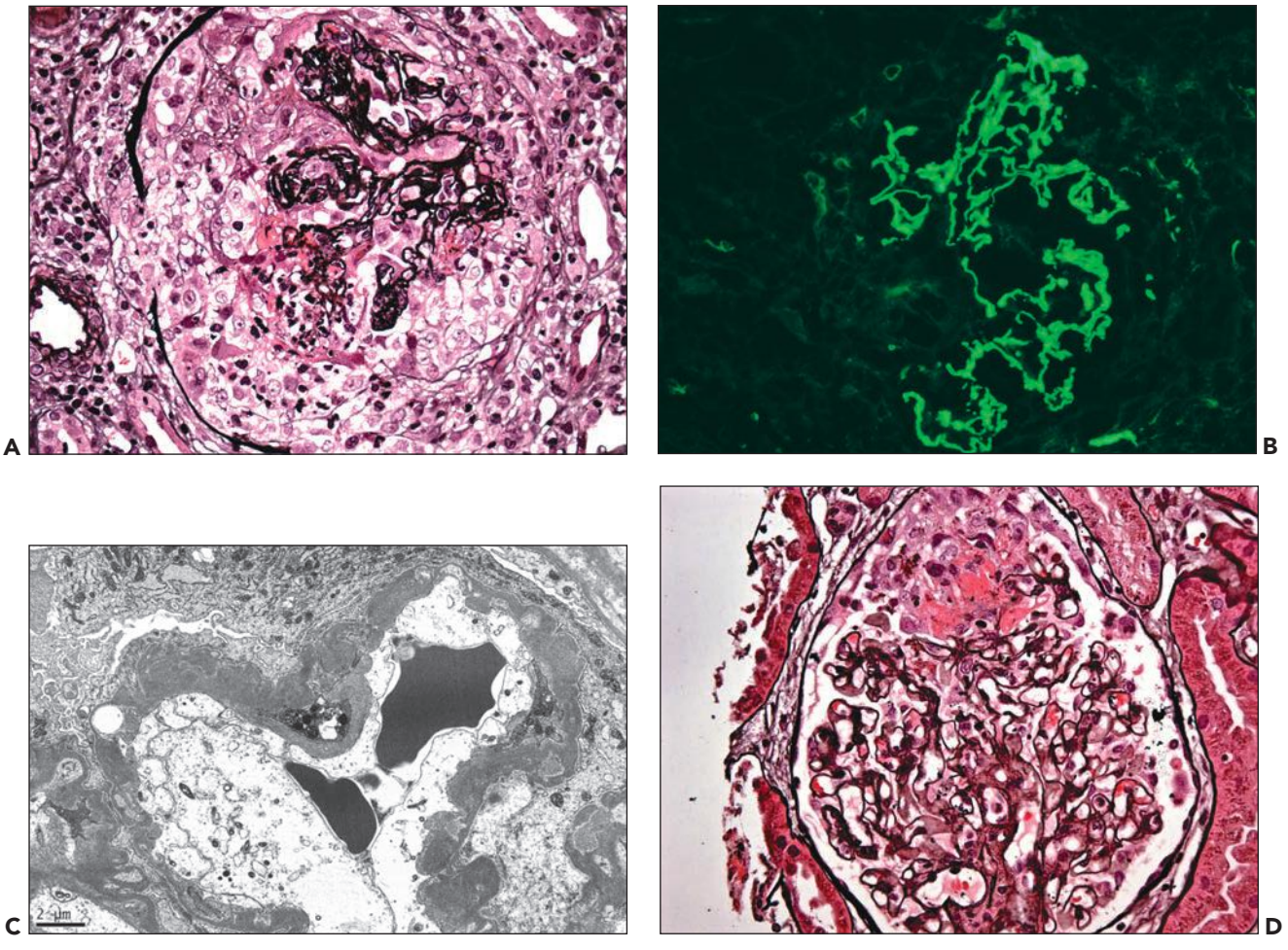


FIGURE 7.34 Combined membranous and crescentic glomerulonephritis. Images **(A)** to **(C)** are taken from the same biopsy. **A:** The glomerular tuft is compressed by a circumferential cellular crescent that extends through Bowman capsule and is associated with fibrinoid necrosis and multifocal GBM rupture. **B:** Immunofluorescence staining for IgG reveals intense linear positivity within the glomerular basement membranes (GBMs) that appear focally ruptured. The patient was subsequently found to have a high-titer anti-GBM antibody. Careful examination of the texture of the deposits suggests an additional layer of delicate granular staining above the linear staining. **C:** An electron micrograph from the same patient demonstrates stage III changes of MGN in this patient with combined MGN and anti-GBM disease. **D:** Fibrinoid necrosis, GBM rupture, and a segmental cellular crescent are seen in a biopsy from a patient with MGN, systemic vasculitis, and ANCA seropositivity. (**A:** JMS, ×400; **B:** IgG, ×400; **C:** electron micrograph × 6000; **D:** JMS, ×400.)

mother was found to have circulating antibodies that bound to both the proximal tubular brush border and podocytes. These antibodies were not present in maternal serum prior to the miscarriage, were seen at 3, 5, and 7 months of the current gestation, were noted in the infant's serum at 13 days after birth, and were no longer present at day 40. Subsequent studies showed that the antibodies were targeted against neutral endopeptidase (NEP). The mother was NEP deficient (with no apparent abnormal phenotype); she developed anti-NEP antibodies during the first pregnancy, which ended in miscarriage, and these antibodies were the basis for the development of antenatal MGN in the second pregnancy. Notably, injection of the mother's serum into rats produced MGN. Thus, NEP became the first human podocyte antigen shown to serve as a target antigen in a rare inherited form of MGN (137).

NEP is a zinc-dependent metallopeptidase with a diffuse organ distribution. Also referred to as CD10, common acute lymphoblastic leukemia antigen (CALLA), and matrix metalloendopeptidase (MME), NEP is thought to play a role in peptide cell signaling at the cell surface (138–140). Importantly, NEP is expressed in renal proximal tubular epithelial cells and podocytes, a pattern of distribution identical to megalin/gp330 in the rat (137). Following the initial report of congenital nephrotic syndrome due to transplacental transfer of anti-NEP antibodies, two similar cases were uncovered (141). Studies on the three kindreds showed that all cases were associated with truncating mutations of the *MME* gene for NEP, demonstrated variable disease penetrance that appeared to correlate with the maternal immune response to NEP, and provided further evidence that NEP deficiency is not associated with an apparent phenotype in humans (141).

M-type Phospholipase A_2 Receptor as a Human Target Antigen

A breakthrough in our understanding of MGN came in 2009 when Beck et al. (5) identified the major human Heymann antigen. Serum samples from 37 patients with primary MGN were run on Western blot against homogenates of normal human kidneys under nonreducing conditions, and a 185-kDa protein band was identified in 26 patients (70%). This band was not present in the serum from 30 normal control patients, 15 patients with other causes of nephrotic syndrome, or 8 patients with secondary etiologies of MGN. Using mass spectrometry and available antibodies, the highly glycosylated 185-kDa protein was identified as the M-type PLA_2R (5). Further studies showed that the anti-PLA_2R antibodies are specific for a conformation-dependent epitope and that PLA_2R is expressed on the surface of podocytes but is not present in the circulation in patients with primary MGN, supporting a mechanism of in situ immune complex formation. In biopsies with primary MGN, PLA_2R colocalizes with IgG4 in the distribution of the subepithelial deposits and, when eluted, the IgG4 binds to recombinant PLA_2R. Finally, anti-PLA_2R serum antibody levels correlate with the degree of proteinuria in patients with primary MGN. Taken together, these landmark studies have established PLA_2R as the human Heymann antigen in most cases of primary MGN (5).

PLA_2R is a transmembrane glycoprotein expressed on the surface of podocytes, type II pneumocytes, and a subset of splenic lymphocytes (142). It has a large N-terminal cysteine-rich extracellular domain and a short intracellular C-terminal region. Binding to PLA_2R by secretory PLA_2 leads to activation of multiple biologic responses including cell proliferation, migration, and cytokine production (142).

Multiple additional studies have confirmed the central role of anti-PLA_2R antibodies in the pathogenesis of primary MGN (70,143–148). Fourteen of eighteen European patients with primary MGN (78%) were found to have IgG4 anti-PLA_2R antibodies, and serum antibody levels correlated with disease activity, declining during periods of remission and increasing with relapse (146). In another European cohort, 24 of 42 patients (57%) had circulating anti-PLA_2R antibodies (70). In a Chinese cohort, 49 of 60 patients (82%) with primary MGN were found to have circulating anti-PLA_2R antibodies, and antibody levels correlated with disease activity (147). In this study, the specificity of anti-PLA_2R antibodies for primary MGN was only 89% because antibodies were also detected in rare cases of MGN associated with HBV infection, SLE, or malignancy (147). Anti-PLA_2R antibodies are present in patients who develop recurrent MGN in the allograft, although not all patients with serologic activity experience a disease recurrence (144,145,148), and anti-PLA_2R antibodies are absent in transplant patients who develop de novo MGN (145). The ability of rituximab to inhibit production of anti-PLA_2R antibodies predicts treatment response in MGN, and the decline in serum levels of anti-PLA_2R antibodies precedes the remission in proteinuria (143).

Anti-PLA_2R antibodies can also be detected within the subepithelial deposits of renal biopsy specimens from patients with primary MGN (70–73) (Fig. 7.35). In one study from Germany, 61 of 88 patients with biopsy-proven MGN had strong immunohistochemical reactivity for PLA_2R within glomeruli (69.3%) (71). In this study, 60 of the 61 patients had serologic evidence of anti-PLA_2R antibodies, while none of the remaining 27 with negative staining had serologic positivity, indicating excellent correlation between the two modalities (71). Antibodies against PLA_2R were of the IgG1, IgG2, IgG3, and IgG4 subclass, with IgG4 antibodies present in all patients. The investigators noted that faint staining for PLA_2R also was present in normal kidneys and must be differentiated from the more intense staining seen in primary MGN. Debiec and Ronco found sensitivities of 57% and 74% for serum and biopsy testing for anti-PLA_2R antibodies, respectively. In this study, 10 of the 31 patients with identifiable anti-PLA_2R antibodies within the biopsy had no evidence of serologic activity, raising the possibility that testing was performed during a period of serologic inactivity (70). It is more difficult to explain the 3 of 24 patients with serum anti-PLA_2R antibodies but no evidence of anti-PLA_2R antibody staining in the renal biopsy (70). Larsen et al. (72) performed immunofluorescence staining for PLA_2R on 165 biopsies with MGN, including 85 with primary and 80 with secondary forms of MGN, and found that positive staining had a sensitivity of 75% and specificity of 83% for the diagnosis of primary MGN. In this study, data on serum testing for anti-PLA_2R antibodies were not provided. A study from the Czech Republic on 66 patients with primary MGN found anti-PLA_2R antibodies in the serum of 65% of patients and detected PLA_2R in the subepithelial deposits in 69% (73). There was excellent correlation between serologic testing and immunofluorescence staining, although there were three patients with positive staining for PLA_2R but no evidence of serologic activity and one patient with detectable anti-PLA_2R in the serum but negative immunofluorescence (73).

The observation that serum anti-PLA_2R antibodies are present in approximately 75% of patients with primary MGN raises questions about why it is not detectable in the remaining 25% of patients. There are several potential explanations. First, some of these cases may represent an unrecognized

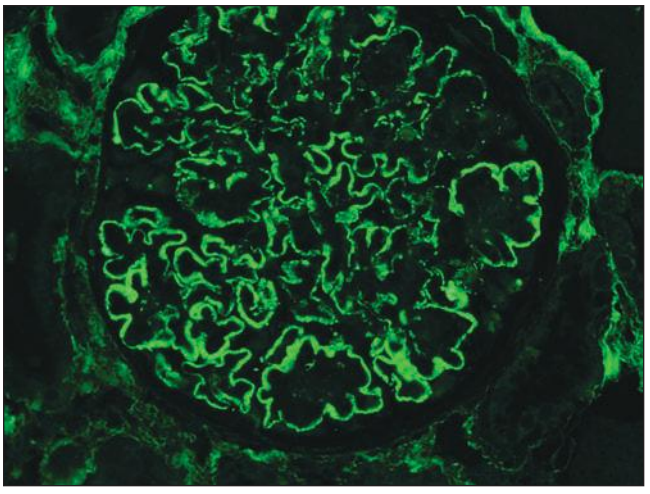


FIGURE 7.35 PLA_2R staining in MGN. Granular global positivity for PLA_2R in the distribution of subepithelial deposits confirms the diagnosis of primary (anti-PLA_2R–associated) MGN in this patient with negative serologies and no evidence of systemic disease. (×400.)

secondary form of disease. Second, it has been proposed that a significant proportion of such patients have anti-PLA_2R–associated MGN but no evidence of immunologic activity at the time of testing (70,71,149,150). This is supported by the observation that in patients with primary MGN who are entering remission, proteinuria persists beyond the time period when anti-PLA_2R antibodies are seen (149), as well as the fact that anti-PLA_2R antibodies may be identified in glomeruli in the absence of serologic activity (70,73). A third consideration is that some of these cases may represent primary MGN associated with an alternative podocyte target antigen, such as aldose reductase (AR), superoxide dismutase (SOD2), or α-enolase (α-ENO) (151–153). In patients with MGN, IgG4 antibodies against AR, SOD2, and α-ENO have been reported in 34%, 28%, and 43% of patients, respectively, including approximately half of the patients who did not have evidence of anti-PLA_2R antibodies (152). It should be noted that the specificity of these antibodies for MGN is considerably less than anti-PLA_2R (152), and it has been suggested that these may represent secondary phenomena related to oxidative stress (150).

Another critical question concerns the significance of anti-PLA_2R antibodies in patients who appear to have a secondary form of disease (147). Svobodova et al. (73) performed immunofluorescence staining for anti-PLA_2R antibody on 19 biopsies with presumed secondary forms of MGN and found positive staining in both patients with HBV infection and the single patient with sarcoidosis but none of the 16 patients with SLE. Another study that included patients with presumed secondary forms of MGN revealed anti-PLA_2R antibody staining in 7 of 11 patients with HCV infection, 3 of 4 patients with sarcoidosis, 3 of 12 patients with cancer, and 1 of 46 patient with autoimmune disease (most commonly SLE) (72). Among the anti-PLA_2R–positive "secondary" forms of MGN, tissue was available in two patients each with HCV, carcinoma, and sarcoidosis. In all six cases, the predominant IgG subtype in the deposits was IgG4, providing evidence in favor of primary MGN with coincidental HCV, carcinoma, or sarcoidosis (72). Anti-PLA_2R antibodies have also been detected in the subepithelial deposits of a patient with MGN occurring in the setting of allogeneic hematopoietic stem cell transplantation (SCT) (154) but in another series were absent in all 25 patients with MGN secondary to SLE (i.e., membranous LN) (155). The significance of anti-PLA_2R antibody positivity in patients with presumed secondary causes of MGN remains unclear. If anti-PLA_2R antibody is determined to define primary MGN, which appears quite possible given its high sensitivity and specificity, then such cases could be interpreted as a chance concurrence of two unrelated disease processes, for instance primary MGN in a patient with unrelated HCV infection. Another unresolved question is whether serologic testing for anti-PLA_2R antibody might obviate the need for renal biopsy in selected patients presenting with idiopathic nephrotic syndrome. Immunostaining for PLA_2R on frozen or paraffin tissue is already being performed by many renal pathology laboratories and is likely to gain more widespread use for identification of primary MGN.

Recent genetic studies have contributed to our understanding of the pathogenesis of primary MGN (156–158). A large genome-wide association study (GWAS) examined single nucleotide polymorphisms in more than 500 European patients of Caucasian ancestry with primary MGN and found significant linkage to two loci, the PLA_2R1 gene on chromosome 2q24 and the HLA-DQA1 gene on 6p21 (158). While these results affirm the critical role of PLA_2R1, the linkage to HLA-DQA1 provides further support for the concept that primary MGN is an organ-specific autoimmune antibody–mediated disease (158). There is also strong evidence that single nucleotide polymorphisms within the PLA_2R1 gene are associated with increased disease susceptibility (156–158). The triggers for this autoimmune response remain unclear. One possibility is cross-reactivity of PLA_2R1 with exogenous antigens, as has been documented with molecular mimicry of bacterial antigens in pauci-immune necrotizing and crescentic glomerulonephritis (159). Because primary MGN typically has its onset in adults, a role for age-dependent conformational changes in target epitopes has also been proposed.

Pathogenesis of Secondary Forms of MGN

In contrast to primary MGN, the pathogenesis of secondary forms of MGN is likely to involve immune responses to nonglomerular antigens that are derived from and specific to the etiologic agent. For instance, tumor antigens, infectious pathogens, and nuclear autoantigens have been documented within the subepithelial deposits in secondary MGN related to neoplasia (160), hepatitis B infection (161), and SLE. This is likely to occur by one of two mechanisms. First, small, cationic target antigens may become planted on the subepithelial aspect of the GBM and then bind in situ to the circulating specific antibody that crosses the GBM. Alternatively, there may be circulating low-affinity antigen-antibody complexes that dissociate within the glomerulus, diffuse across the GBM, and reform in the subepithelial region.

Early childhood MGN secondary to cationic bovine serum albumin (BSA) has recently been described. In this uncommon form of secondary MGN, the target antigen is a dietary protein present in cow's milk (162). Four children with MGN between the age of 5 months and 2.3 years were found to have elevated serum levels of cationic BSA, high-titer IgG1 and IgG4 anti-BSA antibodies (specific for epitopes that are distinct from human serum albumin), and glomerular subepithelial immune deposits composed of colocalizing BSA and anti-BSA antibodies, in the absence of PLA_2R (162). All four children eventually entered remission, at which time a marked decrease in serum cationic BSA and anti-BSA antibody levels was noted. These findings are supported by previous studies showing that injections of cationic BSA, but not anionic BSA, can induce MGN in New Zealand white rabbits (163).

Another rare secondary form of MGN was identified in a child with Pompe disease who developed MGN while undergoing treatment with recombinant human acid alpha-glucosidase (rhGAA) (164). As the infant developed anti-rhGAA antibodies, escalating doses were administered, followed by the development of MGN with subepithelial immune deposits containing rhGAA. When the rhGAA dose was decreased, the nephrotic syndrome remitted.

Tubular and Interstitial Injury in MGN

In MGN, the degree of interstitial fibrosis and tubular atrophy (IFTA) correlates with renal function at the time of biopsy and carries prognostic significance (165). There are multiple

mechanisms of tubulointerstitial injury in MGN. As in other glomerular diseases, glomerulosclerosis in chronic MGN can cause ischemic and functional atrophy of the dependent tubule. Even in early stages of disease, exposure of the tubule to high levels of filtered protein can mediate IFTA through complex cellular mechanisms. Protein overload of the proximal tubules is directly toxic and induces tubular chemokine synthesis and complement activation (166,167). Specifically, tubules synthesize RANTES (168) and monocyte chemoattractant protein-1 (MCP-1) (169), which leads to local recruitment of monocytes/macrophages and T cells. The monocytes/macrophages in turn elaborate fibrogenic cytokines such as TGF-β. TGF-β stimulates fibroblast recruitment, promotes interstitial collagen deposition, and stimulates tubular epithelial to mesenchymal transformation (EMT). EMT is a process whereby tubular epithelial cells decrease production of epithelial proteins such as E-Cadherin, increase production of mesenchymal proteins such as α-smooth muscle actin and fibroblast-specific protein-1 (FSP-1), undergo a phenotypic transformation to a fibroblastoid appearance, and develop an ability to migrate and synthesize collagen (166,167,170,171). The mechanisms by which proteinuria promotes IFTA in MGN are considered applicable to many forms of progressive renal disease (172,173) and provide the rationale for use of angiotensin-converting enzyme (ACE) inhibition to reduce proteinuria and allay progression in all proteinuric glomerulopathies (174).

Differential Diagnosis

From a clinical standpoint, the main differential diagnostic considerations for an adult patient presenting with nephrotic syndrome includes MGN, minimal change disease, FSGS, diabetic glomerulosclerosis, and amyloidosis, all of which are covered in other chapters. In general, these entities are easily distinguished by integrating the findings by light microscopy, immunofluorescence, and EM.

From the viewpoint of pathology, the light microscopic, immunofluorescence, and electron microscopic findings in MGN each have a separate differential diagnosis but when all three are integrated, the diagnosis of MGN is usually easy to establish. For instance, the light microscopic finding of GBM thickening raises a differential diagnosis of MGN, diabetic glomerulosclerosis, hypertensive arterionephrosclerosis, and the Strife and Anders variant of MPGN type 3, the last of which may exhibit vacuolated appearance of the GBM with the JMS stain that can resemble stage III changes of MGN (175,176). By immunofluorescence, the findings in MGN are relatively specific in that there is granular capillary wall staining that typically spares the mesangium and is consistently dominant or codominant for IgG. Nonetheless, codominant capillary wall staining for IgG and C3 can be seen in multiple entities, for instance MPGN types I and III, LN, fibrillary GN, cryoglobulinemic GN, and immunotactoid glomerulopathy. The ultrastructural finding of subepithelial electron-dense deposits with intervening GBM spikes is relatively specific for MGN. In some instances, the subepithelial deposits may be more widely separated and devoid of spike formation, raising the alternative diagnostic possibility of acute postinfectious glomerulonephritis (APIGN). In this instance, the absence of hypocomplementemia, a history of recent infection, or light microscopic findings of endocapillary proliferation with neutrophil infiltration are helpful in establishing the diagnosis of MGN. Nonetheless, some examples of early MGN may be difficult to distinguish from resolving APIGN. There are also cases in which light microscopy and immunofluorescence are typical of MGN, but EM reveals diagnostic features of fibrillary glomerulonephritis or immunotactoid glomerulopathy (96,98–101).

The Burkholder subtype of MPGN type 3 is characterized by GBM duplication with mesangial interposition, akin to changes in MPGN type 1, accompanied by changes more typical of MGN including subepithelial electron-dense deposits with intervening GBM spikes (37) (covered in greater depth in Chapter 8). In some instances, findings of MGN may predominate with only subtle and segmental membranoproliferative changes. Our approach is to reserve the diagnosis of MPGN type 3, Burkholder subtype, for cases in which at least segmental membranoproliferative features are seen in 25% or more of glomeruli. Importantly, the findings of mixed membranous and membranoproliferative changes should prompt testing for HBV, HCV, and SLE.

Given the relatively distinctive findings in MGN, it is usually a greater challenge to exclude secondary forms and variants of MGN than it is to differentiate MGN from an alternative glomerular disease. As previously noted, mesangial proliferation, endocapillary proliferation, mesangial deposits, subendothelial deposits, extraglomerular deposits, "full house" staining by immunofluorescence, and the finding of endothelial tubuloreticular inclusions suggest a secondary form of disease, most often membranous LN (14,33). Some of these features are also encountered in secondary MGN related to HBV infection (32).

Clinical Course

The course of primary MGN is influenced by presenting clinical parameters, severity of pathologic findings, and efficacy of immunosuppressive therapy. In 1975, Row et al. (12) reviewed 12 published series on MGN with available follow-up for 5 years or until death. Among 435 adults with MGN, 82 (19%) died of renal failure and 69 (16%) entered remission (12). A better prognosis was found in the 82 children (defined as less than 15 years of age) with MGN, among which 4 died (4%) and 40 (49%) entered remission (12). A similar analysis by Cameron in 1979 suggested that the remission rate in MGN is approximately 20% at 5 years, 25% at 10 years, and 30% at 15 years (177). In contrast, the end points of death or ESRD are reached by fewer than 10% of patients at 5 years, 30% at 10 years, and 50% at 15 years (177). The percentage of patients with persistent proteinuria and/or nephrotic syndrome progressively declines from greater than 70% at 5 years to 45% at 10 years to 20% at 15 years (177). In a French cohort of 116 adult patients with MGN followed for mean 4.5 years, the 10-year actuarial survival was 76% (178).

More recent studies have provided similar data on the clinical course of primary MGN. Donadio et al. (10) examined 140 patients with MGN at the Mayo Clinic and found that the combined end point of death or ESRD was reached by 29% of patients at 5 years and 42% at 10 years. Wehrmann et al. (46) reviewed 334 cases of MGN in Germany and described renal survivals of 88% at 5 years and 77% at 10 years. Schieppati et al. (179) evaluated 100 consecutive patients in Italy with MGN and found that 12% of patients reached ESRD at 5 years and 27% at 8 years. In this study, approximately 30% of patients had a spontaneous complete remission at 5 years

(179). Cattran et al. followed 77 patients with MGN and found that at 36 months, 19 patients had a spontaneous complete remission (25%) and 5 reached the combined end point of death or ESRD (6.5%) (180). In this study, outcomes were nearly identical for the 77 untreated patients and the 81 patients treated with a 6-month course of alternative day prednisone (180). Based on this study (180) and multiple earlier studies (10,12,46), there is general agreement that prednisone monotherapy is not effective in the treatment of MGN.

Several generalizations can be made from the wealth of clinical data. MGN is usually an indolent disease that progresses slowly so that even when renal insufficiency develops, it often takes years to reach end stage. In general, the rule of one thirds applies, that is, at 10 years of follow-up, approximately one third of patients spontaneously remit, one third progress to ESRD, and one third remain proteinuric, often with associated renal insufficiency (181). The majority of the one third of patients with persistent proteinuria at 10 years will progress over the subsequent 10 years (177). The high rate of spontaneous remission underscores the importance of identifying prognostic factors that could spare this subgroup from unnecessary immunosuppressive therapy. The relatively indolent disease course, even among patients who progress to ESRD, highlights the need for clinical trials with larger cohorts and extended follow-up.

Prognosis

At the time of diagnosis, patients with primary MGN are assessed for clinical and pathologic factors that predict outcome (Table 7.3). Based on these predictors, treatment with either conservative therapy alone or one of several immunosuppressive regimens can be tailored to the individual patient. In this section, pathologic and clinical prognostic factors are considered separately.

TABLE 7.3 Negative pathologic and clinical prognostic factors in primary MGN

Light microscopy
Degree of IFTA
Presence of FSGS
Degree of arteriosclerosis
Presence of mesangial sclerosis
Percentage of globally sclerotic glomeruli
Immunofluorescence
Intensity of staining for C3
Electron microscopy
Heterogeneous electron-dense deposits
Clinical parameters at the time of presentation
Serum creatinine
24-h urine protein
Older age
Male gender
Rising serum anti-PLA_2R antibody titer
Hypertension
Nonselectivity of proteinuria
Clinical parameters at subsequently follow-up
Absence of complete or partial remission
Degree and duration of proteinuria
Serum creatinine

Italics indicate best established prognostic factors.

Pathologic Prognostic Factors in MGN

IFTA have consistently been shown to correlate with outcome in MGN (28,45,46,86,165,178,182–185) and is generally considered a stronger outcome predictor than any other pathologic feature (45,46,165,183,185). Furthermore, in one study, the degree of IFTA was a better outcome predictor than was the degree of proteinuria (46). The reasons for this strong correlation are incompletely understood. A standard renal biopsy may contain anywhere from 5 to 20 glomeruli, but within the biopsy, there is representation of tubules from a far greater number of nephrons. Thus, IFTA may provide a more precise assessment of total nephron injury than the percentage of sclerotic glomeruli. In addition, IFTA likely reflect the component of progressive tubulointerstitial injury resulting from unremitting proteinuria itself that may occur in the absence of glomerulosclerosis (172,173).

Lesions of FSGS are present in approximately 20% of cases of MGN and are widely accepted as negative prognostic indicators (39–42,182). Among patients with MGN, the finding of FSGS is also linked to higher levels of proteinuria (39,42), a greater degree of IFTA (39–42), and a higher stage of MGN (40,41). The prognostic significance of FSGS likely involves critical levels of podocyte injury that eventuate in podocyte depletion in the course of progression to global glomerulosclerosis. It is unclear why the presence of FSGS has received significantly more attention in the literature than the percentage of glomeruli that are globally sclerotic. In at least one study on FSGS in MGN, the percentage of obsolete glomeruli also carried prognostic significance (41), while in another, there was no difference in the extent of global glomerulosclerosis between MGN patients who did and did not exhibit FSGS (42).

The degree of *arteriosclerosis* and the presence of *mesangial sclerosis* in MGN are additional light microscopic findings that have been reported to carry a poor prognosis (8,165,184,186). A single study has suggested that Bowman capsular lesions also have a negative impact, although the description of this finding appears to overlap with FSGS (184). The finding of cellular crescents undoubtedly influences prognosis in MGN, but due to the rarity of this finding, prognostic data are not available.

The *intensity of staining for C3* by immunofluorescence has been reported to be of prognostic significance in MGN (8,187). In a small study on 16 patients with MGN, the presence of C3 staining was associated with a greater degree of proteinuria (187). In a larger study that included 389 adult patients with MGN, the intensity of C3 staining correlated with the degree of proteinuria and was the single light microscopic, immunofluorescence, or ultrastructural finding that correlated with the rate of decline in renal function, although it did not predict renal survival (8).

Ultrastructural findings play a limited role in predicting prognosis in MGN. As discussed previously, whereas the Ehrenreich and Churg (27) staging of MGN has provided important insights into disease evolution, the progression to a higher stage does not necessarily correlate with clinical improvement or worsening. While some studies suggest that a higher stage of MGN is associated with decreased renal survival (46,182), the majority of studies suggest a lack of

prognostic significance (12,87–90). In contrast to staging, the ultrastructural finding of homogeneous, synchronous deposits has been reported to have a superior prognosis as compared to heterogeneous deposits (91). The proposed explanation is that homogeneous deposits may represent a single stage of deposit formation, while heterogeneous deposits suggest multiples phases of deposition (91). In a recent study on 389 patients with MGN, the finding of homogeneous deposits was associated with a higher rate of initial remission but, due to a high relapse rate, did not predict renal survival (8).

Clinical Prognostic Factors in MGN

Similar to most glomerular diseases, the most reliable prognostic factors in MGN are *renal function* and the *degree of proteinuria*. The majority of patients with MGN are initially diagnosed at a time when renal function is relatively intact, as demonstrated by a mean creatinine of 1.08 mg/dL and a mean creatinine clearance of 88 mL/min/1.73 m^2 in six large databases from five different countries (7–10,16). Within these series, renal insufficiency was noted in roughly 25% of patients at the time of presentation (7–10). Renal insufficiency at the time of renal biopsy is a significant risk factor for progressive disease in patients with MGN (8,10,12,46,165,182–184,188–190). That said, many of the patients with initially intact renal function will ultimately progress, which limits the utility of the initial assessment of renal function in predicting long-term outcome.

Assessment of 24-hour urine protein excretion is the single best predictor of outcome in patients with MGN (9,10,165,182,186,189,191). In 1988, Donadio et al. (10) documented progressively worse outcomes in patients with an initial 24-hour urine protein of 0 to 3.4 g/d, 3.5 to 10 g/d, and greater than 10 g/d, with a *P* value of less than 0.001 for the comparison between the latter two groups. Multiple additional studies have also demonstrated the prognostic significance of proteinuria (165,182,186) and/or surrogates of proteinuria including hypoalbuminemia (165,182), hypercholesterolemia (165,184), and the presence of full nephrotic syndrome (10,165,190). In 1992, Pei et al. (189) examined data on 184 patients with MGN from the Toronto Glomerulonephritis Registry and found that the initial assessment of proteinuria was of limited prognostic import but that a combined assessment of duration and quantity of proteinuria carried a high positive predictive value for the development of chronic renal insufficiency. More precisely, a 24-hour urine protein of more than 4 g/d for 18 months, more than 6 g/d for 9 months, or more than 8 g/d for 6 months was associated with more than doubling of risk for the development of chronic renal insufficiency (189). These results were subsequently validated in cohorts of patients with MGN in Finland and Italy (9).

Not surprisingly, subnephrotic proteinuria has a more favorable prognosis in MGN. In 2009, Hladunewich et al. (191) reexamined the Toronto Glomerulonephritis Registry and found that 108 of 395 patients with MGN (27%) presented with subnephrotic proteinuria. Among these patients, 42 (40%) remained subnephrotic over a mean of 55 months of follow-up. The remaining 56 patients developed nephrotic-range proteinuria that, in 70% of patients, occurred within 12 months (191). The rate of progression (i.e., the slope of the decline in creatinine clearance) was –0.93 mL/min/y in the patients who remained subnephrotic, –3.52 mL/min/y in patients who went from subnephrotic to nephrotic range, and –4.76 mL/min/y in the 73% of patients who presented initially with nephrotic syndrome (191). These findings suggest that lower levels of proteinuria are prognostically favorable and that assessment of degree and duration of proteinuria is more important than quantitation alone.

Although this information is unknown at the time of diagnosis, the strongest predictor of long-term outcome in MGN is attainment of a complete or partial remission (192,193). Troyanov et al. (193) examined long-term outcomes in 348 patients with MGN and found that a complete or partial remission, regardless of whether it occurred with or without immunosuppressive therapy, carries greater prognostic significance than any clinical factor at the time of presentation, including initial 24-hour urine protein or serum creatinine. Polanco et al. (192) employed conservative management in 328 patients with MGN and found that 104 patients (31.7%) had a spontaneous complete or partial remission. Over a mean of 69 months of follow-up, only 6 patients (5.7%) had a relapse of nephrotic syndrome and none of the patients reached ESRD, as compared to 18.7% of the 224 patients who did not enter remission (192).

Additional clinical factors influence prognosis in MGN (194). MGN has a more favorable prognosis in females than in males (10,179,183,188,190,195). In a study by Hopper et al. (195) on a series of 100 patients with MGN, 3 of 35 (8.6%) female patients reached ESRD, as compared to 28 of 65 (43.1%) males ($P = 0.006$). MGN has a worse prognosis in adults than in children (12,15,196), and among adults, advanced age is a negative prognostic marker (8,179,183,190). In particular, two studies have shown that the risk of progression appears to increase specifically in patients above the age of 60 years (183,190). MGN may have a more favorable course in patients who are of Japanese descent (183). Hypertension in general is thought to have an adverse impact on outcome in glomerular and other forms of renal disease, but its effect in MGN is likely to be small in that some studies report an adverse effect (8,46,195), but others do not detect an impact (10,179,184). Other, more recent studies suggest that hypertension correlates with outcome but does not have an impact independent of proteinuria and serum creatinine (86,189). In the setting of MGN, urinary findings that have a negative impact on prognosis include nonselective proteinuria and higher urinary levels of IgG and beta-2-microglobulin (197–199). Not surprisingly, serum anti-PLA_2R antibody levels also carry prognostic significance, as declining levels often coincide with entry into clinical remission (143,200).

Treatment of MGN

Optimal therapy for MGN is a complex topic that is beyond the scope of this chapter and is the subject of multiple recent, excellent reviews (194,201–204). Nonetheless, some important points emerge and merit emphasis. First, supportive measures that are beneficial to patients with MGN include ACE inhibition (205,206), blood pressure control, the use of statins for hyperlipidemia (7,207,208), and dietary protein restriction (209). Second, there is significant risk for thromboembolism in more severely nephrotic and hypoalbuminemic patients with MGN, although guidelines regarding the use of anticoagulation in select patients remain highly controversial (207,210). Third, monotherapy with corticosteroids is not an effective treatment for MGN (211). Fourth, given the lack of efficacy of corticosteroids, careful assessment of clinical and pathologic

risk factors for progression is necessary to determine which patients have a risk-to-benefit ratio that justifies more aggressive immunosuppressive therapy.

Two main immunosuppressive protocols are most extensively used in the treatment of primary MGN. In 1984, Ponticelli et al. (212) described a 6-month protocol consisting of intravenous (IV) pulse methylprednisolone following by oral prednisone in months 1, 3, and 5, alternating with oral chlorambucil during months 2, 4, and 6. With this treatment, which has subsequently been referred to as the "Ponticelli protocol," 23 of 32 (71.9%) treated patients were in complete or partial remission, compared to 9 of 30 patients (30%) in the control group at a mean follow-up of 31 months ($P = 0.001$) (212). This randomized controlled trial was subsequently expanded to 81 patients, and similar, beneficial effects of treatment were seen at 5 and 10 years of follow-up (213,214). Specifically, at 10 years, the probability of surviving without ESRD was 92% in the treatment group versus 60% in the control group ($P = 0.0038$) (214). At the last follow-up, 61.9% of patients in the treatment group were in complete or partial remission, as compared to 33.3% of patients in the control group (214). Similar beneficial effects of this protocol, or with cyclophosphamide substituted for chlorambucil, have been seen in subsequent studies although there continues to be reluctance to use this regimen due to short- and long-term side effects of alkylating agents including myelosuppression, hemorrhagic cystitis, infertility, and malignancy (204,215).

The second widely employed regimen consists of 6 months of cyclosporine with low-dose prednisone (216). In 2001, Cattran et al. used this regimen in a randomized controlled trial of 51 patients with MGN. At the conclusion of 6 months, a complete or partial remission was achieved in 75% of treated patients, as compared to 22% of the control group receiving low-dose prednisone alone. Over the subsequent 12 months, 10 of the 21 patients who entered remission had a relapse following discontinuation of treatment. As a result, at 18 months of follow-up, the rate of complete or partial remission was 39% in the treatment group as compared to 13% in the control group ($P = 0.007$) (216). A subsequent randomized controlled trial compared tacrolimus monotherapy administered for 12 months and then tapered over 6 months to a control group that did not receive immunosuppression (217). At the end of 18 months, the remission rate was 94% for the treatment group as compared to 35% for the control group, although 9 of 19 patients who entered remission had a subsequent relapse during the 12 months following discontinuation of therapy (217). Trials that directly compare alkylating agents and calcineurin inhibitors in MGN are lacking, although a recent study comparing these agents in patients with MGN and declining renal function found that treatment with an alkylating agent was associated with better outcomes (218).

Recently, evidence-based clinical practice guidelines for the treatment of MGN were published by Kidney Disease Improving Global Outcomes (KDIGO) (219). After excluding secondary forms of MGN, patients should be assessed for risk factors for progressive disease. When treatment is warranted, the recommended initial therapy is the Ponticelli protocol consisting of 6 months of alternating monthly cycles of IV and oral corticosteroids and oral alkylating agents (219). An alternative initial therapeutic consideration is offered for patients who refuse or have contraindications against the use of alkylating agents. The alternative first-line therapy is cyclosporine or tacrolimus, administered for a minimum of 12 months. The KDIGO guidelines do not recommend any alternative regimens for MGN but do state that monotherapy with corticosteroids or mycophenolate mofetil should not be used as initial therapy for MGN (219). Alternative therapies for MGN that have been employed with success include rituximab (220–223), mycophenolate mofetil (224), and synthetic adrenocorticotropin (225,226).

SECONDARY FORMS OF MGN

Secondary forms of MGN can be subdivided into four broad categories (6,227). First, MGN may occur secondary to autoimmune rheumatologic diseases, most commonly SLE ("membranous LN") but also Sjögren syndrome, rheumatoid arthritis, mixed connective tissue disease, Hashimoto thyroiditis, and Graves disease. Many of these associations are covered in Chapter 14. Second, MGN may follow treatment with certain therapeutic agents, most notably gold and penicillamine. Third, MGN may occur secondary to malignancy, most commonly carcinomas of the lung, gastrointestinal tract, breast, or prostate. Finally, MGN may result from infection, and, on a worldwide basis, infection is the most common secondary etiology of MGN. Infectious pathogens implicated in MGN include HBV, HCV, syphilis, and filariasis.

The majority of cases of MGN represent primary disease. In 1992, Glassock (6) reviewed 9 published series including a total of 943 cases of MGN and found that 214 patients (23%) had a secondary form of disease. This included 62 patients with drug-induced MGN (6.6%), 49 with malignancy-associated MGN (5.2%), 45 patients with SLE (4.8%), and 31 with infection-associated MGN (3.3%) (6). Secondary forms of MGN were most commonly encountered at the extremes of age. In children, the majority of secondary forms relate to infection or autoimmune conditions such as SLE (228). In contrast, the predominant secondary etiologies in the elderly are malignancy and therapeutic agents. For instance, in the analysis by Glassock (6), malignancy was associated with 20 of 103 cases of MGN in patients over the age of 60 (19.4%), as compared to 29 of the 840 younger patients (3.5%). Three more recent, large series on MGN identified a secondary etiology in 29 of 107 patients (27.1%) (229), 40 of 129 patients (31%) (230), and 48 of 161 patients (29.8%) (231). Thus, it is reasonable to assume that a secondary etiology can be uncovered in 25% to 30% of patients with MGN.

Drug-Induced Etiologies of MGN

Gold Therapy

Multiple therapeutic agents have been implicated in the development of MGN, most notably gold, penicillamine, mercury, captopril, and the NSAIDs (232,233). Renal biopsy findings do not distinguish between primary and drug-induced forms of MGN, making this diagnosis dependent on careful clinical correlation.

Gold salts have been used to treat arthritis for more than 75 years (234,235), although they have largely fallen out of favor more recently due to side effects and the availability of more efficacious agents. The most common renal complication

of gold therapy is proteinuria, which is seen in 3% to 7% of patients, including a subset of patients with full nephrotic syndrome (235,236). In general, parenteral gold is more effective than oral preparations but is associated with a higher incidence of proteinuria (235,237–239). Urinary monitoring for proteinuria is mandatory in patients receiving all forms of gold therapy, and proteinuria is the most common indication for withdrawal (237). In general, the development of proteinuria cannot be predicted based upon dosage or duration of therapy (235,236,240).

The most common renal biopsy finding in patients who develop proteinuria during oral or parenteral gold therapy is MGN (235,236,241,242), although other glomerular lesions such as minimal change disease are rarely encountered (240,241). The findings of MGN following treatment with gold are typically of stage I or II (236,242), likely owing to early detection as a result of careful screening of this population. Following discontinuation of treatment, the proteinuria typically resolves (235,237,240). In one series, the proteinuria resolved in 31 of 36 patients following discontinuation of oral treatment, and only 3 of the 31 patients received immunosuppressive therapy (235). Notably, eight of the patients who remitted were subsequently rechallenged with oral gold, seven of which did not have a relapse of proteinuria (235). In another series, all 21 patients who developed proteinuria following treatment with intramuscular gold had complete resolution of proteinuria following discontinuation of therapy at a median of 11 months, in the absence of immunosuppression (240).

In patients who receive gold therapy, gold inclusions can be seen in the proximal convoluted tubule and, to a lesser extent, in the distal tubular, mesangial, and visceral epithelial cells (236,243). Given that gold has not been demonstrated in the subepithelial deposits of MGN (243,244), the localization of gold in the proximal convoluted tubule suggests a pathogenic relationship between tubular injury and MGN. Nagi et al. (245) injected rats with sodium aurothiomalate on a weekly basis for 12 weeks, and the rats developed findings consistent with MGN, including documentation of IgG and C3 along the subepithelial aspect of the GBM. Their findings of gold within proximal tubules but not within the glomerular subepithelial deposits, similar to the situation in humans treated with gold, raise the possibility of a pathogenesis in which gold leads to release of tubular antigens and a subsequent antibody response, akin to the pathogenesis of Heymann nephritis (245).

The topic of drug-induced MGN related to gold or penicillamine is complicated by the fact that both agents are primarily used in the treatment of rheumatoid arthritis, a condition that by itself is also associated with the development of MGN (246,247). This has even led to the hypothesis that gold therapy may be solely exacerbating the proteinuria in patients with rheumatoid arthritis (247). That said, the temporal relationship between gold therapy and the onset of proteinuria, the presence of gold in proximal tubules, the prompt resolution of proteinuria when gold is discontinued, and the animal models of gold-induced MGN strongly support an etiologic role for gold in the pathogenesis of MGN.

Penicillamine

Similar to gold therapy, proteinuria is the most frequent cause for discontinuation of treatment with penicillamine and as a result, regular monitoring for proteinuria is a necessity (248). Proteinuria is seen in 10% to 20% of patients who are treated with penicillamine and most frequently is documented during the initial 12 months of therapy (248–250). Limited data suggest dose dependence such that higher doses are associated with a higher incidence of proteinuria (248,250).

The most common renal biopsy finding in patients who develop proteinuria while receiving penicillamine is MGN, which was present in 38 of 42 patients (90.5%) in three series (250–252). Among the remaining four patients, two had minimal change disease and two had mesangial immune deposits (252). Similar to gold therapy, an early stage of MGN (i.e., stage I or II) is seen in the majority of patients, which likely relates to careful monitoring for proteinuria and early detection of MGN (251,252).

Following penicillamine withdrawal, proteinuria resolves in the overwhelming majority of patients (252–254). In the 33 patients described by Hall et al. (252) (29 of which had MGN), penicillamine withdrawal led to resolution of proteinuria by 6 months in 12 patients, by 12 months in 21 patients, by 18 months in 29 patients, and by 21 months in 32 patients. None of the patients received immunosuppressive therapy. The median duration of proteinuria was 8 months, and the single patient who did not experience a remission expired as a result of carcinoma of the renal pelvis (252). In light of the apparently benign course, some centers in the past advocated continuing therapy until the patient reaches a 24-hour urine protein level of 2 g/d (248).

We know little about the mechanism by which penicillamine produces MGN. Possible mechanisms include modification of immune function or the potential for the drug to act as a hapten and elicit an immune response (252). As noted for gold therapy, the temporal relationship between treatment and the development of proteinuria and the relatively prompt resolution following drug withdrawal provide strong evidence for the association between penicillamine and the development of MGN.

Bucillamine

Bucillamine is a disease modifying antirheumatic drug with similar chemical structure and side effect profile as penicillamine. Bucillamine was developed more recently, is widely used in Japan, and is distinguished from penicillamine by the presence of an extra sulfhydryl group (255). Not surprisingly, the main renal biopsy finding in patients who develop proteinuria while receiving bucillamine is MGN, with more than 40 reported cases in the literature (255–259). Among patients treated with bucillamine, MGN most often occurs during the 1st year of therapy (255–258). Monitoring for proteinuria is required for patients treated with bucillamine, and as a result, renal biopsy typically reveals early stage I or stage I to II membranous changes (255,258). Following discontinuation of therapy, the proteinuria resolves in most if not all cases, usually within 1 year (256–259).

Captopril

Captopril is an ACE inhibitor that has been associated with nephrotic syndrome in up to 1% of patients who are treated with this agent (260,261). Renal biopsy typically reveals MGN (262–266). Proteinuria resolves in some but not all patients following discontinuation of this agent (262,263,265,266). Interestingly, Sturgill et al. (265) described a case of captopril-associated MGN in which a renal biopsy performed prior to commencement of treatment showed no immune deposits,

confirming that the subepithelial deposits of MGN occurred after captopril was administered. Among the ACE inhibitors, captopril appears to be the only agent associated with MGN. The association of captopril and MGN has been ascribed to the presence of an active sulfhydryl group, a finding that captopril shares with penicillamine and bucillamine but not with other ACE inhibitors (267).

Mercury

Mercury is an environmental toxin that has been linked to major disorders of the developing central nervous system, lungs, gastrointestinal tract, skin, and kidney (268). Historically, sources of mercury exposure have included contaminated foods including fish, vaccine preservatives, dental amalgams, occupational contact, traditional Chinese medications, infant teething powders, and more recently, skin lightening creams (268). With respect to the kidney, acute mercury intoxication is associated with the development of acute tubular necrosis (269).

Chronic exposure to mercury is associated with nephrotic syndrome and renal biopsy findings of MGN or, less commonly, minimal change disease (68,270,271). In 2010, Li et al. (68) described 11 cases of mercury-induced MGN from China. Sources of mercury included mercury-containing pills (five patients), skin lightening creams (four patients), hair coloring (one patient), and occupational exposure in a fluorescent light bulb factory (one patient) (68). The duration of exposure ranged from 2 to 60 months, and all patients had elevated urine mercury levels. EM revealed predominantly stage I to II membranous changes. Following withdrawal and, in 4 patients, mercury chelation with sodium dimercaptopropane, 9 of 11 patients had a complete remission over 1 to 4 years (68). The remaining two patients were lost to follow-up. More recently, Miller et al. (270) reviewed the available medical literature on renal biopsy findings in mercury-associated glomerular disease and found that MGN was seen in 15 of 21 cases. Mercury-induced MGN is associated with a predominance of IgG1 immune deposits and, not surprisingly, the absence of antibodies against PLA_2R (68,272). Treatment with mercuric chloride produces an animal model of mercury-induced MGN in Brown-Norway rats (110).

Nonsteroidal Anti-Inflammatory Drugs

NSAIDs are associated with a variety of renal conditions that are discussed throughout this text, including minimal change disease, AIN, hemodynamically mediated acute tubular necrosis, and, less commonly, MGN. There are at least six classes of NSAIDs, and MGN has been reported to occur with multiple agents in different classes including diclofenac, ketoprofen, piroxicam, sulindac, and fenoprofen (49,50,273–275), as well as with the selective cyclooxygenase-2 inhibitors etodolac and celecoxib (276,277). The observation that MGN occurs following use of these agents, which have widely varying chemical structures, argues in favor of a class effect and suggests that MGN is the result of their common pharmacologic action on mediators of inflammation rather than the immunogenicity of the individual agents.

The largest single-center experience with NSAID-associated MGN comes from the Mayo Clinic (278). Over a 20-year period from 1975 to 1995, 125 patients had renal biopsy findings of early (stage I to II) MGN. Criteria for NSAID-associated MGN included (a) onset while taking an NSAID; (b) exclusion of other secondary causes of MGN; and (c) rapid remission following NSAID withdrawal. Thirteen of the 125 patients met these criteria (10.4%), including 4 patients treated with fenoprofen, 3 with ibuprofen, 3 with tolmetin, and 1 each with diclofenac, nabumetone, and naproxen (278). The mean duration of NSAID use prior to biopsy was 35 weeks, and all patients had nephrotic-range proteinuria, with a mean 24-hour urine protein of 7.5 g/d (range 3.5 to 23.8 g/d) (278). The mean time required to see a decline in the 24-hour urine protein to less than 1 g/d was 6 months (range 3 to 12 months), during which time 4 of the 13 patients were treated with steroids.

Additional therapeutic agents have also been associated with MGN, although the literature is more limited than for the previously discussed drugs. There are individual case reports of MGN occurring following treatment with lithium carbonate (279), interferon beta-1b (280), anti-TNFα therapy (281,282), aprotinin (283), fluconazole (284), and probenecid (285). In addition, several small series describe the development of MGN in the setting of treatment with tiopronin for cystinuria (286,287), the anticonvulsant trimethadione (288), and porcine insulin (289). There is also a case series of four patients who developed MGN following exposure to formaldehyde (290).

Malignancy and MGN

The relationship between MGN and neoplastic disease has been recognized for more than 40 years. In 1966, Lee et al. (291) identified MGN in 8 of 11 patients with nephrotic syndrome and malignancy over a 10-year period. In 1975, Row et al. (12) identified malignancy in 7 of 66 patients with MGN, including 2 patients each with carcinomas of the colon or lung. In 1977, Eagen (292) reviewed the available literature on renal biopsy findings in patients with nephrotic syndrome and neoplastic disease. Among 48 patients with epithelial malignancies (i.e., carcinomas), 33 (69%) had MGN. For comparison, among the remaining 86 patients with alternative forms of neoplastic disease including Hodgkin disease, non-Hodgkin lymphoma, leukemia, embryonal tumors, and benign epithelial neoplasms, only 13 had MGN (15%). The most common sites of origin for carcinomas were lung, colon, and stomach, and in the majority of cases, malignancy and nephrotic syndrome developed within the same 12-month period (292). In a few reported cases at that time, a more direct link between MGN and malignancy was established. In one report, immunoglobulins were eluted from glomeruli and found to be specific for antigens from a patient's squamous cell carcinoma of the lung (293), while another report documented tumor-associated carcinoembryonic antigen (CEA) in the subepithelial deposits of a patient with colonic carcinoma (294). Couser et al. (160) reported a case of MGN and colonic carcinoma in which the patient had circulating antibodies against a tumor-associated antigen that was present in the glomerular deposits, although the antigen was not fully characterized.

Multiple large centers have subsequently examined the incidence of malignancy in patients with MGN. Burstein et al. (229) evaluated 87 cases of apparent primary MGN in Chicago, Illinois, and found malignancy in 9 patients (10.3%). Malignancy was diagnosed within 7 months before or after MGN in all patients. Seven of the nine patients had carcinoma and included two of lung origin (229). An examination of the Norwegian Kidney Biopsy and Cancer Registries revealed

161 patients with MGN over a 15-year period, 33 (21%) of which had evidence of malignancy (231). As compared to patients with primary MGN, patients with MGN and malignancy were older and had a significantly higher systolic blood pressure (both $P < 0.05$). Importantly, the significance of these data is limited by the fact that there was often a prolonged time period between the two diagnoses. Specifically, 9 patients were diagnosed with malignancy at a median of 21 months before the diagnosis of MGN, while the interval between the diagnosis of MGN and malignancy was a median of 60 months in the remaining 24 patients (231). An analysis of 240 cases of MGN from 11 centers in Paris, France, revealed 24 cases with malignancy that was diagnosed within 12 months before or after the diagnosis of MGN (10%) (38). Twenty of the twenty four patients had carcinomas, including 8 with tumors of the lung and 5 with cancer of the prostate (38). In this cohort, malignancy was uncovered in 6 of 167 patients below the age of 65 (3.5%), as compared to 18 of 73 patients at or above the age of 65 (24.7%) (38). As compared to patients with primary MGN, patients with malignancy-associated MGN were older and had a higher incidence of heavy tobacco use, defined as greater than 20 pack-years of cigarette smoking (both $P < 0.01$). Cancer remission led to complete or partial remission of proteinuria in 9 of 12 patients, providing strong evidence for this relationship (38). In a meta-analysis of 9 series including 932 patients with MGN, malignancy was identified in 5.8% of patients (6). Notably, in the same series, the incidence of neoplasia in MGN increased to 19.4% when only patients above the age of 60 were analyzed (6).

Light microscopic, immunofluorescence, and electron microscopic findings in malignancy-associated MGN are largely identical to primary MGN. A possible exception is that a single study reported an increase in intraglomerular inflammatory cells in malignancy-associated MGN as compared to primary disease (38).

A few themes emerge from the extensive literature on malignancy-associated MGN. First, MGN is associated mainly with epithelial malignancies, most commonly of lung origin but also frequently originating in the gastrointestinal tract, prostate, or breast. Second, the overall incidence of malignancy in patients with MGN is likely to be in the range of 5% to 15%, although the incidence may well exceed 20% in patients above the age of 60 (295). Third, renal pathologic evaluation does not reliably distinguish malignancy-associated MGN from primary disease, signifying the need for cancer screening in all patients with MGN. While precise screening guidelines are controversial (296), the degree of vigilance should likely be greater in older patients and those with a history of significant tobacco use. Finally, there may be cases in which MGN and malignancy are both present but unrelated. This is demonstrated by a recent report of 10 patients with MGN and malignancy in which 3 patients had circulating anti-PLA_2R antibodies and a predominance of IgG4 in the subepithelial deposits, strongly favoring the coexistence of primary MGN and an unrelated neoplasm (147).

Infectious Etiologies of MGN

Hepatitis B Virus

HBV infection is a major public health problem, with 2 billion people infected worldwide including 350 million with chronic HBV infection (carrier state) (297). More than 500,000 deaths per year are attributed to hepatitis, cirrhosis, or hepatocellular carcinoma resulting from HBV infection (297). HBV is endemic in sub-Saharan Africa, Eastern Europe, the Middle East, and throughout Asia, where the majority of infections occur during childhood, often via perinatal transmission, and infection rates are in the range of 5% to 20%. In contrast, HBV is relatively rare (less than 1%) in North America and Northern and Western Europe, where the majority of cases are seen in adults and are acquired via sexual contact or IV drug use (297). Thus, HBV-associated MGN (HBV MGN) is mainly an international disease with predominance in children.

In the setting of active HBV infection, evaluation of the serum typically reveals hepatitis B surface antigen (HBsAg), hepatitis B e antigen (HBeAg), IgM antibodies against the hepatitis B core antigen (IgM anti-HBc), and HBV DNA (as measured by serum polymerase chain reaction). When HBsAg persists in the serum for 6 months, a patient is considered to be a chronic carrier. Most children with HBV infection become chronic carriers, in part explaining the high incidence of HBV MGN in children. In contrast, the majority of adults seroconvert, which is marked by the disappearance of HBsAg, HBeAg, and HBV DNA and the emergence of anti-HBeAg antibodies. While HBsAg, which is derived from the outer surface envelope of the intact virion, is a reliable and readily available marker of active infection, HBeAg, which is associated with the inner viral nucleocapsid, appears to be more important in the pathogenesis of HBV MGN as it has been reproducibly demonstrated within the glomerular immune deposits, establishing an etiologic link (298–300). In contrast, with some exception (161), most studies have not found HBsAg within the glomerular deposits (298,299,301,302). Successful treatment of HBV leads to significant resolution of proteinuria (303,304), while effective vaccination strategies can profoundly impact disease incidence. For instance, following introduction of universal HBV vaccination in Taiwan in 1984, the incidence of HBV MGN among nephrotic children declined from 11.6% prior to 1984 to 2.1% between 1994 and 2004 to zero during the time period from 2004 to 2009 (305).

MGN is the most common pattern of glomerular disease seen in patients with HBV. The first large series of HBV MGN in adults was published in 1991 (306). Twenty-one cases of HBV MGN were reported, including 17 men and 4 women with a mean age of 30 years. The mean 24-hour urine protein was 4.1 g/d, 12 had full nephrotic syndrome, and 5 had chronic renal failure at the time of presentation. Hepatitis B viral antigens, predominantly HBeAg, were present in the subepithelial deposits in all cases. During a mean follow-up of 5 years, six patients had a progressive decline in renal function, including two who reached ESRD (306). In general, patients with HBV MGN present with proteinuria or full nephrotic syndrome, and only a minority have hematuria, renal insufficiency, hypertension, or hypocomplementemia (307). A recent meta-analysis on HBV-associated patterns of glomerulonephritis in adults considered 12 trials, all originating in China, and a total of 317 patients (304). There was a strong predominance of males, and optimal treatment response was achieved with a combined approach that included steroids and antiviral agents. Renal biopsy findings were available for 129 patients, among whom 73 had MGN (57%), 35 had a mesangial proliferative glomerulonephritis (MesPGN) (27%), and 21 had MPGN (16%). In endemic areas, HBV infection is particular common in children due to vertical transmission and the greater

likelihood of children to become chronic carriers than adults. This leads to a high childhood incidence of HBV MGN, which, as compared to adult disease, is more often asymptomatic at presentation and has a more benign clinical course with up to 50% of children experiencing a spontaneous remission (307–309). Of note, additional patterns of renal disease in patients with HBV infection include IgAN and polyarteritis nodosa (307,308).

Renal biopsy findings in HBV MGN are marked by the presence of multiple findings more typical of a secondary form of disease, including features that overlap with membranous LN (32). By light microscopy, HBV MGN frequently exhibits mesangial hypercellularity and may exhibit endocapillary proliferation, large "wire-loop" subendothelial deposits, and/or overlapping features with MPGN types I and III (32). Immunofluorescence may reveal "full house" staining for immunoglobulins and complement, and mesangial and subendothelial deposits are commonly encountered on ultrastructural evaluation. Lai et al. (32) reviewed the renal biopsy finding in 22 patients with HBV MGN and found that immunofluorescence positivity for IgG and C3 was present in all cases, similar to primary MGN. In contrast to primary MGN, however, staining for IgM, IgA, and C1 were each present in 16 of 22 cases (73%). Similarly, ultrastructural evaluation revealed mesangial and subendothelial deposits and endothelial tubuloreticular inclusions in 50%, 68%, and 13% of patients, respectively. Similar changes were noted in two additional series on biopsy findings in HBV MGN (13,310). The pathogenesis of HBV MGN likely involves trapping of the small, anionic HBeAg and the cationic antibodies it induces in the subepithelial region; based on charge interactions, antibody deposition may precede antigen arrival (307).

Hepatitis C Virus

HCV is an RNA virus that underlies most cases of non-A, non-B hepatitis. HCV is estimated to be present in 2.8% of the world population or approximately 210 million people (311,312). The incidence of HCV infection is greatest is Asia and Africa and is in the range of 1% to 2% in the United States (311,312). Antibody to one of several HCV antigens is diagnostic of viral exposure, and polymerase chain reaction detection of HCV RNA identifies patients with active infection. The majority of patients with HCV infection are asymptomatic.

MPGN, with or without associated type II cryoglobulinemia, is the most frequent pattern of renal disease seen in patients with HCV infection (311,313) (topic covered in Chapter 8). Additional patterns of glomerular disease associated with HCV include mesangial proliferative GN, diffuse proliferative GN, fibrillary GN, immunotactoid glomerulopathy, and MGN. In 2004, Uchiyama-Tanaka et al. (314) reviewed the available literature on HCV-associated MGN. Among 18 reported cases of HCV MGN, 15 occurred in males and the mean age was 48 years (range 29 to 62 years). In all cases, MGN was diagnosed in the absence of concurrent findings of MPGN. Testing for serum cryogobulins was negative in 11 of 12 patients with available data, while cryoglobulin testing was described as "slightly positive" in the remaining patient. Treatment of HCV MGN and other forms of HCV-associated glomerular disease consists of antiviral therapy. In more severe cases, plasmapheresis and immunosuppression may be employed (311,313), although this has produced mixed results in HCV MGN (314).

Available data create some doubt as to the relationship of HCV and MGN. First, the incidence of HCV in patients with MGN is unknown but appears to be in the range of 1% to 2%, similar to the incidence of HCV in the general population. Second, HCV RNA has only rarely been documented within glomeruli of patients with HCV MGN (315). Third, a recent study identified PLA_2R by immunofluorescence in the subepithelial deposits of 7 out of 11 patients (64%) with HCV and MGN, suggesting that these 7 patients are more likely to have primary MGN and coincidental HCV infection rather than a secondary form of disease (72).

Syphilis

The nephrotic syndrome is an uncommon but established complication of congenital, secondary, and latent syphilis, an infection caused by *Treponema pallidum*. The most common pattern of glomerular disease is MGN, particularly in infants with congenital syphilis (316–319). MGN also predominates in adults with syphilis, although mesangial proliferative, endocapillary proliferative, and crescentic patterns of glomerulonephritis and minimal change disease also have been reported (316). It is difficult to provide an accurate assessment of the incidence of syphilis-associated MGN due to the declining incidence of infection. Data from the pre–antibiotic era demonstrate a 0.3% to 0.4% incidence of massive albuminuria and edema in patients with syphilis (320,321). Syphilitic infection should be excluded in all infants with MGN, due in part to the rarity of MGN in this age group.

Similar to primary MGN, patients with syphilis-associated MGN present with proteinuria and/or full nephrotic syndrome. In additional to subepithelial deposits and intervening spikes, which are findings that are typical of MGN, syphilis-associated MGN is frequently accompanied by features that suggest a secondary form of disease including coexistent mesangial or endocapillary proliferation and the ultrastructural findings of mesangial or subendothelial electron-dense deposits (322,323).

Penicillin is the optimal treatment for syphilis-associated MGN and provides a rapid cure with disappearance of the subepithelial deposits in many cases, in particular in infants with congenital syphilis (318,319). The rapid response to penicillin, the increased frequency of MGN in patients with syphilis, and the documentation of treponemal antigens within the glomerular deposits (323–325) form the basis for the acceptance of syphilis as a secondary etiology of MGN.

Multiple additional infectious etiologies have been rarely associated with MGN. Chavaz et al. (326) have reported five cases of MGN associated with filariasis. There are also reports of MGN associated with hydatid disease (echinococcosis) (327–329), *Schistosoma mansoni* infection (330), and tuberculosis (331,332).

Additional Conditions Associated with MGN

Sarcoidosis

Sarcoidosis is a chronic systemic disease of unknown etiology characterized by granulomatous inflammation involving multiple organs, most commonly the lung and lymph nodes. Renal involvement is present in approximately 5% of cases of sarcoidosis. The most common renal manifestations include

granulomatous interstitial nephritis, nephrolithiasis, and nephrocalcinosis, the latter two of which relate to the frequent presence of hypercalcemia (333,334). Sarcoidosis accounted for 29% and 50% of cases of granulomatous interstitial nephritis in two recent studies (335,336).

The most common pattern of glomerular disease encountered in patients with sarcoidosis is MGN (337,338). Prior to 1982, the association between sarcoidosis and MGN was based mainly on individual case reports. At that time, Taylor et al. (338) reported a case of sarcoidosis-associated MGN and reviewed the available medical literature that included 33 patients with sarcoidosis and glomerular disease. The most common form of glomerular disease seen in patients with sarcoidosis was MGN, present in 12 of 33 reported cases (36%), and, more specifically, in 9 of 15 patients with sarcoidosis and full nephrotic syndrome (60%) (338). These incidences far exceeded biopsy series assessing the general population, leading the authors to suggest a causal relationship between sarcoidosis and MGN. More recently, data were pooled on glomerular disease in patients with sarcoidosis from seven large centers in France (337). Among 26 patients with sarcoidosis and glomerular disease, 11 had MGN (42%), 6 had IgAN, 4 had FSGS, 3 had MCD, and 2 had LN (337). MGN was diagnosed before sarcoidosis in five patients, after sarcoidosis in three, and simultaneously in three. At the time of biopsy, the 11 patients with MGN and sarcoidosis had a mean age of 39 years, a mean serum creatinine of 1.3 mg/dL, a mean 24-hour urine protein of 7.4 g/d, and a mean serum albumin of 2.4 g/dL. Seven patients had full nephrotic syndrome, and two had concurrent biopsy findings of granulomatous interstitial nephritis. At a mean follow-up of 10.3 years, seven patients had a complete or partial remission, two had ESRD, one expired, and one was lost to follow-up (337). Available data suggest that biopsy findings in sarcoidosis-associated MGN are no different than those of primary MGN. Staining of such cases for anti-PLA_2R is needed to determine whether there may be a coincidental occurrence of primary MGN.

Bone Marrow and Stem Cell Transplantation

Transplantation of allogeneic (allo-) blood and marrow stem cells or autologous (auto-) stem cells is employed for a variety of hematologic malignancies, as well as for some solid tumors and autoimmune disorders. Renal injury is not uncommon in this setting and has diverse potential etiologies. In the acute phase, there may be renal failure due to chemotherapy, antibiotics, sepsis, tumor lysis syndrome, and/or radiation (339). In the chronic phase, the most common injury is a form of graft versus host disease (GVHD) with features of thrombotic microangiopathy. In addition, some patients with GVHD develop immune complex–mediated glomerular disease presenting as nephrotic syndrome with biopsy findings of MGN. Over 50 cases of MGN following SCT have been reported to date (339).

The first report of MGN in GVHD was by Hiesse et al. in 1988 (340). In 2001, Lin et al. (341) reported two additional cases and reviewed the available literature on this entity. Among 12 cases of nephrotic syndrome following allo-SCT, 9 patients were male and mean age at presentation was 31 years (range 14 to 55 years). Indications for allo-SCT included chronic myelogenous leukemia in seven, acute leukemia in three, and aplastic anemia in two patients. The conditioning regimens included cyclophosphamide in nine patients, of which six also received total body irradiation. In all patients, immunosuppression with cyclosporine was used posttransplantation as prophylaxis against GVHD. Transplant donors were HLA-matched siblings in 11 of the 12 cases. Nine of the 12 patients developed acute GVHD defined as less than 100 days after allo-SCT, and 11 had more chronic GVHD. Nephrotic syndrome developed at a mean interval of 12 months following allo-SCT, with a broad range of 7 to 24 months. Biopsy findings indistinguishable from primary MGN were found in 10 patients, whereas 2 had atypical features with both subepithelial and subendothelial deposits (341). Positive ANA, a feature found in approximately 30% of patients with GVHD (342), was identified in 5 of the 12 (42%) cases, but no patient fulfilled criteria for SLE.

An additional seven cases of MGN following SCT for hematologic malignancies were reported from Stanford University (339). Interestingly, two of these patients had received auto-SCT and five allo-SCT. All cases of MGN had exclusively subepithelial deposits and one also exhibited tubuloreticular inclusions. Rituximab produced sustained remissions of proteinuria in most patients, whereas prednisone and mycophenolate were less effective. The response to anti–B-cell therapy and the occurrence of MGN primarily following allo-SCT in patients with GVHD suggests a role for B-cell alloreactivity. In addition, the development of MGN in rare cases post–auto-SCT raises the question of immune dysregulation and suppressed immune surveillance following immunomodulatory therapy, leading to the emergence of autoeffector T cells recognizing MHC class II antigens (343,344). Experimental models of GVHD and MGN with lupus-like features have been produced in mice (345) and suggest a role for autoantibody to intrinsic glomerular antigens, including laminin and dipeptidyl peptidase IV. MGN in GVHD bears similarities to de novo MGN in the renal allograft, where allotransplantation and ongoing immunosuppression may promote alloreactivity to donor MHC antigens and/or intrinsic glomerular antigens (346). The possibility of development of autoantibody to PLA_2R following allo-SCT deserves study, although such antibody is not identified in most de novo MGN occurring in the renal allograft (347). Differential diagnosis of nephrotic syndrome in the setting of GVHD also includes glomerular thrombotic microangiopathy and, less commonly, minimal change disease (339).

Autoimmune Thyroiditis

Over the last four decades, numerous case reports have described MGN associated with autoimmune thyroiditis, including Graves disease and Hashimoto thyroiditis (348–353). In Graves disease, the major autoantigen is the thyroid-stimulating hormone receptor (TSHR) (354), leading to activation of the receptor and stimulation of thyroid hormone synthesis and secretion. By contrast, patients with Hashimoto thyroiditis typically have more diverse autoantibodies including antibodies to thyroglobulin, thyroid peroxidase (formerly called microsomal antigen), and TSHR (355). In 1979, a case of Graves disease associated with nephrotic syndrome and MGN was reported in a 60-year-old woman; the improvement in proteinuria following thyroidectomy suggested a possible etiologic association (350). The subepithelial deposits stained for IgG, IgM, C3, and thyroglobulin (350), suggesting glomerular deposition of antithyroglobulin antigen-antibody complexes. Both thyroglobulin and thyroid microsomal antigen have been identified in the distribution of the glomerular immune deposits in

several additional case reports (350,356–358). Some patients with MGN and thyroiditis have been documented to have high circulating titers of serum antithyroglobulin antibody (349). In one report, MGN developed after administration of iodine ^{131}I, suggesting a role for the release of thyroid antigens in the course of thyroid ablation (348). There have also been reports of new-onset proteinuria developing in Graves disease patients treated with ^{131}I; however, the proteinuria was independent of the levels of autoantibody to thyroglobulin or microsomes (353). Because proteinuria following ^{131}I treatment was transient and patients were not subjected to biopsy, it is not known whether they developed MGN or had functional proteinuria related to therapy (353).

Because thyroiditis is common in the general population, it will be important in the modern era to exclude the possibility of coincidental development of primary MGN by staining renal biopsies with thyroiditis-associated MGN using antibody to PLA_2R. Differential diagnosis of proteinuria in Hashimoto thyroiditis includes rare reports of minimal change disease, FSGS, IgAN, and amyloidosis, which are likely coincidental associations (352).

IgG4-Related Disease and MGN

IgG4RD is a recently recognized systemic fibroinflammatory condition characterized by mass-forming lesions involving a multitude of organs (359). The most common sites of involvement are the pancreas and hepatobiliary system. Histologic findings in all organs typically include a dense lymphoplasmacytic infiltrate rich in IgG4-containing plasma cells and storiform fibrosis. The kidney is an infrequent site of involvement in IgG4RD, and manifestations typically include diffuse involvement in the form of either IgG4-related TIN or mass-forming lesions (360).

Multiple case reports and a recent case series establish an association between IgG4RD and MGN (361). Alexander et al. (361) reported nine patients with IgG4RD and MGN. The cohort consisted of six men and three women with a mean age of 58 years (range 34 to 75 years). The mean 24-hour urine protein was 8.3 g/d, and the serum creatinine was elevated in six of eight patients with available data. The diagnosis of IgG4RD was established prior to biopsy in seven of nine patients, and extrarenal manifestations were subsequently identified in an additional patient. In addition to MGN, five of the nine biopsies showed concurrent findings of IgG4-related TIN. Similar to primary MGN, the glomerular immune deposits stained most intensely for IgG4, but, unlike primary MGN, staining for PLA_2R was negative in all cases. Furthermore, anti-PLA_2R antibodies are not present in the serum of patients with IgG4RD (362). In light of the findings in the cohort reported by Alexander et al. (361) and multiple additional case reports, a recent international consensus symposium has recommended the adoption of the term "IgG4-related MGN" (363).

Guillain-Barré Syndrome

Guillain-Barré syndrome (GBS) and its chronic counterpart, *chronic inflammatory demyelinating polyneuropathy* (CIDP), are acute and chronic autoimmune inflammatory demyelinating conditions of the peripheral nervous system. There are multiple reports of MGN occurring in patients with GBS and, less commonly, CIDP (364–366). MGN is the most common cause of nephrotic syndrome in patients with these conditions, and outcomes are similar to the associated disease, that is, frequent resolution in patients with GBS and a chronic course in patients with CIDP.

MGN in the Renal Transplant

The major differential diagnosis of MGN in the renal allograft includes recurrence of primary MGN versus de novo MGN. Primary MGN has been reported to recur in the renal allograft in approximately 30% of cases, with up to 300 cases reported to date (367). Not surprisingly, this is almost exclusively seen in adults, consistent with the predominance of primary MGN in the adult patient and the time required for progression to ESRD. Recurrence is most common 2 to 3 years post-transplantation, with a broad range. In one series, recurrence occurred earlier in living-donor allografts (mean 9.3 months posttransplantation) than in recipients of deceased-donor allografts (mean 18.2 months) (368). No clinical features have been identified as predictive of recurrence, although it is likely that monitoring of serum levels of anti-PLA_2R antibody will have a future role. Onset may be insidious with initially mild or absent proteinuria, followed by progressive proteinuria and eventual development of nephrotic syndrome (367). In some cases, the disease was first documented in a protocol biopsy without clinical evidence of proteinuria (369). Recurrent MGN has even been reported to occur in successive renal allografts (370).

A recent study using protocol renal biopsies has elucidated the pathologic evolution of recurrent MGN in the allograft (371). In the 21 cases studied, the mean time to development of pathologic changes was only 2.7 (range 0.3 to 4.1) months. At the time of first detectable recurrence, proteinuria was generally subnephrotic (mean 1.1 g) but ranged from undetectable to 5.8 g. All early recurrences showed normal-appearing glomeruli by light microscopy; however, immunofluorescence revealed finely granular deposits of IgG, kappa and lambda light chains (ranging similarly from trace to 3+ intensity) in an exclusively subepithelial distribution (371). Interestingly, costaining for C4d was consistently observed (with 1 to 3+ intensity), whereas staining for C3 was either negative or only trace in the majority (16/21) of cases. Peritubular capillaries were negative for C4d in all but one case with coexistent acute humoral rejection. Despite the positive immunofluorescence staining for IgG in the glomerular capillary walls, EM showed no evidence of electron-dense deposits in 16 of 21 cases. The remainder showed only rare minute subepithelial deposits. These findings indicate that diagnostic immunofluorescence findings of recurrence precede the development of ultrastructural changes and that it takes time for the deposits to accrete and reach a size visible as discrete electron densities. On the other hand, irregular foot process effacement was already discernible prior to detection of electron-dense deposits, consistent with early podocyte injury. Follow-up biopsies were subsequently performed over the next 5 to 48 months in 11 of 14 patients and typically showed progression to stage I or II MGN (371). Recurrent disease was treated with rituximab in eight, ACE inhibitors or ARB in four, and increased prednisone in two, with reduction in proteinuria in all patients, typically to subnephrotic levels (371).

By definition, de novo MGN is an entity that occurs in a renal allograft from a patient whose original native renal disease

was not MGN (372). De novo MGN typically occurs later than recurrent MGN. In one study comparing the two entities, the mean time to development of de novo MGN was 49 months, compared to 16 months for recurrent MGN (373). Anti-HLA antibodies were more common in patients with de novo MGN, suggesting a role for allosensitization, either to MHC class I or II antigens or to podocyte antigens (372,374). Pathologically, some cases of de novo MGN have identical light microscopic and ultrastructural features as primary MGN occurring in the native kidney; however, others may have overlapping features with transplant glomerulopathy (346). An increased incidence of concurrent antibody-mediated rejection has been seen in de novo MGN, including interstitial capillary C4d deposition and multilayering by EM (375,376), further supporting a role for alloimmunity.

Recent literature suggests that staining for PLA_2R is a useful tool to distinguish recurrent and de novo MGN in the allograft (347). These investigators stained 12 biopsies from 11 patients with recurrent MGN and 12 biopsies from 11 patients with de novo MGN with antisera to PLA_2R on paraffin sections. Ten of twelve (83%) cases of recurrent MGN had positive PLA_2R reactivity in the distribution of the subepithelial deposits, compared to only 1 of 12 (8%) cases of de novo MGN. These results indicate 83% sensitivity and 92% specificity of PLA_2R immunoreactivity for the diagnosis of recurrent MGN in the cohort studied (347). There is a single report of recurrent MGN mediated by monoclonal IgG3K antibody targeting PLA_2R, associated with complement activation via the classical pathway in a patient without evidence of hematologic disorder (377).

Renal Vein Thrombosis and MGN

There is an increased risk for venous thromboembolic events (VTE), most notably RVT, deep vein thrombosis (DVT), and pulmonary embolism (PE), in patients with nephrotic syndrome and, in particular, in patients with MGN. In 1968, Rosenmann et al. (51) described 15 adult patients with nephrotic syndrome and RVT. Renal biopsy was available for 10 patients, 8 of whom appeared to have had MGN. This important early paper continues to be the most detailed description of the renal biopsy findings that suggest a diagnosis of RVT in patients with nephrotic syndrome. In patients with RVT, glomeruli often appear enlarged and congested, with focal intracapillary neutrophil margination and fibrin thrombosis. Another helpful finding is a disproportionate degree of interstitial expansion, owing to edema and/or fibrosis. Acute tubular injury and chronic tubular atrophy are also frequent accompaniments (51).

Hypercoagulability and an increased risk for thromboembolic events are a well-recognized complication of the nephrotic syndrome. The mechanisms that underlie this association are beyond the scope of this chapter, but in brief, they relate to urinary protein loss, an imbalance of serum proteins that favors prothrombotic over antithrombotic factors, impaired thrombolytic activity, and possibly intravascular volume depletion (378–380). Hypoalbuminemia of nephrotic syndrome stimulates hepatic synthesis not only of albumin but of fibrinogen and clotting factors, including factors V, VII, VIII, and X, promoting a procoagulant state. Urinary losses of anticoagulant factors such as heparin cofactor anti-thrombin III may explain the predisposition for thrombosis at the level of the renal vein, prior to dilution with the systemic venous circulation. For unclear reasons, VTEs and, more specifically, RVT are more common in MGN than other forms of nephrotic syndrome. In 1980, Llach et al. (381) studied 151 patients with nephrotic syndrome using IV pyelogram and inferior vena cavagram with selective catheterization of the renal veins. RVT was identified in 33 patients (22%), including 20 of 69 patients (29%) with MGN as compared to 13 of 82 patients (16%) with alternative etiologies of nephrotic syndrome (381). Trew et al. (382) identified RVT in 6 of 90 patients with biopsy-proven MGN. Laville et al. (383) identified 20 patients with nephrotic syndrome and RVT; in 14 of 20 patients, renal biopsy revealed MGN. Wagoner et al. (384) performed retrograde venography of the renal veins and found RVTs in 13 of 27 patients with MGN (48%); this high incidence may in part relate to the high sensitivity of this diagnostic technique. Of note, clinical manifestations that suggest the diagnosis of RVT in a patient with MGN include flank pain, gross hematuria, development of venous collaterals, and rarely AKI in those cases with bilateral acute RVT (51,381–383).

Two recent studies have further examined the association between MGN and RVT (210,385). An examination of the Toronto Glomerulonephritis Registry revealed RVT in 17 of 395 patients with MGN (4.3%), as compared to 2 of 370 patients with FSGS (0.5%) and 0 of 548 patients with IgAN (385). On multivariate analysis of the three groups, the strongest risk factor for VTE was MGN (hazard ratio 10.8), followed by the level of proteinuria, the degree of hypoalbuminemia, and male gender (385). A subsequent study pooled data from the Toronto GN Registry and the Glomerular Disease Collaborative Network and found VTE in 65 of 898 patients with MGN (7.2%), including 26 patients with RVT (2.9%) (210). The only independent predictor of VTE was the degree of hypoalbuminemia, and the risk of VTE increased substantially at an albumin level below 2.8 g/dL (210). These studies raise many important questions. While potential therapies for RVT include anticoagulation, thrombolytic therapy, embolectomy, and IVC filter placement, optimal therapy is not well defined (379,386). Similarly, the issue of whether to prophylactically anticoagulate patients with MGN and significant hypoalbuminemia remains controversial (379).

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CHAPTER 8

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Membranoproliferative Glomerulonephritis

Membranoproliferative glomerulonephritis (MPGN) refers to a morphologic pattern that includes many etiologically distinct forms of glomerulonephritis in which, as the name implies, there is thickening of the glomerular capillary wall (*membrano-*) as well as an increase in the number of cells in the glomerular tuft (*–proliferative*). Since the hypercellularity, which often is most prominent in the mesangium, and capillary wall thickening cause consolidation and expansion of the segments (lobules), there is often accentuation of the lobules of the glomeruli (hypersegmentation). An old term for this pattern that is rarely used today is *lobular glomerulonephritis*. This pattern is also referred to as *mesangiocapillary glomerulonephritis* because of the extensive involvement of the mesangium and the extension of the mesangial cells into the subendothelial portions of glomerular capillary walls. The MPGN pattern of glomerular injury may be either idiopathic (primary) or secondary to a wide variety of disease states (Tables 8.1 and 8.2). The idiopathic category is diminishing as more recognizable etiologies are identified. For example, hepatitis C is associated with a majority of cases that were previously identified as idiopathic MPGN type I and essential mixed cryoglobulinemia (52,53). An additional subset of previously idiopathic type I MPGN is now known to be caused by genetically determined or acquired defects in regulation of the alternative complement pathway (C3 glomerulopathy with MPGN type I pattern) (Fig. 8.1). Hence, MPGN is a morphologic pattern that should be interpreted in the context of etiologies and underlying diseases/conditions. The term idiopathic should be avoided in the pathologic diagnosis because it may impede the search for a recognizable cause.

Historically, the MPGN is subclassified into MPGN type I (the most common form), type II (dense deposit disease [DDD]), and type III based on the combined features of light, immunofluorescence (IF), and electron microscopy (EM). In recent years, there have been great advances in our understanding of the pathogenesis of MPGN, particularly in the area of complement-mediated C3 glomerulopathies, including DDD and C3 glomerulonephritis (52,53,117,118). Thus, the

TABLE 8.1 Pathologic variants of membranoproliferative glomerulonephritis

Membranoproliferative glomerulonephritis (MPGN) type I
Immune complex MPGN type I (Ig and C3 by IF)
Infection (e.g., bacterial endocarditis, hepatitis C)
Autoimmunity (e.g., mixed cryoglobulinemia)
Neoplasia (e.g., carcinoma, lymphoma)
C3 glomerulopathy variant of MPGN type I (C3 with little or no Ig by IF)
Genetic abnormality (e.g., mutations in complement factor H)
Autoimmunity (e.g., anti–complement factor H)
Dense deposit disease (MPGN type II) (C3 with little or no Ig by IF)
Genetic abnormality (e.g., mutations in complement factor H)
Autoimmunity (e.g., anti–complement factor H)
Infection (e.g., streptococcal)
MPGN type III
MPGN type III of Burkholder
Immune complex MPGN type IIIB (Ig and C3 by IF)
C3 glomerulopathy variant of MPGN type IIIB (C3 with little or no Ig by IF)
MPGN type III of Strife/Anders
Immune complex MPGN type IIIS/A (Ig and C3 by IF)
C3 glomerulopathy variant of MPGN type IIIS/A (C3 with little or no Ig by IF)

traditional classification of MPGN requires modification. A useful classification system should meet the following criteria: (a) define the entity clearly so that the precise connotation of the term can be immediately apparent; (b) be clinically significant, useful, and therapeutically relevant; (c) be based on pathogenesis within the limitation of our current knowledge; and (d) be relatively easy for all to use and morphologically reproducible (119). The traditional pathologic classification of MPGN was based primarily on ultrastructural features and included MPGN type I, MPGN type II, and two variants of MPGN type III. The current classification recognizes the importance of IF (or immunohistochemistry) microscopy in further dividing MPGN into immune complex–mediated MPGN with glomerular immunoglobulins and complement deposition and MPGN with abnormalities in alternative complement pathway regulation resulting in isolated C3 deposits with little or no immunoglobulins by IF. MPGN type II is currently designated DDD and is recognized as a variant of C3 glomerulopathy (see Table 8.1 and Chapter 9).

The less well-understood form of MPGN that is called MPGN type III is further divided into two variants. Burkholder et al. (120) identified a variant that has many of the features of MPGN type I but with the added presence of numerous electron-dense deposits on the subepithelial side of the glomerular capillary basement membranes. This pattern has some glomerular capillaries that are indistinguishable from type I, yet other segments of the glomerular tuft show changes similar to membranous glomerulopathy. This form of MPGN is now termed MPGN type III of Burkholder. The issue is complicated by the use of the term *type III* to describe a different form of MPGN described by Strife, Anders and coworkers (121,122). This form has intramembranous deposits of moderate to low electron density that bridge the glomerular basement membrane (GBM) and may connect to irregular subendothelial and the subepithelial deposits. EM of silver-stained sections accentuates the GBM abnormalities by demonstrating irregular silver-negative zones. This form of MPGN is now termed MPGN type III of Strife/Anders.

MPGN was described as a mixed proliferative and membranous glomerulonephritis in early reports prior to the recognition of the characteristic features by EM and IF. Fahr (123) probably included MPGN in the "intracapillary form" of subchronic glomerulonephritis. Cameron (124) concluded that at least two cases originally studied by Richard Bright at Guy's Hospital in the 1820s represented a form of MPGN. Three of the original kidneys in the Gordon Museum at Guy's Hospital were sectioned, and two of the kidneys had the histologic features of MPGN. As Cameron (124) states, it is remarkable that this pattern can still be recognized 150 years later, after preservation first with brandy and then with formalin. MacCallum in 1934 (125) and Ellis in 1942 (126) described patients with chronic progressive glomerulonephritis showing membranoproliferative and lobular features. Bell (127) described a series of patients with "latent chronic glomerulonephritis" or "chronic azotemic glomerulonephritis," which probably represents what we now call MPGN. Allen (128) used the term *chronic lobular glomerulonephritis* and noted that there was a tendency for the "periphery of each lobule to be laminated by two or three layers of endothelial cells" and for splitting of the basement membranes to be present. Churg and Grishman (129) described 28 patients with subacute glomerulonephritis with mesangial cell interposition (i.e., between the glomerular endothelium and the GBM). They also commented that with time, the cellularity of the glomerular lesions decreased and central nodular scars developed. Habib et al. (130), in 1961, presented 108 nephrotic patients at a Ciba Foundation symposium. Fifteen patients had "endocapillary proliferative glomerulitis associated with hyaline nodules" ("lobular glomerulitis"). Seven additional patients had complex or unclassified forms of glomerular disease with thick glomerular capillary walls and endocapillary hypercellularity. The light and electron microscopic findings described at this benchmark symposium (that launched the modern era of renal biopsy) conform to what we now accept as MPGN type I.

David Jones (131), using an elegant staining method (periodic acid-methenamine silver stain) on thin paraffin-embedded and plastic-embedded sections, defined the characteristic glomerular capillary wall lesions in MPGN type I. He demonstrated the formation of a new basement membrane internal to the original GBM and described the continuity of the mesangial region with the peripheral capillary wall lesion. Arakawa and Kimmelstiel (132) described the histologic and ultrastructural appearance of circumferential mesangial cell interposition in a series of patients with diffuse (and often lobular) glomerulonephritis. They concluded that circumferential mesangial cell interposition can be regarded as a distinct form of mesangial proliferation in glomerulonephritis.

West et al. (133) and Gotoff et al. (134) almost simultaneously noted depletion of serum complement in children with chronic renal disease and named it *hypocomplementemic persistent* or *chronic glomerulonephritis*. The glomerular pathologic characteristics in these patients were increased cellularity,

TABLE 8.2 MPGN type I associated with known conditions

Autoimmune diseases
- Mixed cryoglobulinemia (1–4)
- Systemic lupus erythematosus (5,6)
- Sjögren syndrome (7,8)
- Henoch-Schönlein purpura (9)
- Rheumatoid arthritis (10)

Infectious diseases
- Bacterial
  - Infected ventriculoatrial shunts (11)
  - Endocarditis (12)
  - Visceral abscesses (13)
  - Brucellosis (14)
  - Tuberculosis (15)
  - Leprosy (16)
  - Lyme disease (17,18)
  - Mycoplasma (19)
  - Meningococcal meningitis (20)
- Viral
  - Hepatitis B (21–28)
  - Hepatitis C (29–33)
  - HIV (7,34,35)
  - Hantavirus (36,37)
  - BK virus (38)
  - EBV (39)
- Fungal
  - *Candida* endocrinopathy (40)
- Protozoal
  - Filariasis (41)
  - Malaria
  - Schistosomiasis
  - Hydatid disease (42)

Dysproteinemia
- Cryoglobulinemia
- Monoclonal immunoglobulin deposition disease
- Monoclonal gammopathy of undetermined significance (43)
- Waldenström macroglobulinemia
- Fibrillary glomerulonephritis
- Immunotactoid glomerulonephritis

Neoplasms
- Leukemias and lymphomas (44)
- Epithelial tumors (45–49)
- Abdominal desmoplastic round cell tumor (50)
- Mixed-cell germinal ovary tumor (51)

Hereditary or genetic
- Hereditary deficiencies of complement components including regulatory factors (52–66)
- α_1-Antitrypsin deficiency (67,68)
- X-linked (69,70)
- Autosomal dominant (70,71)
- Autosomal recessive MPGN type I (66)
- Down syndrome (72)
- Gaucher disease (73)
- Kartagener syndrome (74)
- Nephropathy-gonadal dysgenesis type II (75)
- Prader-Willi syndrome (76)
- Turner syndrome (77)
- Hereditary angioedema (78)
- Familial Mediterranean fever (79)

Miscellaneous
- Sarcoidosis (80)
- Addison disease (81)
- Castleman disease (82)
- Celiac disease and sprue (83)
- Coexisting glomerulonephropathies
  - Amyloidosis (84)
  - Diabetes mellitus (85)
  - Alport syndrome (86)
  - Polycystic kidney disease (87)
- Cushing disease (88)
- Drug abuse (89)
- Hemolytic uremic syndrome (90)
- Immunoglobulin and IgG subclass deficiency (91)
- Pregnancy related (92)
- Psoriasis vulgaris (93)
- Renal artery dysplasia (94)
- Renal vein thrombosis (95)
- Takayasu arteritis (96)
- Toxic oil epidemic syndrome (97)
- Cryptogenic organizing pneumonia (98)
- Ulcerative colitis (99)
- Hypocomplementemic urticarial vasculitis syndrome (100)
- Bone marrow transplantation (101)

Renal allografts
- Recurrent glomerulonephritis (102–115)
- De novo glomerulonephritis (112,116)

thickening of the glomerular capillary walls, argyrophilic "splitting" of the basement membranes by nonargyrophilic material, and prominent lobulation of the tuft with some central hyaline zones (133,134). Subsequent studies showed similar glomerular lesions in other patients including patients who did not have hypocomplementemia.

Confusion over the diagnosis of MPGN has been caused by the lack of clear understanding of the pathogenesis of the disease and the inability of authors to distinguish between the different types. The term MPGN has been used loosely by both pathologists and clinicians, and its precise meaning is not always apparent. This chapter deals with types I and III MPGN and refers to DDD (type II MPGN) only for comparison. Chapter 9 focuses on DDD and other variants of C3 glomerulopathy and thus also will refer back to the MPGN variants of C3 glomerulopathy. Whenever possible, the more specific term (i.e., MPGN type I, MPGN III of Burkholder, and MPGN type III of Strife/Anders) will be used. Unfortunately, many situations where it is not possible to know what specific MPGN variant is being referenced, the generic term MPGN will be applied.

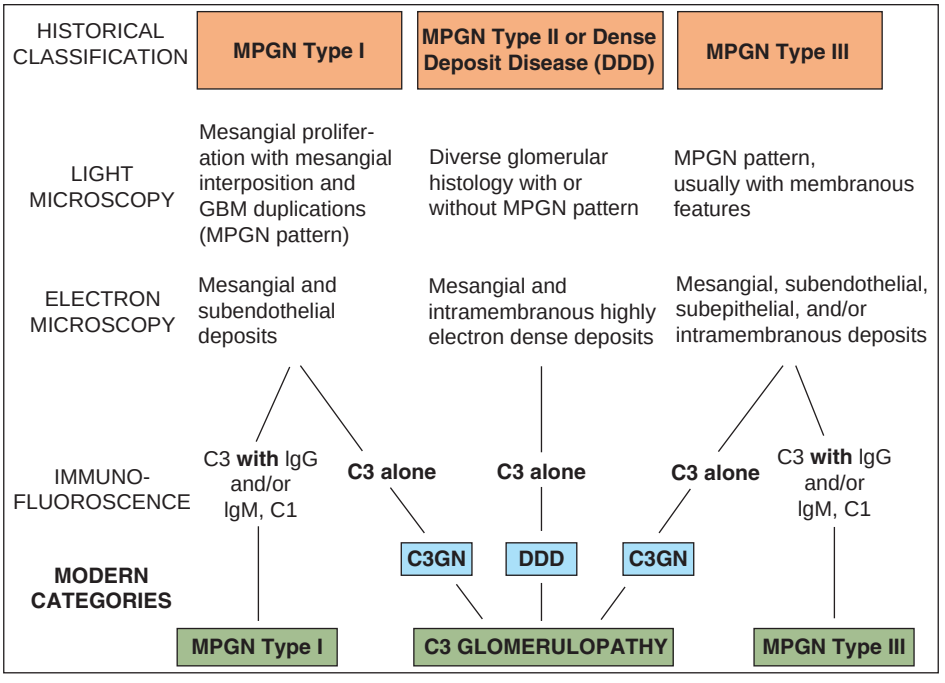

FIGURE 8.1 The evolving classification of membranoproliferative glomerulonephritis. Until recently, the classification of primary MPGN into types I, II, and III was based primarily on histologic features (light microscopy) and the ultrastructural location and electron density of the deposits (electron microscopy). With our increased understanding of the role of complement in the pathogenesis of these conditions, the IF findings now play a crucial role in categorizing MPGN as immunoglobulin-mediated versus non–immunoglobulin-mediated disease; the latter grouping, which is distinguished by isolated C3 staining on IF, has been termed "C3 glomerulopathy." C3 glomerulopathy encompasses C3 glomerulonephritis (C3GN) and DDD. GBM, glomerular basement membrane; IgG, immunoglobulin G; IgM, immunoglobulin M. (Reproduced from D'Agati VD, Bomback AS. C3 glomerulopathy: what's in a name? *Kidney Int* 2012;82:379–381,with permission.)

MEMBRANOPROLIFERATIVE GLOMERULONEPHRITIS TYPE I

Clinical Presentation and Epidemiology

The incidence and prevalence of MPGN vary in different parts of the world and have been declining in most developed countries (135,136) probably because of the decline in persistent infectious diseases. MPGN type I has been recorded in patients of all ages, although it is described most commonly in children (133,137–144). In a study of 79 patients with predominantly MPGN type I, the mean age at diagnosis was 34.6 years old, with a range of 6 to 79 years old, and 20 patients less than 20 years old (135). It has been diagnosed in patients younger than 2 years old (69,137,140,145), but most patients show signs of the disease after the age of 8 years (140). It can appear in adults of all ages, including patients beyond the seventh decade (141,146–149). In a retrospective study of renal biopsies in 150 patients aged 70 years or older during the period of 2000 to 2007 in Western France (150), 45 presented with nephrotic syndrome. Nine (20%) of the 45 patients had MPGN type I. None of these patients had detectable underlying infectious etiology although some had monoclonal gammopathy of undetermined significance (MGUS). This disease may favor Caucasians. There does not appear to be a substantial male or female predominance, although a few series suggest a slight male predominance.

The clinical characteristics are varied depending on the timing of the diagnostic renal biopsy relative to the clinical course. In about half of the patients, the clinical onset is preceded by a history of a respiratory infection (139). Although acute group A streptococcal infections are not thought to play a role in the genesis of this pattern of renal disease, two studies have shown elevated antistreptolysin O (ASO) titers in 38% (151) and 25% (140) of patients, respectively. These figures differ little from the prevalence rate in the general population (139). However, it may be difficult to distinguish MPGN from acute postinfectious glomerulonephritis on clinical and morphologic grounds in some patients. Patients may present with clinical symptoms of a nephritic or a nephrotic syndrome or both. Some patients have a clinical picture resembling acute glomerulonephritis with macroscopic hematuria and red blood cell casts (140). Dysmorphic or distorted red blood cells may be found in the urine. On average, approximately 10% to 20% of patients have an acute nephritic syndrome (140), with oliguria, edema, hematuria, hypertension, and renal insufficiency. Most patients have microscopic hematuria. Attacks of gross hematuria recur in a minority of patients and are more common in children than in adults (148). Persistent microscopic

hematuria is frequently a finding. MPGN may be asymptomatic and detected only, for example, in school urinary screening of children (152). It has been noted that patients diagnosed with MPGN type I on routine urinary screening usually have lower blood pressure, less proteinuria, and less chronic renal disease when compared to those who are diagnosed when symptomatic, indicating that early identification of the disease by urinary screening may allow for early therapy and improve the prognosis of this disease (152).

Mild hypertension is commonly present at the clinical onset (noted in about a third of patients). Some series note it more commonly (141); occasionally, it may be severe (141,147,153–155), and malignant hypertension may even be the presenting sign (153). Hypertension is typically observed as the renal disease progresses and is more common in adults than in children (148). Encephalopathy owing to hypertension is rare at presentation, but has been reported during follow-up in both treated and untreated patients (155).

Proteinuria is almost uniformly present. The nephrotic syndrome is a typical mode of presentation and has been noted in over 1/2 to 2/3 of patients (140,141,144). The nephrotic syndrome was found in more than 80% of patients in one series in children with MPGN type I (137). If the nephrotic syndrome is not evident at clinical presentation of a patient with MPGN, it often develops during the course of the disease. Heavy proteinuria is very common and, when studied, is generally of a moderately or poorly selective type (151). Patients with proteinuria generally also have accompanying microscopic hematuria. Some patients may not have overt clinical symptomatology, and the proteinuria is simply discovered on routine urinalysis. This was true of almost half the children in one study (140). MPGN is one of the major histopathologic patterns found in children with idiopathic nephrotic syndrome. It accounted for approximately 5.8% of cases of idiopathic nephrotic syndrome among pediatric patients in the report of the International Study of Kidney Disease in Children (156). In adults, the relative frequency of type I MPGN as a cause of nephrotic syndrome has declined in the United States from 6% for the period of 1976 to 1979 to 2% for the period of 1995 to 1997 (157). However, it should be noted that MPGN type I is much more common in underserved countries where there is a higher frequency of MPGN type I secondary to persistent infectious disease. For instance, in Asia (Saudi Arabia), South America (Peru), and Africa (Nigeria), MPGN type I is one of the most common causes of nephrotic syndrome and accounts for approximately 30% to 40% of all cases (158).

Blood urea nitrogen (BUN) and serum creatinine are elevated at clinical onset in about a fourth of patients. These values may stay elevated (presaging the onset of permanent renal failure) or return to normal over a few weeks in about half the patients. Depression of the glomerular filtration rate (GFR) is more often noted in adults than in children (148). Renal tubular dysfunction or injury has been described in patients with MPGN type I, as evidenced by increased urinary excretion of *N*-acetyl-beta-glucosaminidase (159), defects in maximal urinary concentration and urinary acidification, and elevated levels of the fractional excretion of sodium (160). Potassium-losing nephropathy, generalized aminoaciduria, and glycosuria (reversible with steroid therapy) have also been described (161).

The commonly encountered feature of hypocomplementemia was recognized (and was the impetus for the discovery of this type of glomerulonephritis) by West et al. (133) and Gotoff et al. (134). There is often a decline in C3 levels in the serum (141,144,146,147,162,163), although the levels tend to fluctuate. Depressed levels of serum C3 have been found at the time of diagnosis in approximately a third to half of the patients (137,139,144,164). In most patients, serial determinations usually reveal hypocomplementemia sometime during the course of renal disease. Some patients do not appear to have depression of the serum complement level. A normal level may persist throughout the course of the illness; alternatively, as mentioned earlier, the level may drop at a later time (146,163). In the series of Habib et al. (130) and Servais et al. (144), as many as 40% and 54% of patients with MPGN did not have depressed serum complement, respectively. Serum concentrations of the early (i.e., C1q, C4, and C2) and terminal (C5, C6, C7, or C9) components of the classic pathway as well as components of the alternative pathway (i.e., factor B, properdin) are also frequently low (163–165). The complement profile (either classical or alternative complement pathway activation) depends on whether the cause is an immune complex disease or C3 glomerulopathy (52,53).

Immune complex MPGN type I but not the C3 glomerulopathy variant of MPGN type I might have detectable circulating immune complexes (CICs). CICs have been searched for using a number of different techniques and have been found in approximately 20% or more of patients with MPGN; this percentage depends on the sensitivity of the technique used for identifying the complexes (166–168). Davis et al. (167) demonstrated the presence of CICs when renal disease was mild or silent, but CICs were almost always absent by the time renal impairment developed. This finding suggested to the authors that either the CICs detected were not nephritogenic or that they programmed subsequent renal events that augment renal parenchymal injury in the absence of CICs. These workers also suggested that the measurement of CICs was of minimal value in the diagnosis or prognosis of patients with MPGN. Some groups have failed to find evidence of CICs altogether (168). IgM rheumatoid factors (i.e., autoantibodies to IgG) have been noted (169), as has cryoglobulinemia (1), in patients with MPGN type I.

Renal vein thrombosis can occur with MPGN. In one series, MPGN was the most common form of nephropathy associated with renal vein thrombosis (95). Successful pregnancies are the norm in affected patients (170), although Surian et al. (92) noted a high incidence of complications. Abrupt deterioration of renal function during pregnancy in a patient with preexisting MPGN has been reported (171). Plasmapheresis, albumin replacement, and antihypertensive therapy allowed for continuation of the pregnancy until a healthy infant could be delivered (171).

Although several formulas have been proposed (based on clinical and laboratory findings) to establish the diagnosis of MPGN without renal biopsy (156,172), biopsy is still the only way to determine with certainty the exact pattern of glomerular disease in the individual patient. Despite recent attempts to identify new biomarkers for MPGN (173), none has been identified.

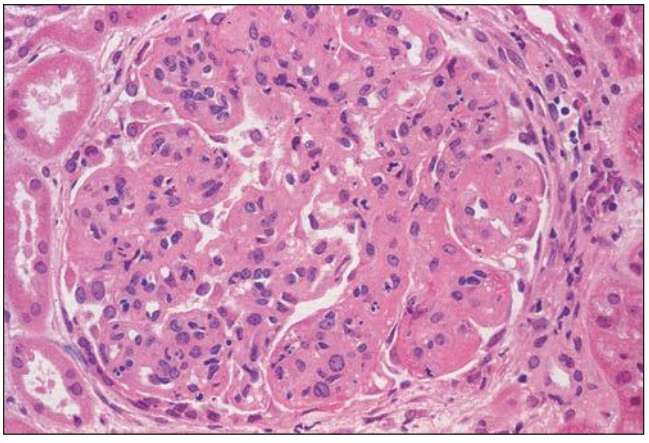

FIGURE 8.2 MPGN type I. There is increased lobulation, intracapillary hypercellularity (including mild neutrophil infiltration), and thickening of the capillary walls. (H&E, ×400.)

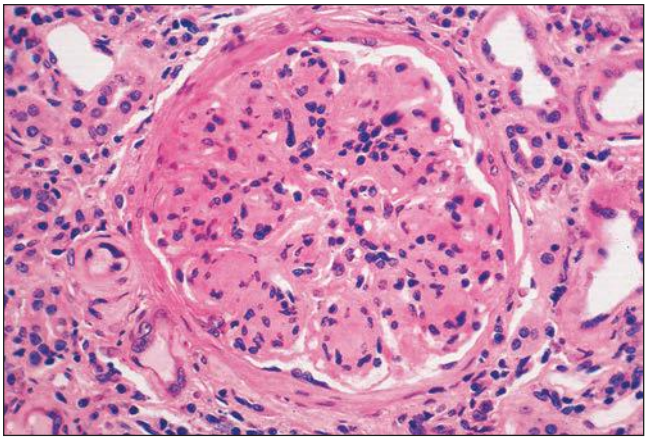

FIGURE 8.4 MPGN type I. Accentuation of the lobular pattern with sclerotic mesangial nodules. (H&E, ×400.)

Pathologic Findings

Gross Pathology

By the time the gross appearance of the kidneys is studied, either at nephrectomy before transplantation or at autopsy, the kidneys are usually pale. Yellow flecking may be seen in the cortex that is caused by the accumulation of lipid in tubular epithelial cells and interstitial foam cells. With advancing disease, the kidneys become small and have a granular surface. There is a firm consistency to the renal parenchyma, and the arteries may be prominent.

Light Microscopy

Glomeruli

The glomeruli have characteristic and uniform changes. Glomeruli typically are enlarged, with a diffuse increase in glomerular tuft cellularity (Figs. 8.2 and 8.3). The intracapillary hypercellularity is usually global (i.e., involving all portions of each glomerular tuft to about the same degree). The increase in cellularity within each glomerular lobule creates an accentuation of the normal lobularity of glomerular tufts (Fig. 8.4). The term "lobular glomerulonephritis" is purely descriptive and nonspecific and should not be used as a diagnostic term.

The increase in cells in the mesangial regions and the increase in the amount of mesangial matrix create a much larger mesangial (centrilobular) area with the lobules sometimes assuming a club shape. In some patients, however, there is widespread glomerular hypercellularity with little accentuation of the lobular pattern. It has been suggested that the severity of the mesangial lesions, especially sclerosis, relates to the duration of renal disease. In some repeat biopsies, as the lobular lesion progresses, the cellularity tends to diminish and is replaced by mesangial matrix (sclerosis). In approximately one fourth of the cases, there is a marked polymorphonuclear leukocytic infiltration (exudative form) (Fig. 8.5) (174). Laohapand et al. (175), using α_1-antitrypsin as a marker for mononuclear leukocytes, noted an abundance of monocytes in

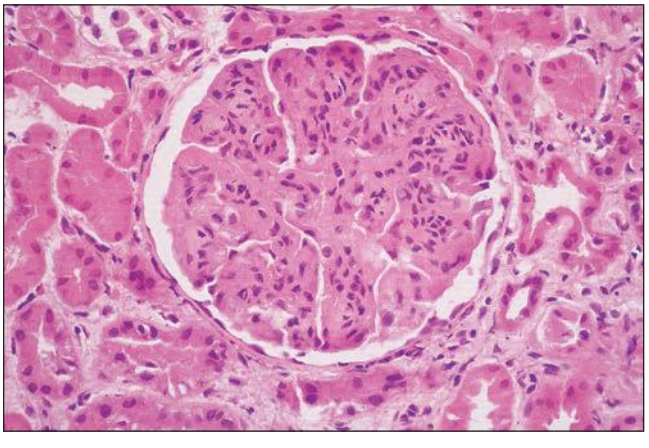

FIGURE 8.3 MPGN type I. There are capillary wall thickenings, increased cellularity, and pronounced lobulation. (H&E, ×360.)

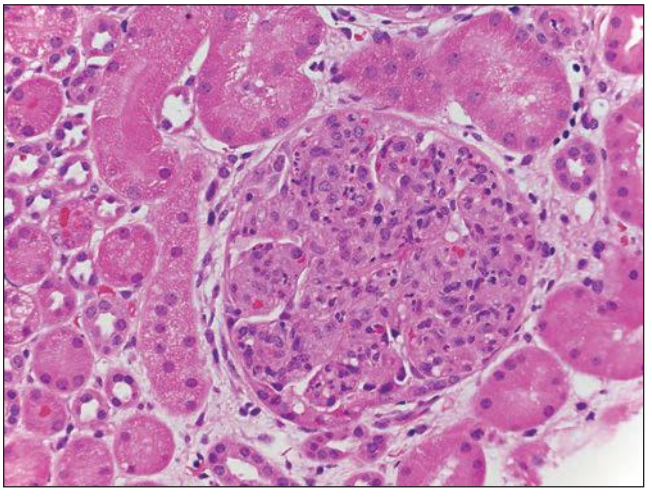

FIGURE 8.5 MPGN type I. There are numerous infiltrating neutrophils (exudative form) resembling acute postinfectious glomerulonephritis by light microscopy. (H&E, ×400.)

severe cases of MPGN. The greatest numbers of monocytes were noted in renal biopsies with the most glomerular hypercellularity and the largest number of glomerular subendothelial and subepithelial deposits. Soma et al. (176) examined the nature of the intraglomerular immune cell infiltration and its relationship to C3 deposits over time. These investigators found monocytes/macrophages and leukocytes to be the predominant cell type at first biopsy (with many fewer T cells). Second biopsy showed either less complement deposition with fewer leukocytes of all types or greater complement deposition with a positive correlation between the number of intraglomerular T cells and monocytes/macrophages (176). Yang et al. (177) and Lan et al. (178), using double immunostaining for CD68 and the proliferating cell nuclear antigen (PCNA), demonstrated that MPGN (presumably type I) is associated with marked macrophage infiltration, with proliferating macrophages ($CD68^+PCNA^+$ cells) accounting for up to 42% of total macrophage population. Macrophage proliferation was largely restricted to areas of severe tissue damage (i.e., glomerular hypercellular lesion and foci of tubulointerstitial damage), suggesting that local proliferation is a mechanism for amplifying macrophage-mediated tissue injury. Macrophage accumulation may be partially related to the marked up-regulation of renal expression of macrophage migration inhibitory factor (MIF). In addition, the glomerular and interstitial macrophage proliferation correlated with loss of renal function and histologic lesions but not with proteinuria. In a recent study, Wu et al. (179) characterized and quantified the proliferating cells in MPGN (presumably type I) using monoclonal antibodies for various cell markers. They demonstrated marked mesangial proliferation/activation coupled with increased neutrophils, macrophages, and T cells. However, endothelial cell proliferation was not obvious. Cases of primary mixed or essential cryoglobulinemic glomerulonephritis with a membranoproliferative glomerular pattern generally have a large number of infiltrating monocytes and macrophages (180,181).

Podocyte changes also develop, especially in patients with nephrotic proteinuria. The early events are characterized by molecular alterations of the slit diaphragm followed by podocyte detachment, hypertrophy, and death if early damage is not reversed. Patrakka et al. (182) investigated the nephrin expression by immunohistochemistry in pediatric kidney diseases including six cases of MPGN type I. The findings did not reveal major alterations of nephrin in MPGN type I when compared with normal controls. In another study, Wang et al. (183) demonstrated a down-regulation of nephrin in patients with MPGN (types not specified) in the glomeruli.

There is marked diffuse thickening of the glomerular capillary walls. The thickening can be more prominent in some glomeruli and in some capillary loops than in others. Periodic acid-Schiff (PAS) and methenamine silver stains show that the thickened glomerular capillary walls often have two basement membranes with a clear or nonargyrophilic region between them. This double contour is sometimes termed *tram tracking, splitting*, or *reduplication* of the GBM (Fig. 8.6). In some capillaries, the production of basement membrane–like structures is very complex, resulting in multiple laminations. The double contour is brought about by mesangial interposition, which refers to the outward migration of mesangial cells, infiltrating mononuclear cells, or even margination of portions of endothelial cells along the inside of the capillary walls, interposing

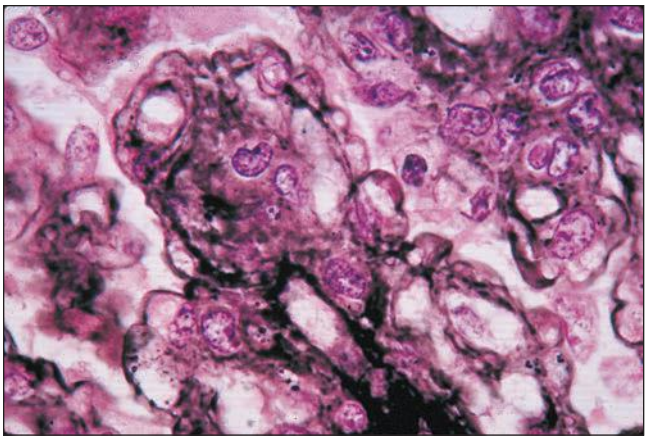

FIGURE 8.6 MPGN type I. Glomerulus with silver stain shows tram tracking or reduplication of the GBM. (Jones silver methenamine, ×600.)

themselves between the endothelium and GBM. Mesangial interposition can be circumferential or partial depending on whether the entire circumference or only a segment of the peripheral capillary wall is involved. Because mesangial or endothelial cells can produce basement membrane–like material, the cytoplasm of these cells and immune complexes are covered on the outside (the Bowman space side) by the original basement membrane and on the inside by the newly formed GBM-like "membrane." Both the membranes stain positively with silver and thus give rise to the double contour.

The newly formed basement membrane–like material (the inner contour) may be thin, incomplete, and at times difficult to discern because of extreme glomerular hypercellularity. Although circumferential mesangial interposition can be seen in a wide variety of glomerular lesions, it is most common, marked, and diffuse in MPGN type I. Nakamoto et al. (184) theorize that this interposition is related to low-grade mesangiolysis and subsequent passive dislocation of the mesangial cells toward the peripheral glomerular capillary walls because of a high hydraulic pressure of blood flow penetrating the lysed mesangium. A widely accepted alternative theory proposes that an active movement by the muscle-like mesangial cells from the contiguous mesangial regions along the lamina rara interna of the GBM, probably in response to subendothelial immune deposits. In certain cases, capillary loops show the spiking phenomenon noted in membranous nephropathy as a result of subepithelial deposits. This finding is more pronounced in the so-called type III MPGN of Burkholder (120,137,138,140).

The glomerular capillary lumens are often diffusely and globally diminished by the increase in matrix and cellularity in the mesangial regions as well as by the thickening of the capillary walls. Generally, the subendothelial deposits contribute little to this luminal narrowing. Infiltrating inflammatory cells also may contribute to this endocapillary hypercellularity and capillary lumen closure. Intraglomerular lipid deposition (mainly apolipoprotein B) can be noted (185). Discrete glomerular subendothelial deposits may be identified with the use of trichrome stains, although they are better demonstrated using EM. Mesangial deposits are generally small and difficult to identify by light microscopy. In some cases,

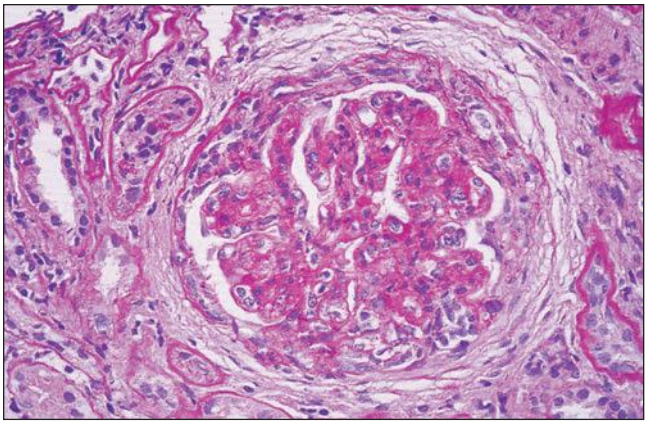

FIGURE 8.7 MPGN type I. Glomerulus from a case of MPGN type I with crescent. (PAS, ×400.)

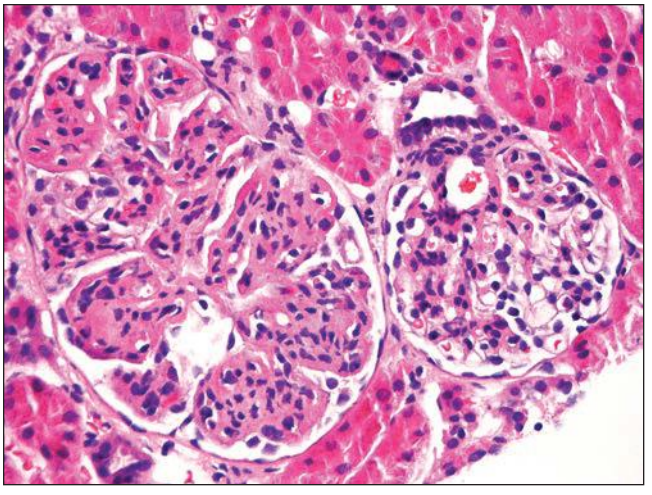

FIGURE 8.8 Focal MPGN type I. One glomerulus shows typical changes of MPGN type I, while the other glomerulus reveals only mild mesangial hypercellularity. (H&E, ×400.)

scattered glomerular fuchsinophilic subepithelial humps may be detected with trichrome stains and oil immersion. Bohle et al. (186) have suggested that "hyperperfusion injury" can be seen with great frequency in MPGN. This is defined as the presence of glomerular adhesions (synechiae), glomerular subendothelial hyalinosis, and fat droplets in the hyaline material.

Crescents occur in approximately 10% of patients (139) (Fig. 8.7). These crescents may be small and focal (147) or large, affecting most of the glomeruli (138). They are often indicative of a poor prognosis (138–140,148,187). In several studies of all types of crescentic glomerulonephritis in children, up to approximately one fourth of the cases are MPGN type I (188). Crescent formation has been noted to develop within weeks following an initial biopsy showing only an MPGN type I pattern with no crescents (189). Parietal epithelial cells may be prominent without the presence of obvious crescents (190).

Serial biopsies are not commonly performed, but in those few patients in whom they have been reported, the glomerular tuft hypercellularity may become less pronounced with an increase in the amount of mesangial matrix (sclerosis) (178). Taguchi and Bohle (191) have described sequential biopsies (separated by a mean of 39 months from initial biopsies) from 33 patients with MPGN type I and DDD. Twenty-four of twenty five patients with diffuse forms of MPGN maintained that pattern on subsequent biopsies, whereas 4 of 6 patients with a focal MPGN pattern showed signs of a diffuse form on the second biopsy. Two patients who had no histologic findings of MPGN on the initial biopsy (one had focal MPGN and another had mild mesangial proliferative glomerulonephritis with small crescents) later showed evidence of a diffuse form of MPGN on subsequent biopsy. End-stage sclerotic glomeruli can develop later.

Striker et al. (192) studied the extracellular components of several renal diseases with progressive glomerular sclerosis (including MPGN) using a variety of immunohistochemical analyses. In advanced stages, the amount of types IV and V collagens, laminin, and fibronectin was increased in the mesangial and sclerotic lesions; however, the staining intensity for type IV collagen, laminin, and fibronectin gradually declined during the progression of glomerular sclerosis. The authors have found types I and III (interstitial) collagens in the glomeruli of those patients with severe damage to the Bowman capsules (as with crescent formation).

There are reports of focal or segmental MPGN (Fig. 8.8) (138,154,193). In these reports, in which only some glomeruli show lesions while others do not, it is not always clear whether the glomeruli that are normal by light microscopy contain deposits when viewed by electron microscopic and immunofluorescence methods. Focal MPGN may progress to typical MPGN, and typical MPGN may regress to focal MPGN. Therefore, focal MPGN is considered to be an early type of typical MPGN or a stage of recovery from typical MPGN. In a case report, Kano et al. (194) described a girl with MPGN type I diagnosed by the third biopsy. The first biopsy revealed endocapillary proliferative glomerulonephritis, and the second biopsy showed focal MPGN. D'Amico and Ferrario (195), in a review of a large number of patients with MPGN type I and DDD, suggest that there are six characterized morphologic variants: classic, nodular, exudative, focal segmental, with massive subendothelial deposits, and crescentic. They believe that these different forms involve different etiologic and pathogenetic factors and that the clinical outcome correlates with the histopathologic patterns. Other researchers believe that these different patterns in MPGN do not relate well to specific etiologic or pathogenetic factors or clinical findings, but rather, represent different points in a continuum of morphologic manifestations of MPGN. In renal biopsies of MPGN, it is important for the pathologist to look for refractile eosinophilic hyaline globules in the glomerular capillary lumens ("hyaline thrombi") suggestive of cryoglobulin deposits. More is discussed about this in the section dealing with cryoglobulinemia later in this in chapter.

Quantitative studies have been conducted on renal biopsies of patients with MPGN type I (196). Glomerular and mesangial volume fractions were increased and related to a diminished GFR, enhanced glomerular permeability to protein, hypertension, and volume fraction of the cortical interstitium. The percentage of the glomerular capillary endothelial circumference (filtration surface) was also smaller. Thus, quantitative measures of glomerular structure were highly correlated with glomerular function.

Tubules

Morphologic changes in the tubules and interstitium generally reflect the changes noted in the glomeruli (139). The tubules may contain hyaline droplets that are protein and lipid resorption droplets (phagolysosomes). These droplets are directly related to the glomerular permeability to proteins and lipids. Tubular lumens may also contain red blood cells. With evolution of the disease toward more severe renal parenchymal damage, interstitial inflammation and edema as well as tubular atrophy and fibrosis develop. However, the study by Schmitt et al. (197) suggests that the tubulointerstitial findings are unrelated to the severity of the glomerular alterations. Severe glomerular lesions can arise in the absence of tubulointerstitial disease; conversely, severe tubulointerstitial disease can be seen with mild glomerular disease. These authors suggest that the tubulointerstitial changes result in many of the renal functional disturbances.

Interstitium

Clusters of interstitial foam cells are observed quite often in MPGN type I and, to an even greater extent, in Alport syndrome. Clefts—sometimes noted in the lumina of tubules—probably are caused by cholesterol ester. Cholesterol granulomas are rare. There is a good correlation between interstitial fibrosis and the level of serum creatinine (198) and other functional abnormalities (196,199). Various cells have been found in the renal interstitium of patients with MPGN type I. Segerer et al. (200) found a predominance of T cells that are positive for CXCR3 (a receptor for the CXC chemokines IP-10 and Mig) and CCR5 (a receptor for the C-C chemokine RANTES). In addition, the number of CXCR3- as well as CCR5-positive T cells correlates with renal function, proteinuria, and percentage of globally sclerotic glomeruli, suggesting an important role during progressive loss of renal function, and as such may represent a potential therapeutic target.

Blood Vessels

Arteries and arterioles are affected in those patients in whom renal failure and hypertension develop. There is severe arterial intimal thickening in patients with long-standing renal disease and in those in whom dialysis has been instituted. If vasculitis is identified, cryoglobulinemia, hepatitis B– or hepatitis C–related MPGN, as well as antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis should be ruled out.

Immunofluorescence Microscopy

As noted earlier, findings by IF microscopy (or immunohistochemistry) are used to classify MPGN into an immune complex variant and a complement dysregulation variant (see Fig. 8.1 and Table 8.1). IF staining patterns are generally quite characteristic (137,140,141,201–204). In the immune complex variant of MPGN, the most consistent finding is positive staining for IgG in a fine to coarse granular pattern along the glomerular capillaries (Fig. 8.9) (201,204). A characteristic picture is produced, with the glomerular capillaries around the periphery of the expanded lobules predominantly (and often solely) affected, so that the lobules stand out quite clearly as a negative zone, cloaked by strongly positive IF. In some patients, staining for IgG decreases as the disease progresses and the deposits become replaced or obscured by the increase in mesangial matrix. Serial renal biopsy studies have shown that some patients have IgG deposits during the early stages

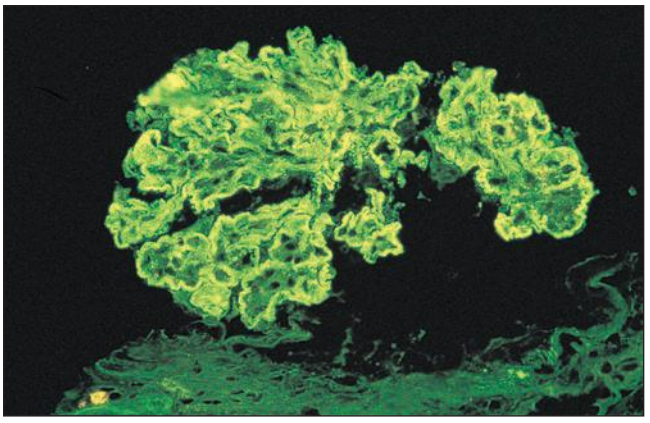

FIGURE 8.9 Immunofluorescence of MPGN type I. There is intense glomerular mesangial and capillary wall staining with anti-IgG antiserum. (×400.)

of the disease, with subsequent biopsies showing only deposits of complement (163). This may prove to be a confounding problem for classification based on relative predominance of immunoglobulin versus complement. Doi et al. (205) demonstrated all four IgG subclasses in renal biopsies of MPGN, but in contrast, other studies (206,207) noted an excess of IgG3 compared with the other classes. IgM is less commonly evident than IgG, but it was present in 86% of patients in one series (204), 73% in another (202), and 60% in a third (147) (Fig. 8.10). A predominance of IgM is typically observed in MPGN type I stemming from chronic bacterial infection, such as osteomyelitis or infected ventriculoatrial shunt. IgA is found even less often but has been observed in one third of the patients in some studies (147,204). It is important to ascertain whether the IgA is the predominant or codominant immunoreactant to diagnose a membranoproliferative form of an IgA nephropathy or an IgA-dominant postinfectious glomerulonephritis, both of which are rare. Orfila et al. (208) noted the presence of both kappa and lambda light chains in MPGN; however, MPGN type I with typical features by light microscopy and electron microcopy can be caused by monoclonal

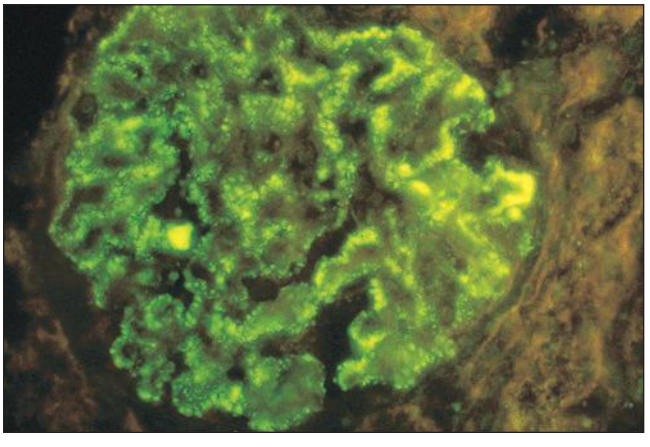

FIGURE 8.10 Immunofluorescence of MPGN type I. There is moderately intense staining for IgM along the glomerular capillary walls in a granular pattern. (×400.) (Courtesy of Dr. Zoltan Laszik.)

immunoglobulin deposition (52). Conspicuous IgM or IgA even in the absence of IgG is indicative of an immune complex MPGN rather than a C3 glomerulopathy variant of MPGN.

In immune complex MPGN type I, C3 is noted in a similar pattern to IgG in all patients and may stain more intensely (Figs. 8.11). In the C3 glomerulopathy variant of MPGN type I, staining for C3 is intense with little or no staining for immunoglobulin (52,53,118). Staining for immunoglobulin and/or C3 typically produces a granular to semilinear staining along the capillary walls. Smooth outer contour of the deposits (due to their conformation by the delimiting outer GBM) provides a useful clue indicating that the deposits are subendothelial (rather than subepithelial). In some instances, the peripheral glomerular capillaries show coarse, somewhat elongated areas of IF that may impart a broken, wide, or band-like pattern.

Immunoglobulin and/or C3 may also be noted in the glomerular mesangium. When there is a great increase in the amount of mesangial matrix, mesangial deposits may be obscured or absent. Early components of the classic pathway of complement activation (especially C1q) are sometimes visible and are present in about one half to two thirds of the patients (201,204). Yamashina et al. (209), using an avidin-biotin-peroxidase complex method and proteolytic digestion of formalin-fixed paraffin-embedded sections, verified the presence of all complement components. Properdin is virtually always present (139). Properdin deposits were found in 90% of cases in one series (147) and in 100% in another (203). Kazatchkine et al. (210) found normal staining of the glomerular visceral epithelial cells (podocytes) with antibodies to C3b receptor in renal biopsies of MPGN type I. Although IF findings along the tubular basement membranes (TBMs) are usually negative, a minority of patients have immune complexes in this area (211).

Early studies by Levy et al. (140,163) of the IF patterns in MPGN type I are consistent with the current concept of two immunopathologic variants, one medicated by immune complexes and one by complement dysregulation. In their study of 36 children, group 1 (26 patients), which appeared to be immune complex mediated, exhibited immunoglobulins and C3; 15 of them had immunofluorescent staining along the glomerular capillary walls but not in the mesangial regions (163). In these 15 patients, IgG and IgM were the most common immunoglobulins, and C1q and C4 were also present. The other 11 patients in group 1 had C3 and immunoglobulins (mainly IgG) along the glomerular capillaries but also mesangial deposits of C3. C1q and C4 were noted in a location similar to that of the immunoglobulins in all patients studied. Group 2 (10 patients) displayed the presence of C3 only, without any immunoglobulin, and thus are consistent with C3 glomerulopathy. C3 was noted along the glomerular capillary walls and in the mesangial regions. No early complement components of the classic pathway were found in group 2.

IF techniques also have been used to search for antigens other than immunoglobulins and complement. Murphy and d'Apice (212) and Nakamura et al. (213) studied the kidneys with MPGN with a variety of monoclonal antibodies to glomerular proteins and demonstrated fibronectin in both the GBM and mesangium. Hara et al. (214), using antisera to the human GBM, type IV collagen, and P3 antigen (which is a nephritogen in rats), noted that in MPGN, the expanded mesangium and expanded glomerular capillary walls reacted positively with anti-GBM and anti–type IV collagen antibodies; only the outer portion of the capillary walls was positive with anti-P3. Büyükbabani and Droz (215) further studied alterations of the matrix compartment. They observed strong accumulation of fibronectin in the expanded mesangial regions (as well as along the migration track of the proliferating mesangial cells), with accumulation of laminin, α_1/α_2 chains of type IV collagen, and heparan sulfate proteoglycan. Type I collagen was also present in the central part of the mesangial regions. The distribution of these matrix components was different in cases of MPGN than in those of other glomerular lesions, such as membranous glomerulopathy, focal segmental glomerulosclerosis (FSGS), or crescentic glomerulonephritis.

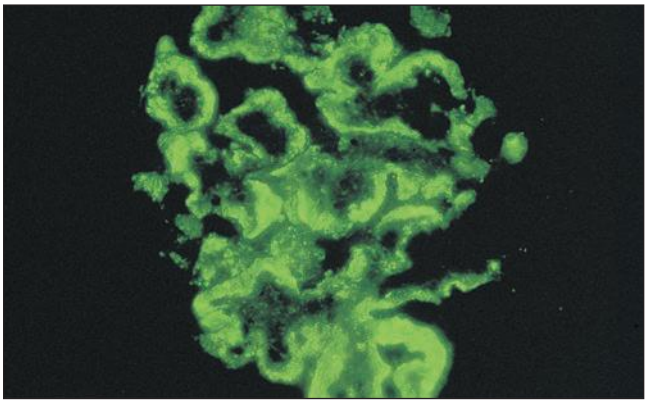

FIGURE 8.11 Immunofluorescence of MPGN type I. There is intense staining aong all glomerular capillary walls for C3. The granular staining is quite broad in this instance. (×400.)

Electron Microscopy

EM has helped to distinguish classic MPGN type I from other glomerular lesions with membranoproliferative features and clarify the findings of light microscopy (120,137,140,141,147,151,204,216–218) (Figs. 8.12 to 8.16). Ultrastructural studies have shown subendothelial dense deposits (see Figs. 8.12 to 8.14) with varying amounts of mesangial, intramembranous, and subepithelial deposits. There are mesangial hypercellularity and increased mesangial matrix, both of which are often present between the normal-appearing GBM and the glomerular endothelium (mesangial interposition) (see Fig. 8.15). As described earlier, the new mesangial matrix–like material produced by the migrating mesangial cells and endothelial cells creates an inner "basement membrane." The thickened capillary wall is therefore composed of two or more layers of basement membrane–like material, interposed mesangial cells, and electron-dense immune-type deposits (see Figs. 8.12 to 8.15). In some cases, the double contour of the peripheral glomerular capillary wall is caused by the interposition not of mesangial cells but of monocytes instead (2); this finding is especially common in patients with cryoglobulinemia and MPGN. Some have suggested that cells in these positions are portions of invaginated endothelial cells.

The electron-dense deposits are generally described as subendothelial but are really nearer the inner aspect of the original basement membrane. Their exact position is somewhat obscured because of the migrating mesangial cells and the new layers of basement membrane–like material. The deposits

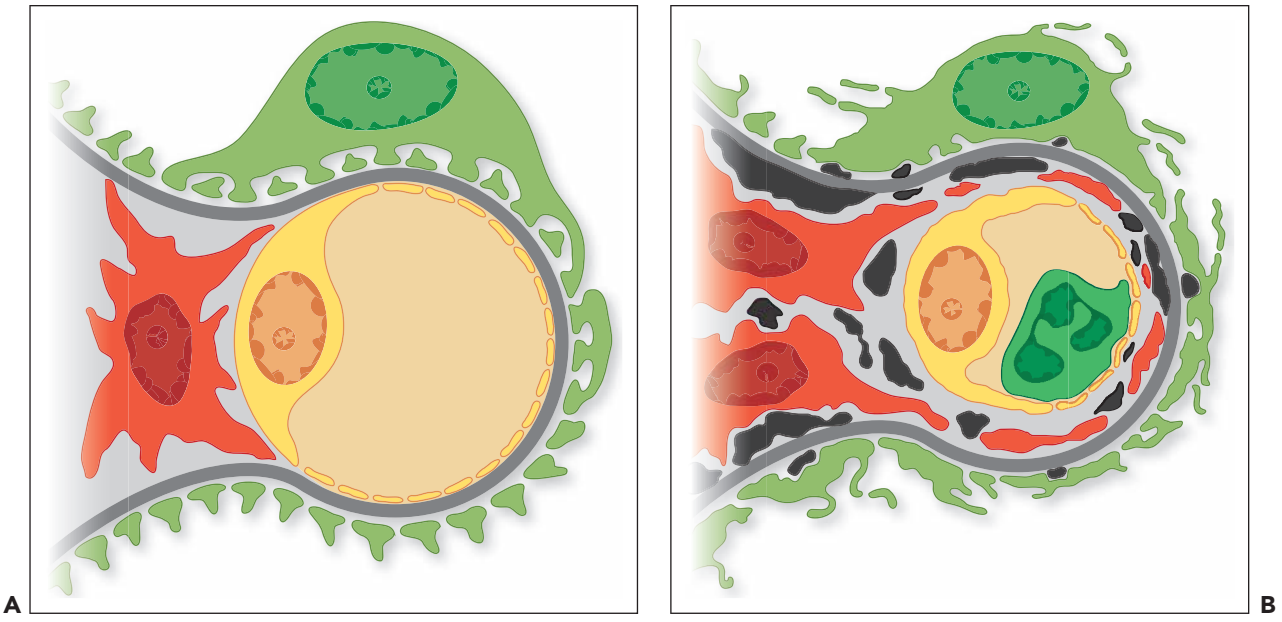

FIGURE 8.12 Drawing depicting a normal glomerular capillary and adjacent mesangium **(A)** compared to the ultrastructural changes of MPGN type I **(B)**. Note the subendothelial, mesangial and few subepithelial dense deposits (*black*), capillary wall mesangial interposition (*red*), new layers of subendothelial matrix material (*gray*), and increase in mesangial cell numbers.

range from small and discrete to large and elongated; they are found both along the periphery of the filtering glomerular capillary walls and just under the paramesangial GBM as it overlies the mesangium. Discrete electron-dense deposits also may be found within the mesangium; at this site, they are usually small, but sometimes, they are more bulky. They are associated with an increase in mesangial or endocapillary hypercellularity (see Fig. 8.16). Sometimes, the IF discloses intense and widespread positive staining along the capillary walls, whereas only scant deposits are present on the EM.

Some patients have scattered, small glomerular subepithelial deposits quite similar to the humps noted in classic acute postinfectious (poststreptococcal) glomerulonephritis (137,141,149,204). They are found in as many as 30% (141) to 50% (140) of cases studied. Small subepithelial deposits may have accompanying protruding spikes of GBM-like material similar to that noted in membranous nephropathy. Sato (219) evaluated the glomerular subepithelial deposits in patients with various forms of MPGN. Most patients also had undergone serial biopsies. Despite diminished glomerular cell proliferation in most second biopsies, the glomerular subepithelial deposits were increased along with thickening and irregular structuring of the GBM (219). As described later, the presence of a large number of glomerular subepithelial deposits forms part of the pattern of MPGN type III of Burkholder. Occasionally, intramembranous deposits are noted in MPGN type I, and fragmentation of the GBM can occur (149). The application of silver impregnation to renal EM may help resolve the various patterns of MPGN (220). Ultrastructural studies at high magnification (e.g., ×30,000) are important to determine if the deposits have a microtubular substructure such as seen in immunotactoid glomerulopathy or cryoglobulinemia (1).

There is an increase in mesangial cellularity and matrix formation. Hypercellularity, production of matrix (sclerosis), and movement or extension of the mesangial cells around the glomerular capillary wall are all manifestations of the great activity on the part of the mesangial cells. Platelets or fibrin tactoids may be seen in one fourth of the biopsies studied by EM. Glomerular visceral epithelial cell foot process effacement is common. Using immunoelectron microscopy, Huh et al. (221) observed that the expression of nephrin in human glomerular disease (including MPGN type I) was lower in regions where the foot processes were effaced and comparable to normal controls where the foot process interspaces were preserved. Bonsib (222) used enzymatic digestion to remove cellular elements and deposits, coupled with scanning electron microscopy, to study the three-dimensional aspects of the glomerulus. The picture of MPGN type I is illustrated in Figure 8.17.

Clinical Course, Prognosis, Therapy, and Clinicopathologic Correlations

MPGN type I is generally progressive, and overall, renal prognosis is poor. However, the clinical course of patients can be quite variable (52,53,117,137,140,144,147,223). The nephrotic syndrome persists in some, whereas others have intermittent nephrotic or nephritic episodes with abnormal findings on urinalysis between the episodes. Rarely, patients may become entirely asymptomatic, with normal renal function and urinary findings (151,224). This clinically silent phase may last for many years despite persistence of the renal morphologic abnormalities.

Clinical remission has been noted in 5% to 20% of patients (138,175,225). Complete remission occurred in only

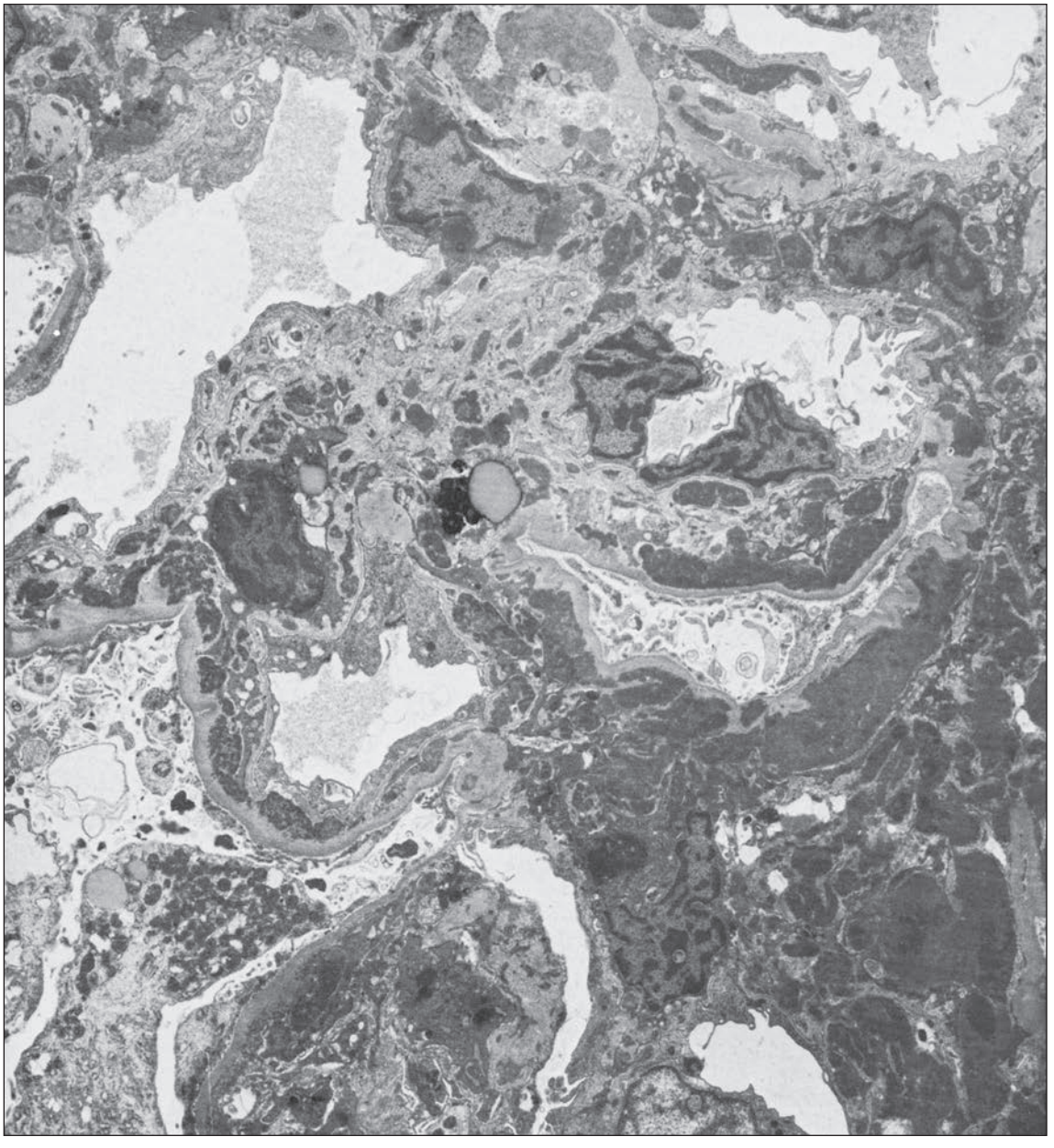

FIGURE 8.13 MPGN type I. Note the presence of a large number of discrete electron-dense osmiophilic deposits throughout the glomerular structures. There are numerous large subendothelial deposits and scattered mesangial deposits. Some of the glomerular capillaries are closed, and others are patent. (Uranyl acetate and lead citrate, ×4785.)

a few patients for whom there has been long-term follow-up (124,140,148). The series of Levy et al. (140) showed complete remission in only 4 of 84 children. In this study, 17 children went into remission, but 13 relapsed; in only 4 patients was the remission maintained for periods of up to 4 years (140). Kim et al. (139) noted complete clinical remission in 5 of 63 patients.

End-stage renal disease (ESRD) develops in a large number of patients (124,140,141,144,147,148,195,226). Survival rates are not uniform from study to study, not only because of inclusion of patients with different severities of renal disease but also because of different starting points for calculating the time course of the patients (i.e., from the clinical onset or from the point of the diagnostic renal biopsy). In the studies of Cameron et al. (124,148), the actuarial survival was 50% at 11 years, which was similar to the survival rate found by Habib et al. (137). Death and the need for chronic dialysis or renal transplantation were regarded as equivalent. In the large series of children from Paris referred to earlier (140), 84 were followed for periods of up to 18 years; about 25% died from renal insufficiency or on long-term hemodialysis, 11% continued in chronic renal failure, 21% had persistent nephrotic syndrome, 38% had isolated proteinuria, and only 5% appeared

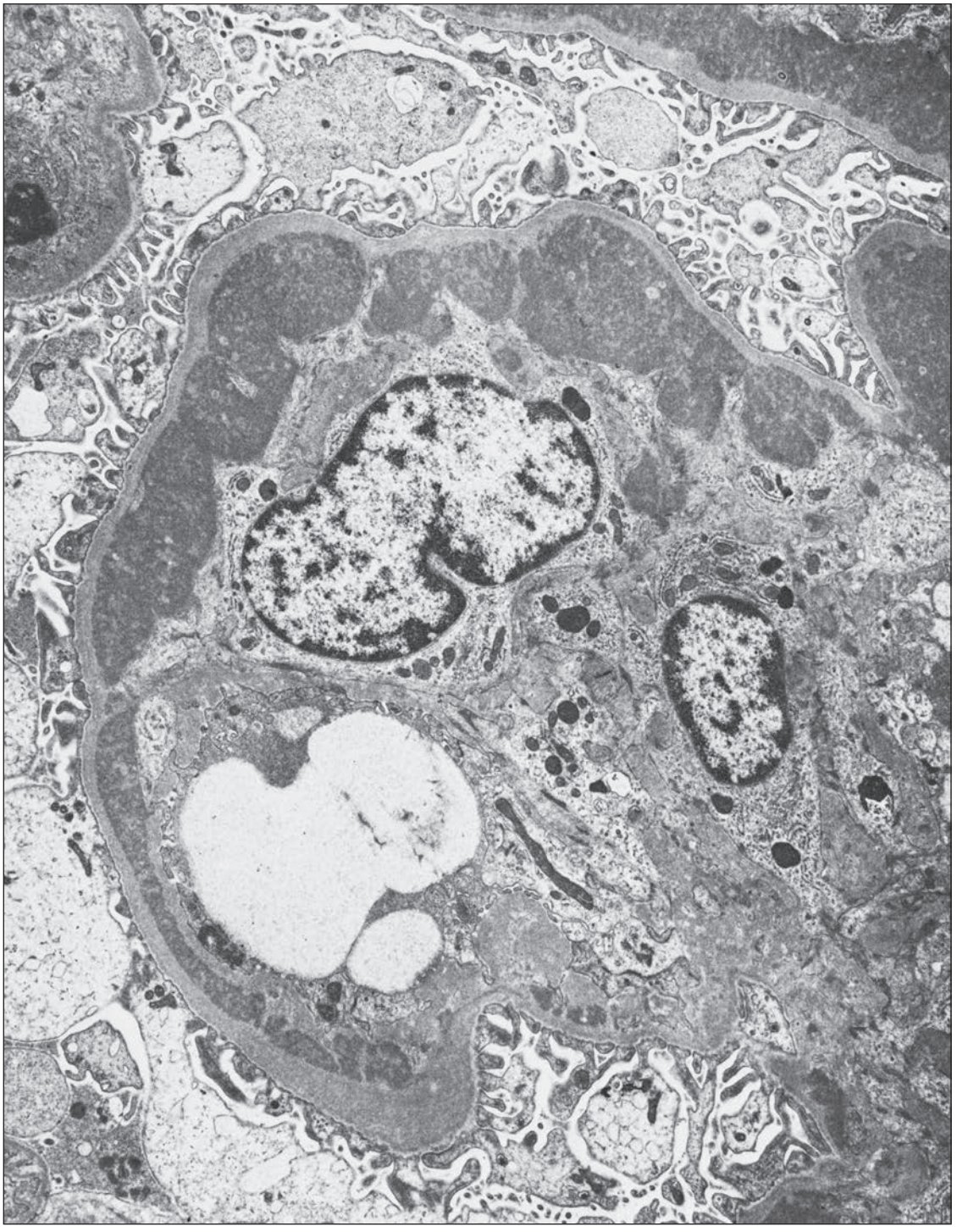

FIGURE 8.14 **MPGN type I.** Electron micrograph shows a segment of a glomerular capillary with large, discrete, electron-dense deposits in the subendothelial space. (Uranyl acetate and lead citrate, ×5844.) (Courtesy of Dr. Edith Hawkins.)

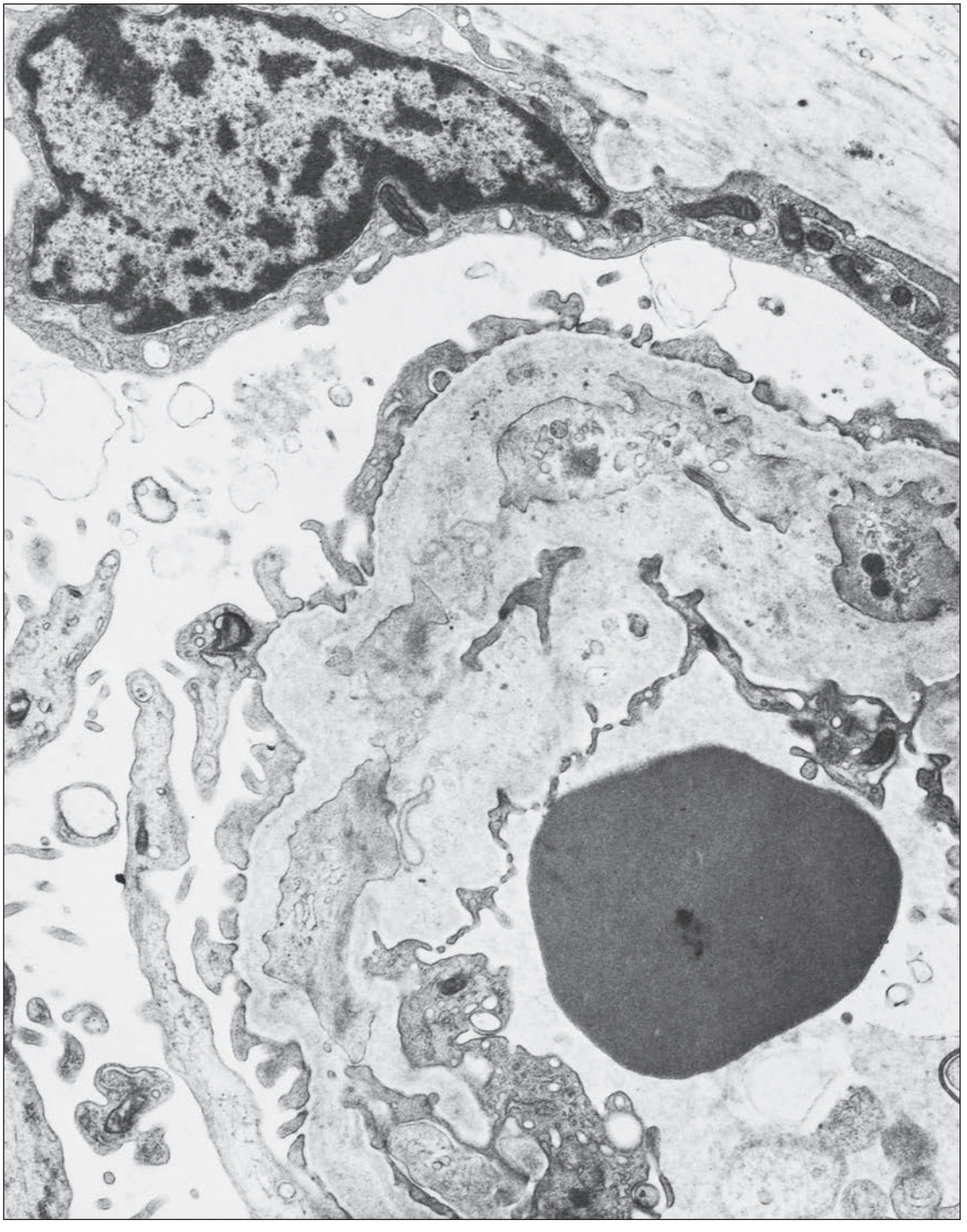

FIGURE 8.15 MPGN type I. Electron micrograph of portions of the glomerular capillary wall shows double basement membrane–like material. The mesangial cell has interposed itself between the endothelium and basement membrane and in so doing has also produced an inner (subendothelial) mesangial matrix/basement membrane–like material. (Uranyl acetate and lead citrate, ×13,475.) (Courtesy of Drs. Srinivasan Rajaraman and Tito Cavallo.)

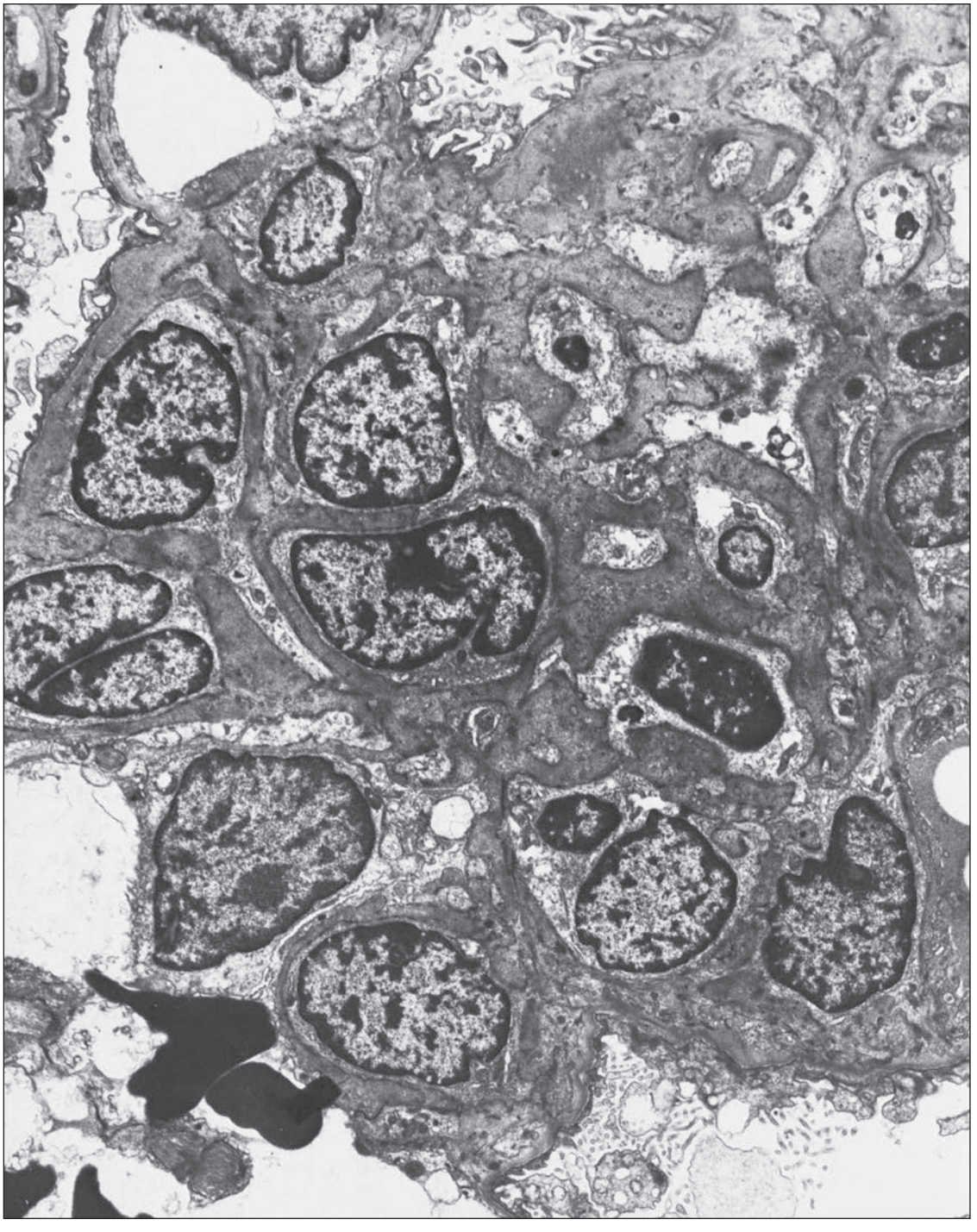

FIGURE 8.16 MPGN type I. A portion of a glomerulus shows increased numbers of cells in the mesangial or centrilobular regions. Although a number of these cells may represent native mesangial cells, it is also possible that many of them are migrant monocytes from the peripheral circulation (i.e., hematogenous). (Uranyl acetate and lead citrate, ×5850.)

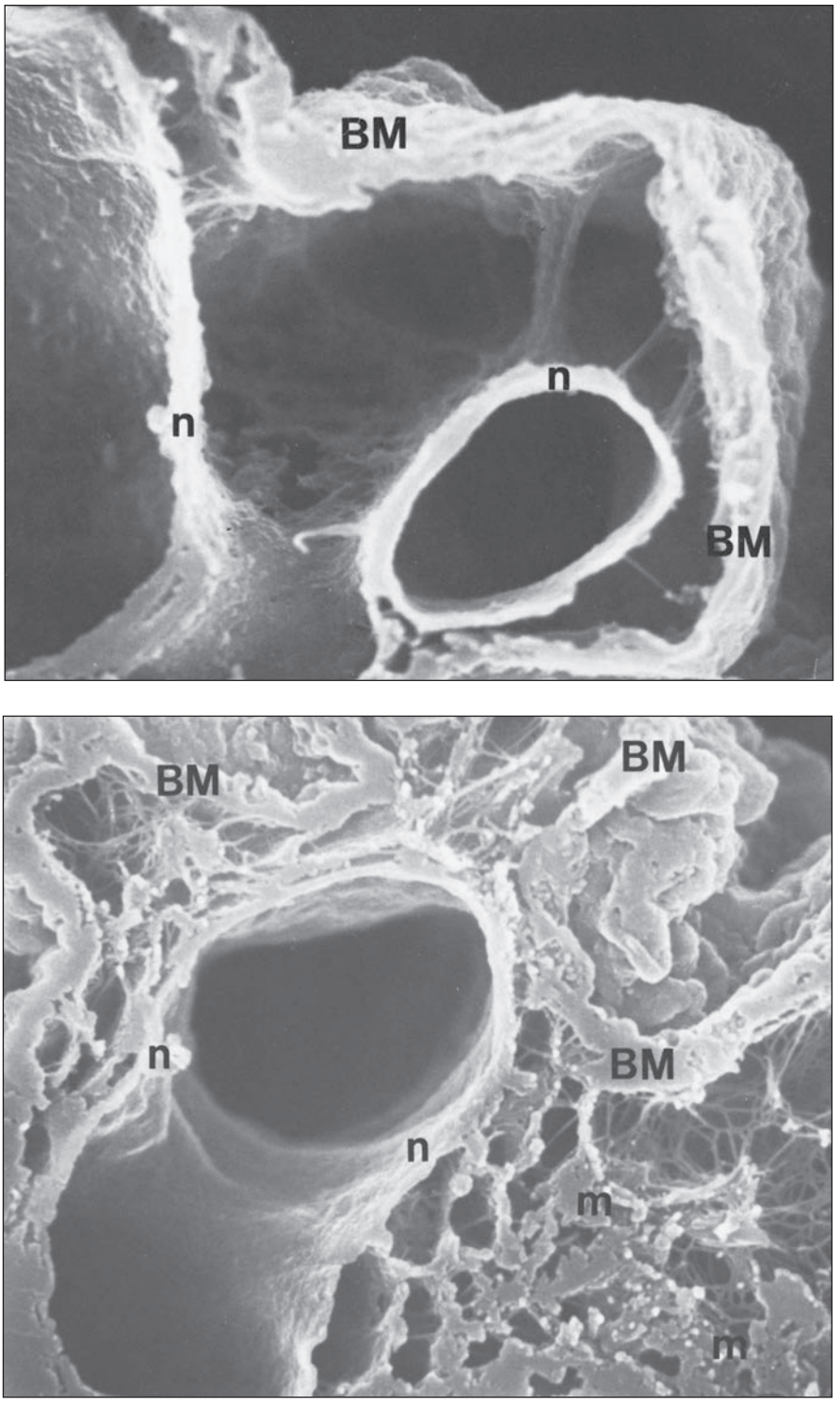

FIGURE 8.17 MPGN type I. Scanning electron microscopic technique of Bonsib (222) in which the cellular elements and deposits have been removed by enzymatic digestion, leaving behind only extracellular basement membranes and basement membrane–like material from a renal biopsy of MPGN type I. **A:** The enlarged subendothelial space is clearly seen. **B:** Greater complexity of new basement membrane–like material, compared with **(A)**, is evident within the subendothelial space. Also visible is the continuity of the enlarged subendothelial space with the mesangial matrix. BM, original or native GBM; n, new basement membrane–like material; m, mesangial matrix. (×12,000.) (Courtesy of Dr. Stephen M. Bonsib.)

to experience spontaneous renal remission. Subsequent renal biopsies sometimes showed a decrease in mesangial cellularity or disappearance of double contours, but these features were not always related to clinical improvement. Donadio et al. (147) studied mainly adults and observed that ESRD developed in 40% during the course of follow-up; the mean time of onset of renal failure was just over 5 years. In the large series of 220 patients with MPGN type I from Germany, 23% of patients died during follow-up, 26% experienced ESRD, 24% suffered chronic renal failure, and only 27% stabilized in terms of renal function (with an average follow-up of 5 years) (226); 5 years after biopsy, 49% of the patients had died or required regular dialysis. D'Amico (195,227), in a survey of the literature, found no substantial differences in the average renal survival times between different geographic regions (the average renal survival at 10 years in his review of MPGN type I was 60% to 64%). A number of patients have persistent proteinuria (with or without the nephrotic syndrome) with no renal insufficiency. In two series (140,147), the patients in this category accounted for 27% of patients. In another report, renal survival was 80% at 10 years in MPGN type I (228). A more recent study revealed a 10-year renal survival of 63.5% (144).

Features that are considered to influence the outcome of the disease are listed in Table 8.3. There appears to be no major difference in clinical outcome between children and adults, although the data are often difficult to interpret because of possible differences in biopsy policies between children and adults; that is, the entry criteria or reasons to perform renal biopsy may be different for children and adults. The study of Magil et al. (141) found that the 50% survival time in children was 76 months, whereas the 50% survival time in adults was 44 months. Men tended to experience renal failure in a relatively shorter time than do women and children.

TABLE 8.3 Indicators of poor renal prognosis in patients with MPGN type I

Strong association
- Hypertension (147,226,229,230)
- Impaired renal function (137,144,147,149)
- Low hemoglobin (231)
- Nephrotic syndrome (102,124,137,138,140,149)
- Urinary polymers of albumin and proteinuric pattern (232)
- Crescents (>20%) (102,149,187)
- Mesangial proliferation (102)
- Tubulointerstitial disease (102,198,199)
- Glomerular and interstitial α-smooth muscle actin expression (233)
- Intensity of glomerular C1q deposition (138)

Less strong association
- Macroscopic hematuria (137,231)
- Male sex (141)
- Adults (144,148)
- Glomerular and interstitial macrophage proliferation (179)
- Interstitial T-cell infiltration (200)

No correlation
- Serum complement (137,144,231,234)
- Nephritic factors (137,144)
- Circulating immune complexes (167,235)

Nephrotic syndrome at clinical onset may be indicative of a poor prognosis (102,124,137,138,140,141,148,154). Bazzi et al. (232) found that the presence of urinary polymers of albumin was associated with progression to chronic renal failure in MPGN type I; this correlation is enhanced by the simultaneous presence of sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) proteinuric pattern with low molecular weight proteins up to 10 kDa, which is known to be associated with diffuse tubulointerstitial lesions. Other features suggestive of a poor prognosis include the absence of clinical remission during the course of the disease, initial depression of renal function/low GFR (144,147,149,229), persistent hypertension (154,226,230), and the presence of gross hematuria (140,146,147,223,230), although Watson et al. (154) did not find that gross hematuria was a sign of poor prognosis. Patients with hypocomplementemia do not fare worse than those with normal levels of complement (144,146,223,231,234). Although some researchers have suggested that depression of Clq and C4 (191)—in addition to depression of C3—presages a poor renal prognosis, others do not agree. In adult patients, renal survival is inversely correlated with age at diagnosis (144). Treatment with angiotensin-converting enzyme inhibitors and/or angiotensin receptor blockers but not immunosuppressive agents was associated with a better renal survival (144).

Morphologic indicators of poor renal prognosis are also not absolute. Patients with large numbers of crescents do not do well (102,139,140,148,187). Glomerular C1q staining and its intensity is associated with poor renal outcome (135). Glomerulosclerosis is also thought to signal a poor prognosis (148). Little et al. (102) reported that the degree of mesangial proliferation is associated with a higher propensity to ESRD. As noted in other renal diseases, an increase in renal interstitial fibrosis correlated directly with the level of serum creatinine (102,198,226). The role of tubulointerstitial injury on MPGN progression was questioned in studies comparing MPGN with IgA nephropathy, possibly reflecting differences in the mechanisms of interstitial leukocytic infiltration (236,237). Kawasaki et al. (233) demonstrated that increased glomerular and interstitial α-smooth muscle actin expressions correlate with disease progression in children with MPGN type I. The infiltration of glomerular and interstitial macrophages ($CD68^+$ cells) has no prognostic value for the clinical outcome (233). However, as mentioned earlier, the glomerular and interstitial $PCNA^+$ macrophages correlated with loss of renal function (177,178). Watson et al. (154) suggested three subtypes with different outcomes: those with focal segmental "duplication" of the GBM, those with diffuse duplication of the GBM, and those with mixed segmental and global duplication of the GBM. Those patients with focal and segmental duplication had a favorable renal outcome compared with the others with more diffuse disease. Clinical remission accompanied by morphologic evidence of regression on subsequent renal biopsy has been noted by a few investigators (225,238).

There are numerous reports of recurrence of the original disease in the kidneys grafted into patients with ESRD caused by MPGN type I (102–108,116,148). The true incidence of recurrence of MPGN type I is difficult to determine because it has clinical and histologic features somewhat similar to those of chronic transplant glomerulopathy, which is a component of chronic allograft rejection (103,109,110). Some series are marred because the diagnosis of recurrence is based on clinical rather than morphologic evidence. Thus, strict morphologic

criteria (including light microscopy, EM, and IF) must be applied, and knowledge of the primary disease leading to renal failure must be available.

The percentages of reported recurrence of MPGN type I range from 27% to 65% (52,53,102,104,107,108,111). These wide differences may be due to the small number of patients studied, dissimilar patient populations or selection, changing criteria for morphologic diagnosis, different etiologies, and heterogeneity of patients with MPGN type I (107,108,139). The incidence of recurrence increases with time (111). The clinical manifestations of recurrence of MPGN type I may be mild or even absent following renal transplantation, although proteinuria, the nephrotic syndrome, hypertension, and renal insufficiency may develop (104,107,139). The presence of large, discrete, subendothelial immune-type electron-dense deposits on EM, accompanied by broad glomerular capillary wall deposits of immunoglobulins and C3, suggests recurrence of MPGN type I rather than transplant glomerulopathy or thrombotic microangiopathy. Some researchers feel that this differential diagnosis may be challenging even with the aid of the electron microscope (112). In a study using protocol biopsies, recurrent MPGN type I is diagnosed in 12 of 29 patients (41.4%) (107). All recurrence occurred during the first 14 months posttransplant (median 3.3 months, range 1 week to 14 months). Recurrence was significantly more common in patient with low levels of C3 or C4 or both. Recurrence appears to be more common in recipients of living donors although the difference does not reach statistic significance. An increased risk of recurrence was observed in patients with the histocompatibility leukocyte antigen (HLA) haplotype B8DR3 (113); others did not find such an association (107).

To address whether MPGN type I has an impact on renal allograft, Angelo et al. (108) analyzed allograft survival, causes of graft failure, and outcomes using the United Network for Organ Sharing (UNOS) database covering the period of 1987 to 2007. Among the 189,211 primary kidney transplants during this period, 811 individuals (0.4%) had MPGN type I. Patients with MPGN type I were significantly younger at the time of transplant (mean age 36 years) compared with other forms of GN (mean age 44 years) and all other disease groups (mean age 46 years). Graft failure rates were significantly higher in the MPGN type I group (44.5%) compared with cohort of other forms of GN (38%). The 10-year death-censored graft survival (56.2%) was significantly worse than the GN cohort (65.2%) and the population with other diseases (60.0%). Disease recurrence was the primary cause of graft failure representing 14.5% of cases, which was significantly higher than the GN cohort (6.6%) and all-other-disease recurrent failure (4.4%). Similarly, others reported the incidence of graft loss at 2 years and 10 years owing to recurrence is 14% and 15%, respectively (105,106).

MPGN type I has been reported to recur in successive renal transplants. Angelo et al. (108) also analyzed the 11,441 primary transplant recipients who received a second kidney transplant during the 20-year study period. Similar to the initial transplant, the death-censored 10-year survival rate was significantly worse in patients with MPGN type I than other GN or other diseases. Andresdottir et al. (111) observed a high risk of recurrence (80%) in a second graft in patients who had experienced a recurrence in the first graft. Whether any therapy can prevent the recurrence of MPGN type I is unclear. Schwarz et al. (116) concluded that cyclosporine A did not prevent recurrence or de novo renal disease, including MPGN type I, although the clinical course seemed to be mitigated by cyclosporine A therapy. Case reports have shown that graft survival may be improved by the addition of cyclophosphamide to immunosuppressive drugs (114,115). Interestingly, there is a report of two renal allograft recipients with the electron microscopic picture of MPGN type I transmitted via donor kidneys (239); the glomerular subendothelial deposits initially present resolved over a period of 6 to 9 months following transplantation.

In general, supportive measures to reduce proteinuria and control hypertension and hyperlipidemia should be considered an integral part of therapy. Such measures may ameliorate the disease progression without major adverse effects. In a recent retrospective study consisting of 49 patients with MPGN type I, the authors found that renin-angiotensin blockade was associated with a better renal survival but not with immunosuppressive treatment (144).

It should be emphasized that most clinical trials included a mixture of patients with unknown proportions of MPGN type I, MPGN types III, and DDD (MPGN type II). Furthermore, MPGN type I was not classified into the immune complex variant versus the C3 glomerulopathy variant. Therefore, caution needs to be exercised in drawing conclusions. Several studies (225,228,240) reported that long-term alternate-day prednisone therapy is beneficial in children with MPGN and successfully stabilizes renal parenchymal damage. This experience was gained over a 30-year period. Although glomerular sclerosis was apparently increased with therapy, the glomerular capillary walls appeared thinner, with more patent glomerular capillaries; moreover, there was less mesangial hypercellularity in the second renal biopsy taken after therapy (225). West concluded that long-term use of alternate-day high-dose prednisone appears to be an effective regimen in both controlled and uncontrolled studies (240). McEnery (241) observed that the long-term cumulative renal survival improved between 1957 and 1987, reaching 75% to 80% in the 10th year and almost 60% in the 20th year.

The International Study of Kidney Disease in Children (242,243), in a randomized, controlled clinical trial of 37 children with MPGN, suggested that alternate-day steroid therapy could slow the progression of renal disease. However, there was no statistical improvement in the GFR, and there were substantial side effects to the drugs. Further studies were conducted by the same group, and one randomized, double-blind, placebo-controlled clinical trial of 80 patients with idiopathic MPGN (42 with MPGN type I) showed that alternate-day prednisone appeared to improve the outcome of children with this disease (155). There were fewer treatment failures in the treated group (40% compared with 55% in the untreated group) and a renal survival rate (at 130 months) of 61% among treated patients compared with 12% among untreated patients (155). Others (244) also have suggested that prednisone therapy can retard the development of ESRD in children with MPGN. Yanagihara et al. (245) investigated the long-term prognosis in 19 children with MPGN type I who were diagnosed via school urinary screening. Except for 1 patient on short-term therapy, 18 of the 19 patients received long-term (4 to 12 years) alternate-day prednisolone following pulse methylprednisolone. As of the last observation (10 to 24 years after disease onset), urinary abnormalities and hypocomplementemia had disappeared in 15 patients, whereas mild proteinuria without hypocomplementemia remained in 4.

No patients required hemodialysis. The authors concluded that early detection and therapy using pulse methylprednisolone followed by alternate-day prednisolone were a safe and effective method for treating MPGN type I (245).

Although immunosuppressive trials in children have been encouraging, many immunosuppressive trials in adults with MPGN have not revealed any significant benefit (246). However, it has been reported that an intensive and prolonged regimen of intravenous boluses of methylprednisolone plus oral cyclophosphamide and prednisone is effective in inducing remission and halting progression of MPGN to ESRD (247). In one study, pulse cyclophosphamide plus prednisolone produced transient reductions in six patients (248). Another study suggested that cyclosporine can be considered in steroid-resistant primary MPGN (249). Preliminary studies suggest that the combination of steroid and mycophenolate mofetil (MMF) may reduce proteinuria and preserve renal function in both adults and children (250,251). Plasmapheresis also has been recommended as a form of therapy (252).

Because of the evidence of increased platelet activation and consumption (253), a number of prospective studies used platelet inhibitors (254–257). Although there was a beneficial effect on renal function, a high complication rate related to the drugs was noted in one of the investigations (256). In one other, Donadio et al. (254) reported stabilization of both renal function and structure in patients treated with the platelet-inhibitor drugs aspirin and dipyridamole (although they subsequently retracted this conclusion). In a third study (255), proteinuria was significantly lower in the treatment group compared with the control group. Finally, in a small uncontrolled study (257), the authors showed that MPGN type I in adults with nephrotic-range proteinuria and normal/moderately impaired renal function, aspirin and dipyridamole significantly reduced proteinuria with stable renal function during the 2-year observation period. These authors suggested that aspirin plus dipyridamole may be of value in reversing nephrotic syndrome and the associated risks (e.g., thrombosis, sepsis) in patients with MPGN and moderately impaired renal function (255,257). Chapman et al. (258) reported a favorable response in a small number of children with a combination of immunosuppressive drugs and anticoagulation.

Recently, more targeted therapies have shown promising results in anecdotal case report and small clinical trials (259–261). Dillon et al. (259) conducted an open-label trial of rituximab (a chimeric murine/human monoclonal antibody against CD20, which is primarily found on the surface of B cells) in six adults patients with MPGN type I (four idiopathic and two with cryoglobulinemia) and followed the patients for 1 year. Rituximab administration is associated with peripheral blood B-cell suppression and at least a partial remission of proteinuria in five of six patients. In a case report (260), eculizumab (a monoclonal antibody against complement C5) is used to treat refractory MPGN type I in a 16-year-old girl who showed dramatic response to therapy, supporting the role of complement dysfunction in the pathogenesis of MPGN type I (as in DDD and C3 glomerulonephritis).

Taken together, widely accepted and evidence-based therapeutic regimens aimed to prevent or slow down the natural progression of MPGN type I are not currently available. The published controlled trials generally consist of a small number of patients and are short term in nature, while the larger trials carried out to date have been uncontrolled. In addition, many studies are composed of various types of MPGN (immune complex MPGN type I, C3 glomerulopathy variant of MPGN type I, MPGN type III, and DDD) in unknown proportions making the analysis of therapeutic results more difficult. Thus, caution must be exercised when interpreting the published therapeutic studies of MPGN. Well-controlled prospective studies involving large numbers of patients are needed because of the prolonged and variable natural history of the disease.

MEMBRANOPROLIFERATIVE GLOMERULONEPHRITIS TYPE III

There is no consensus regarding whether the two variants of MPGN type III are distinct entities or variants of MPGN type I and C3 glomerulopathy. In this chapter, we described MPGN type III as distinct entities, based primarily on their distinctive pathologic features, with the caveat that their relationships to each other and to type I and C3 glomerulopathy are not resolved. Dense deposit disease, previously classified as MPGN type II, is currently classified as a complement-mediated C3 glomerulopathy and is discussed in Chapter 9.

Burkholder et al. (120) discussed a type of MPGN under the name of mixed membranous and proliferative glomerulonephritis. This pattern had some of the features of typical MPGN type I, such as thickening of the glomerular capillary walls, double contours, mesangial interposition, and subendothelial deposits. In addition, there were silver-positive spikes along the outer GBM and trichrome-positive subepithelial deposits such as are seen in stage II membranous glomerulopathy. Ultrastructural studies confirmed the presence of glomerular electron-dense deposits, and immunofluorescent staining showed a heavy granular pattern along the glomerular capillary walls and mesangium for C3 and sometimes for IgG and IgM. The clinical features were similar to those of MPGN type I. Serum C3 was depressed in two of five patients. This pattern was described subsequently in a patient with both hepatitis B surface and e antigens (262). Many renal pathologists consider this form of glomerulonephritis to be a variant of MPGN type I with an extreme degree of the glomerular subepithelial immune complex deposition that is frequently observed to a lesser extent in typical MPGN type I.

Another pattern of injury was also designated MPGN type III by Strife et al. in Cincinnati (122,263,264) and independently by Anders et al. in Mainz (121). It is characterized by a distinctive pattern of GBM disruption observed by EM. This form of MPGN is often called MPGN type III of Strife/Anders (type IIIS/A) to distinguish it from MPGN type III of Burkholder (type IIIB). The following discussion is mainly focused on MPGN type IIIS/A with a brief mention of type IIIB.

Clinical Presentation

The clinical and laboratory findings in MPGN type III are generally similar to those of patients with MPGN type I. In a comparison of MPGN types I and III, Braun et al. (228), Jackson et al. (263), and West and McAdams (265,266) noted that type III was more frequently detected by the chance discovery of hematuria and proteinuria in otherwise healthy individuals; this finding suggests that the onset is insidious and

remains subclinical for some time. The nephrotic syndrome is also a common mode of presentation. MPGN type III has been noted in patients with primary Sjögren syndrome (267), HIV infection with pulmonary hypertension and hepatic cirrhosis (268), and as a prodrome to systemic lupus erythematosus (SLE) (5).

Especially, in MPGN type IIIS/A, serum C3, C5, and properdin levels are low in about half of the patients, but the early classic pathway complement components (C1q and C4) are generally at normal levels, suggesting alternative pathway activation. One or more of the other terminal complement components (C6, C7, and C9) are commonly depressed. There is no evidence of classic pathway activation. C3 nephritic factor (C3NeF) is associated with the complement perturbation (7,263) and may be involved pathogenetically as discussed in Chapter 9. The serologic and immunohistologic features of MPGN type IIIS/A are most often consistent with a C3 glomerulopathy whereas the serologic and immunohistologic features of MPGN type IIIB more often resemble MPGN type I, suggesting that this is merely a variant of type I with numerous subepithelial deposits.

Pathologic Findings

Light Microscopy

In MPGN type IIIS/A, the light microscopic findings include varying degrees of accentuation of the glomerular lobular pattern, mesangial hypercellularity, and diffuse glomerular capillary wall thickening (Fig. 8.18). In general, there is less pronounced glomerular hypercellularity and enlargement in type III compared with type I (121,263). In MPGN type IIIB, subepithelial spikes are commonly noted. The pattern may be focal and segmental by light microscopy.

Immunofluorescence Microscopy

IF microscopy (264) shows IgG and/or C3 in a finely granular pattern along the glomerular capillaries and in the mesangial regions (Fig. 8.19). IgM is visible in some patients. Properdin is often present and prominent and, like C3, occurs in a granular pattern along the glomerular capillary walls and in the mesangial regions. Like MPGN type I, some cases of MPGN types III disclose only C3 deposition without immunoglobulin. These cases are best classified as C3 glomerulonephritis, whereas those with substantial staining for immunoglobulin are more likely immune complex–mediated glomerulonephritis (see Table 8.1) (52).

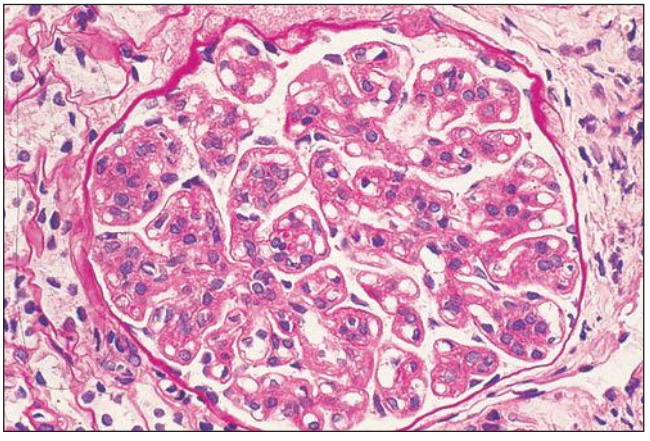

FIGURE 8.18 MPGN type III of Strife/Anders. This representative glomerulus shows a global increase in cellularity in the tuft. There is accentuation of the lobular pattern, and the light microscopic pattern is similar (if not identical) to MPGN type I. (PAS, ×400.) (Courtesy of Dr. Zoltan Laszik.)

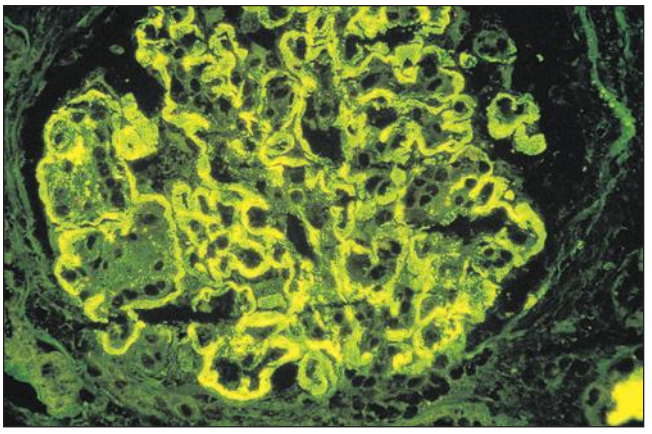

FIGURE 8.19 Immunofluorescence of MPGN type III of Strife/Anders. Note the intense granular to band-like glomerular capillary wall and mesangial staining for C3. (×400.)

Electron Microscopy

There are glomerular subendothelial and subepithelial deposits that are often contiguous or connect through intramembranous deposits in the lamina densa of the GBM (121,122,217). In MPGN type IIIB, the deposits are electron dense like those of MPGN type I or membranous glomerulopathy (Fig. 8.20). In MPGN type IIIS/A, the deposits have a washed-out or electron-lucent appearance. There is often layering of the lamina densa–like material. This pattern was initially described on the basis of ultrathin silver-impregnated plastic-embedded sections studied with the electron microscope (220) (Figs. 8.21 and 8.22), although this distinctive pattern of injury can be identified by routine EM. There is complex disruption of the GBM (lamina densa), often with thickening and expansion of the basement membrane and layering by a silver-negative basement membrane–like material. The complex lesions of the GBM unique to type IIIS/A may originate from several generations of subepithelial and subendothelial deposits forming in conjunction with multiple interruptions of the lamina densa such that the deposits are partially confluent. Since each generation of deposits is covered by new lamina densa–like material, the lesions develop a complex laminated appearance. In contrast to the MPGN type IIIB (120), subepithelial deposits and spikes are less common in MPGN type IIIS/A (122). Strife et al. (122) also considered that their type III differed from that of Burkholder in the presence of disruption and extensive duplication of the GBM, features not commented on by Burkholder. They concluded that although some features were similar to those seen in patients with type I, their type III was distinctive.

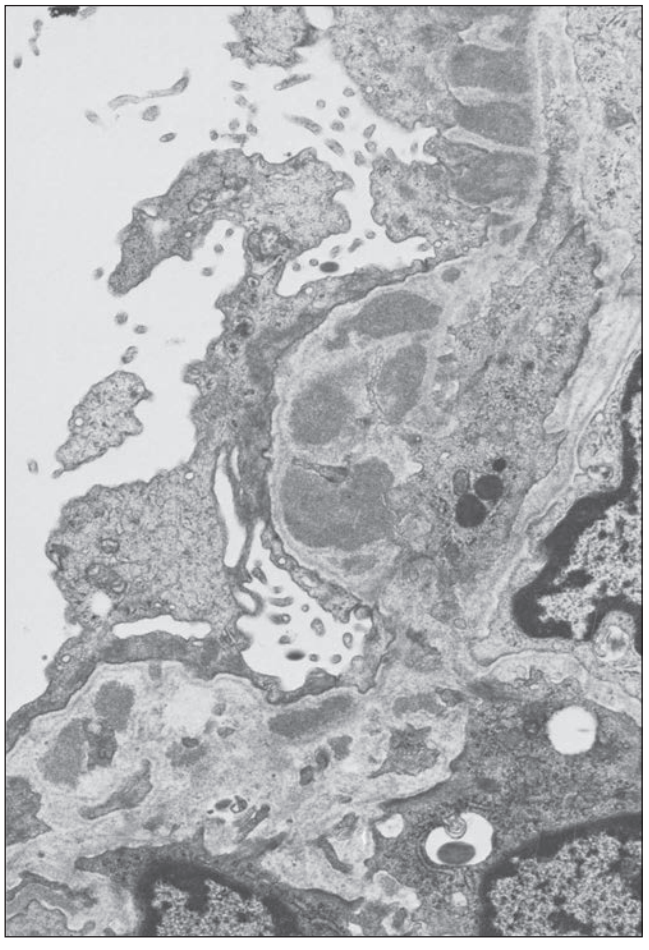

FIGURE 8.20 MPGN type III of Burkholder. There are large intramembranous deposits surrounded by a matrix and subepithelial deposits with adjacent spikes of GBM-like material (top right). (×15,000.) (Courtesy of Dr. A. James McAdams.)

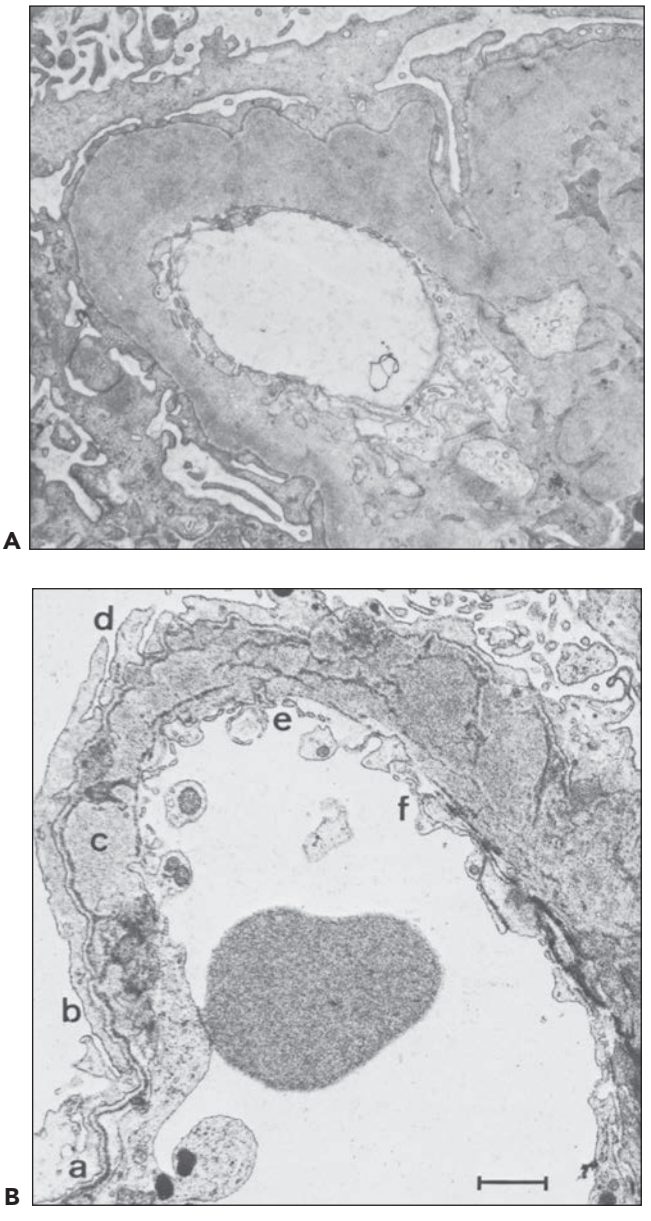

FIGURE 8.21 MPGN type III of Strife/Anders. A: Electron micrograph (not impregnated with silver) shows diffuse, ill-defined basement membrane thickening. **B:** Silver-impregnated material allows resolution of basement memabrane thickening. Several stages are shown starting from lower left: *a*, intact lamina densa; *b*, disrupted and distorted argyrophilic material; *c*, subendothelial deposits; *d*, subepithelial and subendothelial argyrophilic layer; *e*, multifold layering; *f*, complete loss of argyrophilic linear structure or replacement of the lamina densa, respectively, by accumulating masses of nonargyrophilic material in places reminiscent of subepithelial deposits. (×9000.) (From Anders D, Agricola B, Sippel M, et al.. Basement membrane changes in membranoproliferative glomerulonephritis. II. Characterization of a third type by silver impregnation of ultrathin sections. *Virchows Arch A Pathol Anat Histopathol* 1977;376:1.)

West and McAdams (265,266) reported that in patients with MPGN type III, as the hypocomplementemia becomes normocomplementemic and the disease goes into remission, the electron-dense deposits disappear. The first to disappear are glomerular subendothelial deposits, followed after approximately 1 year of normal C3 levels by the disappearance of paramesangial deposits. Finally, after a number of years of normocomplementemia, the complex GBM lesions can also disappear, but there is no evidence that this is inevitable. The timing of the disappearance of glomerular subepithelial deposits is not clear.

Clinical Course, Prognosis, Therapy, and Clinicopathologic Correlation

Studies on the outcome of MPGN type III are compromised by inadequate characterization of the patients with respect to type IIIB versus type IIIS/A and with respect to evidence for immune complex mediation versus C3 glomerulopathy. In the studies of MPGN type III that have been reported, the nephrotic syndrome, hypertension, and impaired renal function at the time of renal biopsy are harbingers of a poor prognosis (102,228,264). Although some studies have suggested that type III will stabilize or improve following treatment with alternate-day prednisone (264,269), other studies (228) disagree. Braun et al. (228) compared the course and

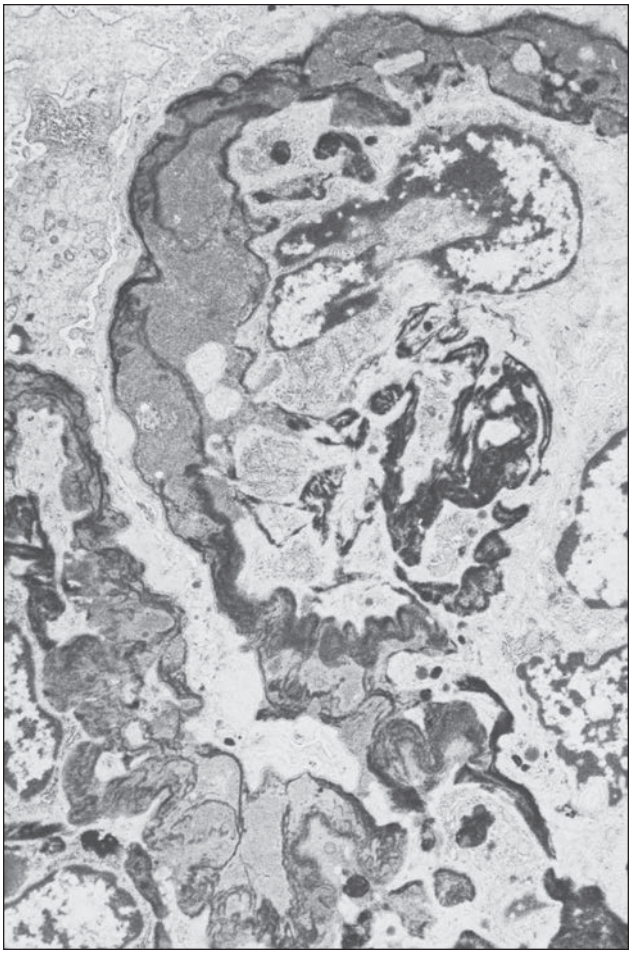

FIGURE 8.22 MPGN type III of Strife/Anders. Higher magnification of the silver impregnation of the plastic-embedded sections for transmission electron microscopy; a segment of a glomerulus from a patient with MPGN type III of strife. The remnant GBM is quite argyrophilic (electron dense) but contains numerous large (and sometimes confluent), less-argyrophilic regions representing deposits. These large deposits are contiguous throughout the GBM and lead to complex disruptions of the lamina densa. (×10,000.) (Courtesy of Dr. A. James McAdams.)

long-term outcome of 21 patients with MPGN type I and 25 patients with MPGN type III. They found that MPGN type III patients have longer-lasting hypocomplementemia, hematuria, and proteinuria; experience more disease relapses; and have significantly greater loss of renal function during alternate-day prednisone therapy when compared with MPGN type I. In addition, survival analysis implies a more guarded prognosis for long-term renal survival in patients with type III compared with type I. Several reports (102,228,234) failed to demonstrate any relationship between the presence of nephritic factors (NeFs), the duration or severity of hypocomplementemia, and either renal survival or disease progression in MPGN type III.

Information on recurrent rates for MPGN type III has been limited because of the lack of sufficient numbers of reported cases. Morales et al. (270) reported the first case of recurrent MPGN type III in a 48-year-old man with recurrence 16 months post–cadaveric renal transplantation, with graft failure at 7 years. Briganti et al. (106) reported recurrence of MPGN type III in one of two patients, resulting in graft loss. However, further details are not provided. Ramesh Prasad et al. (271) reported a 57-year-old white man with recurrent MPGN type III 18 months after a living-related renal transplantation that resulted in graft failure shortly after. This pattern also has been described in a patient with plexogenic pulmonary arteriopathy and acquired immunodeficiency syndrome (34). Little et al. (102) showed recurrence of MPGN type III in 4 of 12 patients (33%). Younger age at initial diagnosis and the presence of crescents on the original biopsy were independently associated with recurrence on multivariant analysis. Thus, MPGN type III can recur in the renal transplant. The clinical picture of recurrence may be proteinuria and progressive decline in allograft function (106,270,271).

PATHOLOGIC DIFFERENTIAL DIAGNOSIS OF MEMBRANOPROLIFERATIVE GLOMERULONEPHRITIS

Accurate diagnosis of MPGN requires the combination of clinical history, laboratory tests, and renal biopsy examination by light microscopy, IF, and EM. As our understanding of the pathogenesis of MPGN deepens and the concept of MPGN evolves, the traditional classification of the disease has been modified (see Fig. 8.1 and Table 8.1). Once an MPGN pattern of glomerulonephritis is identified by light microscopy, appropriate diagnostic classification of MPGN requires (a) categorization by immunohistology as having overt immunoglobulin deposits (immune complex mediated) versus C3 with little or no immunoglobulin (C3 glomerulopathy); (b) categorization by EM as having features of type I, DDD/type II, type IIIB, or type IIIS/A; and (c) accessing available clinical and laboratory data to identify possible etiologies and disease associations (e.g., see Table 8.2 for type I).

The approach to the differential diagnosis of MPGN type I or III requires careful analysis of IF to distinguish immune complex–mediated glomerulonephritis (with immunoglobulin and C3 deposition in the glomerular capillary walls and mesangium) from the complement-mediated C3 glomerulopathies (reviewed in detail in Chapter 9). In the immune complex–mediated glomerulonephritis with an MPGN pattern, the underlying secondary causes listed in Table 8.2 should be carefully considered (especially infection-associated and autoimmune-mediated conditions). Once the secondary forms of MPGN have been excluded, then the subtypes (i.e., type I, type IIIB, or type IIIS/A) should be differentiated by EM. Regarding secondary MPGN, the possibilities of infections (such as endocarditis, hepatitis B/C, infected ventriculoatrial shunts, or malaria), autoimmune diseases (such as SLE or Sjögren syndrome), dysproteinemia (such as cryoglobulinemia or light/heavy chain deposition disease), and numerous other conditions must be sought by physical examination, clinical history, and serologic studies. The morphologic features of glomerular diseases that can mimic MPGN, especially by light microscopy, are described in depth throughout the book and will not be repeated here. Monoclonal immunoglobulin

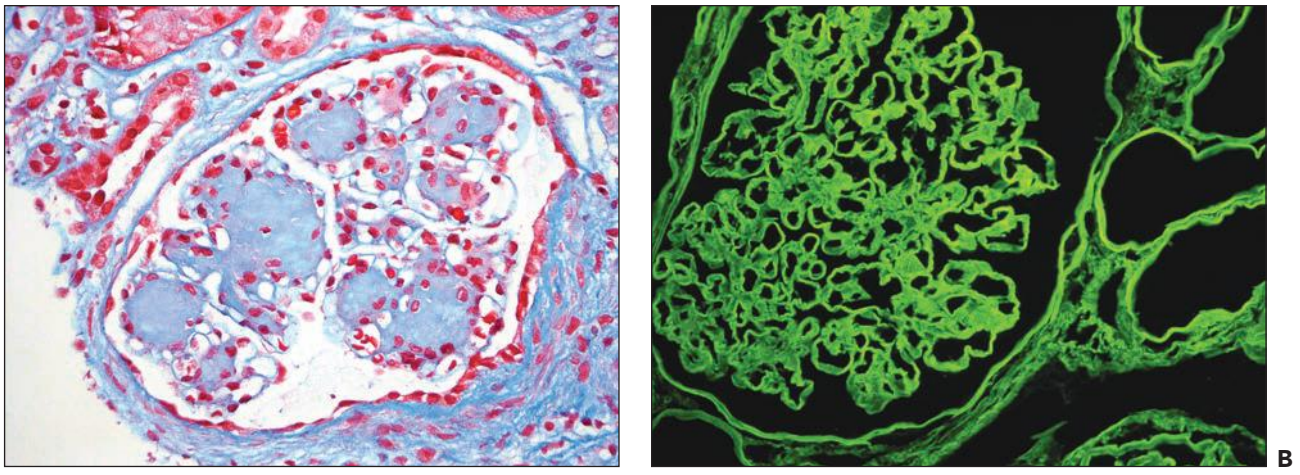

FIGURE 8.23 Kappa light chain deposition disease. A: There is solidification in mesangial areas that also show higher numbers of cells. Lobulation is accentuated. (Trichrome, ×400.) **B:** Immunofluorescence microscopy reveals extensive staining of the expanded mesangial regions, glomerular basement membranes, Bowman capsule, and tubular basement membranes with an antiserum for kappa light chain (×400).

deposition disease (MIDD) can be identified (Fig. 8.23) by IF staining with both kappa and lambda light chain antisera and heavy chain antisera. Ultrastructural studies are useful in distinguishing many MPGN mimics; for instance, fibrillary glomerulonephritis is characterized by randomly arranged fibrils (diameter of 16 to 24 nm) in the mesangium and GBMs coupled with polyclonal IgG and complement deposition on IF microscopy, and immunotactoid glomerulopathy is characterized by microtubular structures ranging 30 to 50 nm in diameter (218).

Membranoproliferative pattern can also be seen in non–immune-mediated diseases that can be easily distinguished from MPGN by immunohistology and EM. For example, in subacute or chronic thrombotic microangiopathy, which can have marked thickening of capillary walls with GBM replication, IF is negative for immunoglobulins and complement components except for fibrin/fibrinogen. EM reveals widening of subendothelial space (lamina rara interna) with accumulation of electron-lucent "fluff." No immune-type electron-dense deposits are present.

ETIOLOGY AND PATHOGENESIS

Role of Complement Activation and Nephritic Factors

The complement system is composed of over 30 plasma and cell surface–associated proteins and functions in both innate and adaptive immunity for defense against microbial agents. It contains three activation pathways (i.e., classic, lectin, and alternative) that converge on the cleavage of C3 (272,273). The classic pathway is activated by immune complexes or aggregates of IgG and IgM. The lectin pathway is activated via plasma mannose-binding lectin (MBL) and ficolins binding to carbohydrates, for example, on microbes. In contrast, the alternative pathway is continuously "turned on" because of the spontaneous activation of C3 and its promiscuity in binding to a wide range of suitable acceptor sites (272,273). The activation of complement is tightly regulated by cell-associated and circulating regulatory proteins. Complement activation generates chemoattractants (C3a, C5a) for leukocytes and terminal components (C5b-9) that directly mediate cell injury. Refer to Chapter 9 for diagrams of the complement activation and regulation pathways.

MPGN was initially described by a series of authors in the context of its association with hypocomplementemia (133,134). The term coined by West et al. (133) was *hypocomplementemic persistent glomerulonephritis*. Depression of the serum C3 level has been found in MPGN type I, type III (144,146,265,266,274,275), and DDD (type II), which is reviewed in Chapter 9. Serum levels of the early components of the classic pathway of complement activation (e.g., C1q and C4) are not as commonly or severely depressed in MPGN type III (especially IIIS/A) as in MPGN type I (140,275). Terminal complement pathway activation in plasma has been studied, and elevated levels of terminal complement complexes have been identified in the sera of patients with MPGN (276). Clardy et al. (277) measured serum levels of C3 through C9 in hypocomplementemic glomerulonephritides and noted that the late terminal components were activated to a greater extent in MPGN type III than in type I.

Several possible explanations have been advanced to account for the low levels of serum C3. Interpreting some of these studies is complicated by not knowing what proportion of the MPGN patients had immunohistologic evidence for immune complex–mediated MPGN (which would involve classic pathway activation) versus C3 glomerulopathy variant of MPGN mediated by complement dysregulation, which would involve alternative pathway activation. Causes for decreased circulating complement in MPGN patients include CICs activating the classic complement pathway, decreased synthesis, increased consumption of C3 in the glomerular lesions, extravascular sequestration of C3, genetically determined abnormalities in complement regulation, and the presence of autoantibodies that interfere with complement regulation (including NeFs) in the serum that lead to consumption of C3. There is little direct evidence of decreased synthesis (278,279), although Charlesworth et al. (280) found reduced rates of C3

synthesis in patients with hypocomplementemia caused by negative feedback produced by the circulating C3 breakdown products. Increased consumption of C3 in the glomerular lesions (e.g., by glomerular immune complexes) is considered unlikely because of the absence of correlations between disease activity in the glomerulus and the levels of serum complement (275) and by the observation that removal of both kidneys does not restore serum complement levels to normal (281). There is also little evidence of extravascular sequestration of C3 (280).

The concept of enhanced breakdown of C3 received initial support from the classic studies of West et al. (282), who detected C3d, a breakdown product of C3, in the serum of patients with MPGN type I. A C3-activating factor was noted in similar patients (283). Much investigation has been conducted on characterizing and determining the role of C3-activating factors, which are now referred to as nephritic factors (NeFs) or C3 nephritic factors (C3NeFs) (275,283–287). C3NeF is an autoantibody directed against the convertase of the alternative pathway of complement activation (C3bBb).

C3NeF activates the alternative pathway of complement by stabilizing the alternative pathway C3 convertase, the production of which requires C3b, factor B, and factor D. Because C3b is constantly being generated by convertase and is at the same time an essential subunit of the convertase, the system constitutes an amplification loop. Under normal circumstances, C3bBb is formed in small amounts and is regulated by two control proteins, factor I and factor H. Factor I inactivates C3b to iC3b, while factor H displaces Bb from C3bBb, making the C3b molecule vulnerable to the action of factor I. C3NeF is an IgG autoantibody with specificity directed against newly formed determinant on C3bBb that binds to and stabilizes the fluid phase and the membrane-bound C3bBb so that it becomes resistant to factor I and factor H and yet retains the ability to cleave additional C3 molecules (165,275,284,288). The exact mechanism by which this stabilization occurs is unknown and may vary among patients. Both C3NeF and properdin bind to and stabilize C3 convertase (as opposed to factors I and H, which degrade C3 convertase). The difference between C3NeF and properdin is that properdin is a physiologic protein normally present in the serum, whereas C3NeF was once thought to be present only in serum in pathologic conditions. However, studies by Spitzer et al. (289) have suggested that the ability to make C3NeF is present in normal individuals from the time of birth, indicating that C3NeF may play a more important physiologic role than previously thought (289). In addition, the stabilizing function of properdin on C3 convertase is reversible by the action of factor H, whereas the stabilizing action of C3NeF is not. The activity of C3NeF is properdin independent and heat insensitive (7); this allows rapid, continuous fluid-phase C3 breakdown through the C3 amplification loop with little effect on the terminal complement components (54,165). C3NeF has been found in the serum of 20% to 30% of patients with MPGN type I; it has been demonstrated in up to 50% of patients with MPGN pattern and associated with cryoglobulinemia (3,290), SLE (291), and shunt nephritis (11). Various techniques have been used to enhance the sensitivity and to detect and characterize C3NeF (292–294).

Nephritic factor of the terminal pathway (NeFt) also has been described. NeFt is a properdin-dependent and heat-sensitive factor that slowly converts C3 and activates terminal complement components (7,54,165,295). Because activation of C5 requires at least two C3b molecules in close proximity (7,277), NeFt-stabilized convertase is thought to have the composition (C3b)nBbP (P, properdin). NeFt has been found among 20% to 30% of patients with MPGN type I and 78% of patients with MPGN type III (7,277). NeFt has not been reported in healthy subjects.

A third nephritic factor, C4NeF, is an autoantibody directed against C4b2b, the classic pathway C3 convertase. C4NeF has been found in some patients with MPGN type I (with or without accompanying C3NeF) (296).

Several observations have provided evidence to support the notion that uncontrolled systemic activation by NeFs or other factors of the alternative complement cascade plays a significant role in the pathogenesis of MPGN (particularly MPGN type III). First, NeFt have been shown to be responsible for hypocomplementemia in MPGN type III. Second, in MPGN type III, subepithelial deposits on the GBMs overlying the mesangium correlate with a depressed level of C3 (or a depressed level in the recent past) and the subendothelial deposits correlate strongly with hypocomplementemia. Finally, heterozygous absence of a factor H–binding site on C3b (55) has been shown in a patient with MPGN type III. Factor H is essential for the inactivation of C3bBb, which is constantly being formed in vivo; C3bBb accumulates and leads to hypocomplementemia with factor H dysfunction. NeFs have been less frequently noted in MPGN type I, presumably because some and possibly most MPGN type I is mediated by immune complexes rather than complement dysregulation. However, it is believed that the complement is activated by C4NeF in some patients with MPGN type I, and high titers of functionally significant factor H autoantibodies have been reported in a patient with MPGN type I (56).

The pathogenic potential of NeFs is not clear. For example, no direct correlation has been shown between the NeFs or their surrogate, hypocomplementemia, and the glomerular lesions or its progression (144,228,234). NeFs often can be detected in patients with nonhypocomplementemic MPGN. These differences may be partially explained by the fact that not all NeFs are directed against the same epitope and that epitopes can change in individuals over time. In a study by Ohi et al. (297), NeF not able to activate the alternative pathway was identified in some patients, indicating that C3NeF exhibits functional heterogeneity (e.g., in the ability to stabilize C3 convertase in the presence of control proteins, factors H and I).

NeFs may persist in the circulation (accompanied by low levels of C3 and CH50) after bilateral nephrectomy (281). However, a patient with ESRD caused by DDD was sequentially studied after renal transplantation (298). C3NeF activity disappeared following renal transplantation and bilateral nephrectomy; there was no change in other antibodies. This case suggested to the authors that the C3NeF autoimmune response is an antigen-driven expansion of self-reactive B-cell clones in response to a specific process occurring in these diseased kidneys.

Role of Complement Deficiency

Abnormalities in complement can participate in the pathogenesis of immune complex MPGN by enhancing the generation or impeding the clearance of immune complexes (299,300). Abnormalities in complement can participate in

the pathogenesis of C3 glomerulopathy variant of MPGN by causing abnormal regulation of complement activation. MPGN has been associated with a number of complement-deficient states, such as genetic deficiencies/mutations of C2 (57,58,163), C4 (59,60), C3 (57,61), C6 (57,62), C7 (57), C8 (57), C9 (63), factor B (57), factor H (64,65,144,301), factor I (144,302), and C1 inhibitor (303). Complement abnormalities can facilitate immune complex MPGN by (a) impairing immune defense against infections that predisposes to chronic bacterial and viral infections and subsequent immune complex formation (57,299,300); (b) impairing the solubilization, disaggregation, and clearance of deposited immune complexes (57,304); and (c) reducing complement-dependent phagocytosis of apoptotic cells or impairing negative selection of autoreactive B cells resulting in nephritogenic immune responses (61). Coleman et al. (57) noted complement deficiencies with a significantly higher incidence rate (23%) in patients with MPGN types I and III than among normal subjects (7%) or patients with other types of glomerulonephritis (5%). These complement deficiencies in patients with MPGN were partial in nine patients and virtually complete in another. They were present for long periods of time and were found in family members. The deficiencies in six patients were thought to be the result of null structural genes, and in two, they were associated with synthesis of a structurally abnormal component. Welch et al. (304) noted inhibition of immune complex solubilization in the sera of patients with MPGN types I and III; the inhibition was more dramatic in those with active disease, but it did not correlate with the form of therapy, proteinuria, level of CICs, or serum level of complement.

Prolonged hypocomplementemia induced by chronic administration of zymosan (305) or cobra venom factor (306) failed to induce chronic glomerulonephritis. There are limited experimental models of immune complex nephritis or nephritis mediated by indirect activation of the complement pathway that closely resemble MPGN type I. MPGN type I has been described in young Finnish Landrace lambs (307) and dogs (308) that are C3 deficient. The early lesion in the lambs is a predominant deposition of C3 that later develops into a more generalized immune complex renal disease with the deposition of immunoglobulins (IgM, IgA, and later IgG). Likewise, characteristic lesions of MPGN type I were developed in dogs (308). In addition, mouse models of cryoglobulinemia-associated MPGN has been established, which may provide a useful tool to further study the pathogenetic events of MPGN (309).

Infection and Chronic Antigenemia

Information on the etiologic agents and the exact pathogenesis in MPGN is not completely understood; this is particularly true in childhood and adolescent cases since many clinicians believe that MPGN type I in adults is frequently secondary to known causes (e.g., infective endocarditis, hepatitis C, and other chronic infections). It has been suggested that infectious disease may provoke immune responses that lead to immune complex deposition within glomeruli and that the type of infection influences the resultant glomerular pathology. The exact nature of the putative antigen(s) in most patients (especially in children) with MPGN type I is unknown, but there are many examples of secondary MPGN type I (especially in adults) that appear to be caused by immune complexes generated by infections or autoimmune or neoplastic diseases. Elevated ASO titers are noted in some patients with MPGN type I (140,151). A variety of bacterial organisms have been associated with and implicated in the genesis of the forms of MPGN type I in the context of infective endocarditis and infected ventriculoatrial shunts. Meningococcal infection has been reported in patients (children and adults) with MPGN type I, depressed complement levels, and NeFs (20). Investigators have found evidence of enhanced gut permeability in patients with non-IgA immune complex glomerulonephritis (including MPGN) (310), suggesting the role of mucosal immunity in primary glomerulonephritis.

The role of viruses in the induction of MPGN is not fully elucidated. Antibodies to certain viruses, such as BK papovavirus, have common antigenic determinants present on human immunoglobulins and are known to give a false-positive IF reaction because of this cross-reactivity (38). Thus, caution must be exercised in interpreting the presence of viral antigens as the cause of MPGN. MPGN type I owing to hepatitis B and C is discussed later in this chapter. Much of the older literature is confusing because of the failure to distinguish between the different types of MPGN (and mixed with unknown proportions of DDD and C3 glomerulonephritis), and information based on the current approach is rare. EM and IF studies are often missing from these publications, and of course, hepatitis C was not known or demonstrable in the earlier reports.

Role of Immune Complexes and Humoral Immunity

There is much evidence to suggest that the immunoglobulin-rich variants of MPGN type I are a chronic immune complex–mediated glomerulonephritis. This includes the finding of immunoreactants in the glomeruli, the presence of serum and glomerular cryoglobulins (1), the presence of CICs in the serum in about half of the patients (167,168,235), and the occurrence of secondary MPGN type I in patients with known immune complex diseases, such as SLE (6), Sjögren syndrome (311), shunt nephritis (11,312), chronic bacteremia (147), and chronic hepatitis B or C infections (21,313). In addition, the pattern of complement activation is via the classic complement pathway in many patients, favoring the presence of deposited CICs or in situ immune complex formation. Most specimen with MPGN type I with substantial glomerular IgG also have prominent C1q staining consistent with classical complement pathway activation. In other cases, complement could be activated by the MBL pathway. MBL has been localized to the immune deposits in five of six patients with MPGN type I (314). It is also noteworthy that purified human cryoglobulins injected to mice induced MPGN type I (315). However, the value of the finding of CICs, by whatever assay, can be questioned because CICs are found in conditions in which glomerulonephritis is not present and does not develop. Waldo and West (316) only rarely identified CICs in patients with MPGN types I and III. The proportion of B-lymphocyte subsets with surface IgG or other determinants is increased in a number of primary glomerular diseases, including MPGN (317), which suggests enhanced antibody production that could contribute to immune complex formation.

As noted earlier, complement deficiency impairs the solubilization and clearance of deposited immune complexes (57,304). McGinley et al. (318) studied splenic reticuloendothelial

function in patients with membranous glomerulopathy and MPGN and found that clearance rates of heat-damaged red blood cells were normal or enhanced. The clearance rates of red blood cells in patients with MPGN correlated with the degree of hypocomplementemia but not with disease activity or the HLA haplotype. MPGN type I was noted in several children with end-stage liver disease who were awaiting liver transplantation (319). These patients had higher levels of serum IgG, IgA, and IgM as well as IgG- and IgM-bound CICs. Tanuma et al. (320) showed that serum from patients with MPGN accelerated the decay of the cell-bound classic pathway C3 convertase and C4 hemolytic activity and reduced the C4NeF stabilizing activity of the C3 convertase. These authors suggested that, in vivo, accelerated decay of C3 convertase might interfere with the clearing and processing mechanism of the CICs by lessening deposition of C3b on the immune complex lattice.

Role of Toll-Like Receptors

Toll-like receptors (TLRs) play key role in the innate immune system by recognizing pathogen-associated molecular patterns (PAMPs) derived from invading microbes and danger-associated molecular patterns (DAMPs) released from damaged/dying cells. TLRs, following activation by ligands, activate multiple signaling pathways leading to local release of inflammatory mediators by immune cells and resident glomerular cells (273,299). TLR ligation also modulates adaptive immune system by facilitating conversion of dendritic cells to antigen-presenting cells. Accumulating evidence supports the role of TLRs in immune complex–mediated glomerulonephritis, including MPGN. In a mouse model of cryoglobulinemic MPGN, Banas et al. (321) showed that TLR4 is up-regulated in podocytes and that ligation of podocyte TLR4 leads to release of chemokines. They demonstrated that TLR4 ligands or fibrinogen results in similar patterns of chemokine expression profile, suggesting that TLR4 functions as a DAMPs receptor for endogenous ligands and may mediate glomerular injury by stimulating innate immunity. In fact, it has been shown that TLR4 antagonist CRX-526 protects against renal injury in a mouse model of diabetic nephropathy (322).

Role of Cellular Immunity

The importance of T-lymphocyte immunoregulation in patients with MPGN is unclear. It has been shown that the balance of T-helper lymphocyte subtypes 1 and 2 (TH1 and TH2) was altered with TH1 function predominant in MPGN (types not specified) (207). Brando et al. (323) noted a decrease in the $CD4^+/CD8^+$ ratio and in suppressor cell function in hypocomplementemic nonnephrotic patients with MPGN type I who had normal renal function. However, other studies (324) failed to find alterations in the $CD4^+/CD8^+$ ratio of peripheral T cells. Hotta et al. (325) observed a significant increase in $CD8^+CD57^+$ lymphocytes and a decrease in the $CD4^+/CD8^+$ ratio in elderly patients (mean age 62.5 years) when compared with age-matched normal controls or children with MPGN type I. Infiltration of $CD8^+CD57^+$ lymphocytes was noted within glomerular capillary lumina. Expression of endothelial-leukocyte adhesion molecule-1 was seen in a focal and segmental fashion in glomerular endothelial cells and in the endothelium of arteries and arterioles. These findings suggest that cell-mediated cytotoxic mechanisms may be involved in the pathogenesis of MPGN type I in elderly patients.

Role of Platelet Activation

Platelets secrete vasoactive, chemotactic, and mitogenic substances that interact with a number of soluble mediators generated by renal resident or inflammatory cells and could contribute to glomerular injury. Platelet-derived growth factor (PDGF) can recruit and mitogenically stimulate mesenchymal cells (326). PDGF is expressed in both experimental and human glomerulonephritis in which mesangial cell proliferation occurs, and infusion of PDGF into rats induces mesangial cell proliferation. Inhibition of PDGF in an experimental model reduces the mesangial proliferation, supporting the role of PDGF in the progression of glomerular disease (326). Progressive glomerular disease is frequently associated with extracellular matrix accumulation and sclerosis. It is believed that growth factors released from platelets and inflammatory cells play an important role in this process (327). It has been shown that transforming growth factor–β (TGF-β) can induce (a) podocyte apoptosis leading to podocytopenia, (b) mesangial cell proliferation and extracellular matrix synthesis, and (c) endothelial to mesenchymal transition, all of which lead to glomerulosclerosis (327). In addition, TGF-β can induce tubular epithelial to mesenchymal transition and fibroblast proliferation, stimulate tubular and fibroblast matrix production, and cause epithelial death, all of which result in tubular cell death and interstitial fibrosis (327). Although ultrastructural identification of platelets is quite difficult because of their evanescence or loss/destruction of structural features, platelet antigens have been identified using antiplatelet antibodies in both the glomerular capillaries and the arterial walls of the kidneys from patients with MPGN type I (328,329). In a case report of MPGN type I developed in a patient with polycythemia vera, platelets and megakaryocytes were detected in glomerular capillaries, coupled with increased expression of PDGF receptor β and thrombomodulin in the glomerular capillaries and mesangium, respectively. Antiplatelet and anticoagulant combination therapy together with hydroxyurea resulted in improvement of nephrotic syndrome, supporting that the role of activated platelet/enhanced coagulation state may contribute to MPGN associated with polycythemia vera (330).

Loss of negative charge of the GBM precedes increased glomerular permeability or proteinuria. Polycationic macromolecules derived from platelets or other inflammatory cells have the potential to bind to the negatively charged GBM and alter the electrostatic and size barriers to circulating macromolecules, thereby facilitating the deposition of CICs. Indeed, the polycationic PDGF, platelet factor 4, and β-thromboglobulin have been identified in glomerular structure, in patients with MPGN type I and DDD (328,329), which may contribute to increased glomerular permeability in MPGN. Structural components of the GBM and mesangial matrix can be enzymatically digested by several enzymes released from platelets including elastase, collagenase, cathepsins, and heparitinase. Thus, degradation of collagen IV, fibronectin, entactin, nidogen, and heparan sulfate would conceivably lead to structural defects in porosity and/or charge barriers. In addition, several platelet secretory products could theoretically alter glomerular hemodynamics, although their role in human MPGN remains to be assessed.

Patients with MPGN have enhanced platelet activation, as established by lower intraplatelet concentrations of serotonin, higher levels of free plasma serotonin, and nonthrombin platelet-aggregating material (253,331). Although there is some correlation with disease activity, there is considerable overlap between normal and abnormal values, and several types of glomerulonephritis seem to be involved. George et al. (332) found selective platelet consumption in patients with different types of glomerulonephritis, including MPGN. Donadio et al. (254) provided evidence of diminished platelet survival in more than two thirds of their patients; the GFR stabilized or improved after treatment with antiplatelet drugs (dipyridamole and aspirin). Taken together, although the actual role and importance of in vivo platelet activation are still not totally clear, platelets and their secretory products promote a wide range of biologic activities including stimulating inflammatory cell recruitment and modulating tissue remodeling by eliciting cellular migration, proliferation, or extracellular matrix synthesis. In addition, various platelet secretory products have the potential to interact with the glomerulus and induce permeability changes favoring immune complex deposition.

Genetic Factors

Hereditary predisposition is important in the pathogenesis of some MPGN. The role of complement deficiency in the pathogenesis of MPGN has been discussed earlier and is reviewed further in Chapter 9. Rashid et al. (333) noted an association between Bw44 antigens and MPGN. Welch et al. (334) searched for genetic markers within the major histocompatibility complex in 34 patients and their families and in 29 normal families. They found the extended haplotype HLA-B8, DR3, SCO1, GLO2 more frequently in patients with MPGN types I and III (compared with normal subjects) and noted a higher incidence of renal insufficiency than in those without it. They theorized that a specific extended haplotype of the major histocompatibility complex is associated with a susceptibility to the development of MPGN and that patients who have this extended haplotype have a poorer renal prognosis. Wank et al. (335) studied the association between MPGN and HLA markers. They phenotyped patients with various primary forms of glomerulonephritis for alleles of the major histocompatibility complex–linked complement genes *C4A, C4B*, and *BF*. A rare variant of the *C4B* locus, *C4B29*, was significantly associated with MPGN (335). Other studies (336) of C3 genetic polymorphisms in MPGN failed to show any relationship.

Bishof et al. (337) studied DP polymorphism in HLA-A1, HLA-B8, HLA-DR3 extended haplotypes in patients with MPGN; they concluded based on restriction fragment length polymorphisms that the strong linkage disequilibrium of this haplotype breaks down between the DQ and the DP loci. They also concluded that loci important to disease susceptibility are more likely to occur telomeric to DP (337). A number of reports of familial clustering of MPGN type I have been published (66,69,338). Bakkaloglu et al. (338) described two separate families in which multiple siblings had signs of MPGN type I on biopsy. HLA typing in these two families revealed a common antigen HLA-A2 in all affected siblings. Berry et al. (66) described MPGN in two sibships. In one, the sister had type I and the brother had type III. In the second family, there were two brothers; both had type I with similar manifestations. Sherwood et al. (71) reported an unusual association of uncommon facies including telangiectasia in a butterfly distribution, a similar skin lesion on extensor areas, sparse hair, and MPGN in a 4-year-old boy and his father. The mode of inheritance of these features seems to be autosomal dominant. Stutchfield et al. (69) described two related males with MPGN inherited as an X-linked disorder. Bilge et al. (339) suggested that homozygosity for the A allele of paraoxonase 192 gene appears to be a risk factor for MPGN type I and perhaps associated with poor prognosis in Turkish children. Human paraoxonase is a serum protein that exhibits esterase and antioxidative activities. The relationship between the AA homozygosity and the development of MPGN type I is probably through both alterations in lipid peroxidation and inflammatory processes (339).

Reports of familial MPGN type III are rare (70,340). An Irish family with eight affected members in four generations was reported (70). Significant evidence for linkage was observed on chromosome lq31-32 (70). Another family was originally reported as a familial MPGN type III and has now been shown to be a familial form of C3 glomerulopathy caused by mutation involving the genes encoding for complement factor H–related proteins 1 and 3 forming a hybrid gene (340).

Animal Models

Both spontaneously developed and genetically manipulated animal models of MPGN type I are available (341). MPGN has been found to occur spontaneously in dogs (308,342), horses (343), sheep (344), mice (345), and Finnish Landrace cross lambs (307); these naturally occurring models may be useful in determining the origin and pathogenesis of this glomerular pattern. Studies in Bernese mountain dogs (342) show the spontaneous development of MPGN type I. These dogs had a high level of antibodies to *Borrelia burgdorferi*. Studies in dogs of other breeds have found MPGN type I in those with a genetically determined deficiency of C3 and accentuation of renal disease by treatment with complement-containing blood products (308). Molecular analysis in these animals reveals a deletion of a cytosine at position 2136 (codon 712), leading to a frameshift and a generation of a premature stop codon 11 amino acids downstream (308). By opsonizing the CIC, complement plays a physiologic role in removal of immune complex from circulation, and its deficiency can cause immune complex accumulation in the circulation and deposit in various organs/tissues including kidney.

Thymic stromal lymphopoietin (TSLP) transgenic mice develop MPGN mimicking cryoglobulinemic GN in human (346). Macrophage ablation confers protection in this model indicating a predominantly deleterious effect of macrophages in the progression of renal injury in this model (347). Another murine model of cryoglobulinemic GN results from either the presence of IgG3 produced by murine hybridoma cells or overexpression of IgG3 by the mouse itself (348).

There are still other experimental animal models of MPGN (349,350). Isaacs and Millet (349) produced MPGN by the administration of polycationic dextran-antidextran immune complexes. Experimental work in rabbits shows that long-term immunization with egg albumin produces an MPGN type I (351). In this model of chronic serum sickness, rabbits producing precipitating antibodies of high avidity show signs of MPGN.

MEMBRANOPROLIFERATIVE GLOMERULONEPHRITIS WITH RECOGNIZABLE ETIOLOGIC AGENTS OR ASSOCIATED DISEASES

MPGN has been described in a number of specific clinical situations (see Table 8.2). However, an association with a particular disorder does not equal causation and one must exercise caution when interpreting these association studies. In some of the reports, MPGN apparently corresponds well to the accepted forms just described, but in other reports, there appear to be differences despite the terminology used. In most instances, the morphologic pattern resembles MPGN type I, but in others, there are certain atypical morphologic or immunofluorescence patterns. In some cases, renal biopsy may provide evidence of additional features, such as characteristic ultrastructural deposits in patients with cryoglobulinemia. In certain cases, the criteria for MPGN type I are not met at the light, electron, and IF microscopic levels, and the lesion is better termed *diffuse proliferative glomerulonephritis of immune complex origin*. Low serum C3 and NeFs are frequently noted in patients with secondary MPGN.

Hepatitis C Infection and Cryoglobulinemia

Hepatitis C and cryoglobulinemia are the most widely identified causes for secondary MPGN. The hepatitis C virus (HCV) is mainly spread through the parenteral route, although familial, sexual, and maternal transmission may occur rarely. It is estimated that 3% of the world population and approximately 2% of the US population are infected with HCV (352). Patients with long-standing HCV infection are associated with increased frequency of proteinuria and glomerulopathies (313). However, the relationship between HCV infection and incidence/prevalence of renal failure has not been established (353). The most common form of HCV-associated renal disease is MPGN type I in patients with cryoglobulinemia (3,29,313,352), although other patterns, such as membranous glomerulopathy, IgA nephropathy, postinfectious glomerulonephritis, focal segmental glomerulosclerosis, fibrillary and immunotactoid glomerulonephritis, thrombotic microangiopathies with or without concurrent anticardiolipin antibodies, and Waldenström macroglobulinemia have been reported (30). The extremely high prevalence (up to 90%) of anti–HCV antibodies in the serum and cryoprecipitate along with serum HCV RNA suggests a close etiologic relationship between mixed cryoglobulinemia and chronic HCV infection (30,352). The pathogenesis of HCV-associated cryoglobulinemia is not well understood. It appears that HCV envelope protein E2 can interact with B-cell surface receptor (CD81) leading to IgM rheumatoid factor production and cryoglobulin (31). Chronic infection with HCV may lead to persistent stimulation of innate immunity and adaptive immune response, which stimulates the production of anti-HCV antibodies and monoclonal rheumatoid factor. The rheumatoid factor binds to immunoglobulins producing type II cryoglobulins (30,352). Studies are needed to elucidate the nature of cryoglobulinemic renal disease and why some cryoglobulins are associated with renal damage whereas others are not.

The most common renal presentation is moderate to severe proteinuria (nephrotic range in approximately 70% of cases) and impaired renal function. Nephritic features and hematuria are present in approximately 25% of cases. Many patients show features of systemic manifestations of cryoglobulinemia including palpable purpura, arthralgias/arthritis, peripheral neuropathy, Raynaud phenomenon, and abdominal pain. Patients often (but not always) have elevated liver function test results (e.g., elevated serum aminotransferase levels), hypocomplementemia, cryoglobulins, and CICs. The serum and cryoprecipitates often contain HCV RNA and IgG anti-HCV antibodies to the nucleocapsid core antigen (HCVc or c22-3). Circulating IgM rheumatoid factors present in patients bind anti-HCV IgG.

In patients with cryoglobulinemic glomerulonephritis, renal biopsy usually discloses MPGN type I pattern of glomerular injury (Figs. 8.24 to 8.26), although other pattern of proliferative glomerulonephritis occurs. If there is no evidence of cryoglobulinemia, the term *hepatitis C–associated MPGN type I* is appropriate. If cryoglobulinemia is present, then the term *hepatitis C–associated cryoglobulinemic glomerulonephritis* is preferred. There may be massive infiltration of the glomeruli by monocytes (32,176,195) and the diffuse thickening of the glomerular

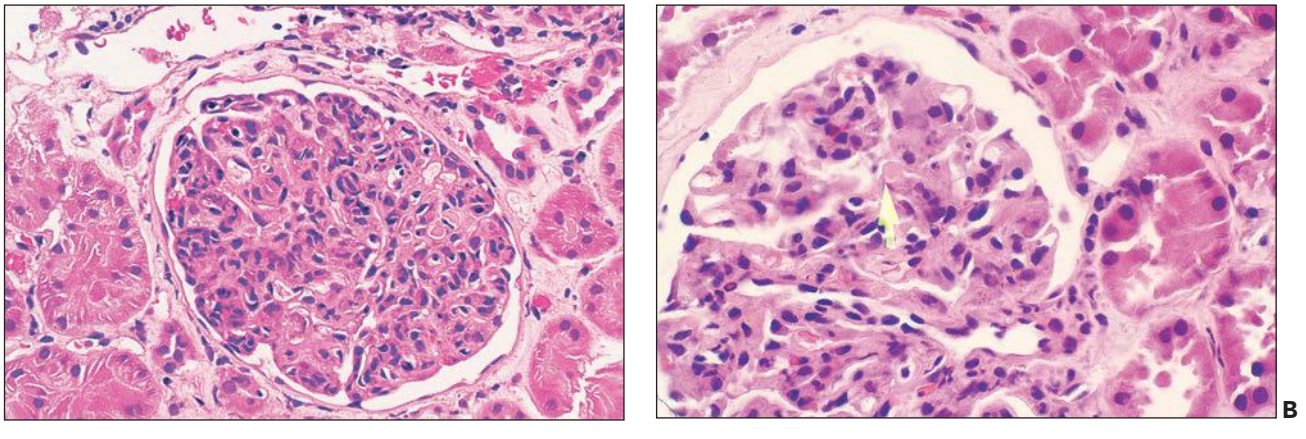

FIGURE 8.24 Cryoglobulinemic MPGN type I. There are thickened capillary walls and hypercellularity **(A,B)** and a few hyaline thrombi (**B,** *arrow*). (H&E, **A:** ×350, **B:** ×500.)

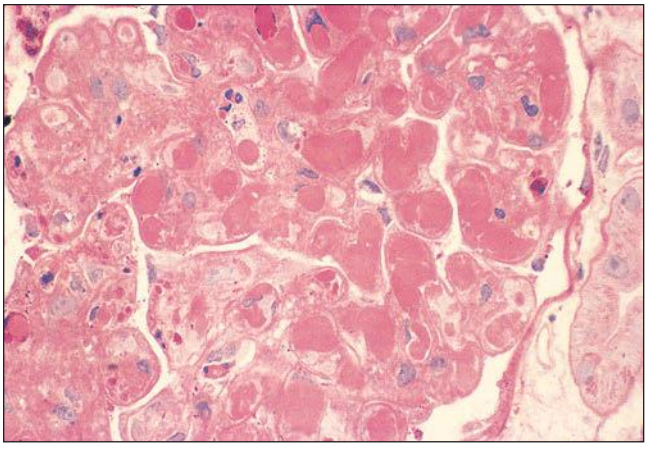

FIGURE 8.25 Cryoglobulinemic glomerulonephritis. There are numerous acidophilic hyaline thrombi in capillary lumens. (PAS, ×750.)

capillary wall with its double-contoured appearance, which may be caused by the peripheral interposition of monocytes with less obvious mesangial expansion/interposition (32,195). In some cases, eosinophilic refractile "hyaline thrombi" are noted by light microscopy within the glomerular capillary lumina (see Figs. 8.25 and 8.26). These are intensely PAS-positive hyaline masses and may also occur in small arteries or arterioles. The light microscopic appearance may include numerous neutrophils. In transplant patients, it may be difficult to distinguish from allograft glomerulopathy by light microscopy (354). Leukocytoclastic small-vessel vasculitis can be seen both within the kidneys and in other organs, such as the skin, small intestine, and rarely lung (355). Although MPGN is the most common histologic phenotype caused by cryoglobulinemia, some specimens show a focal or diffuse proliferative glomerulonephritis that does not have adequate features to be called MPGN.

IF reveals glomerular capillary wall and mesangial deposition of large amounts of IgG, IgM, and C3. Sometimes large intraglomerular deposits of C3 and other immunoreactants are noted within the glomerular capillaries that correspond to

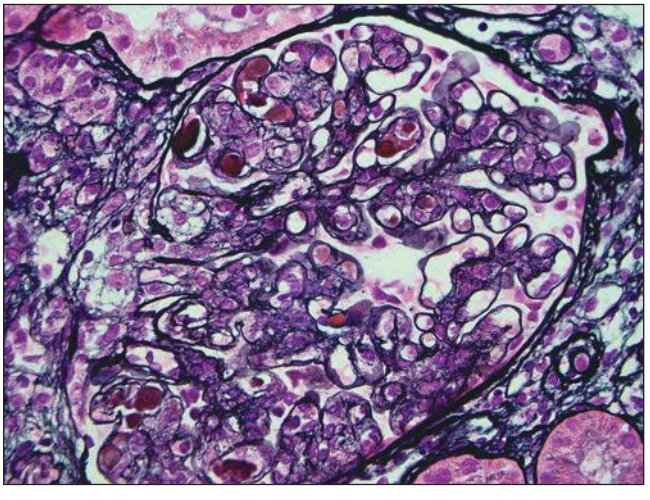

FIGURE 8.26 Cryoglobulinemic MPGN type I. There are multiple silver-negative hyaline thrombi and segmental double contours. (Jones silver, ×400.)

hyaline thrombi. These should not be overlooked because they raise or support the possibility of cryoglobulinemia. IgA, C1q, and occasionally other immunoreactants may be found in the glomeruli (29).

EM shows glomerular mesangial and subendothelial electron-dense deposits (Fig. 8.27). Intramembranous and subepithelial deposits may be present. The deposits often but not always show, at high magnification, ultrastructurally organized tubular, cylindrical, or crystalloid organization (32,356). These microtubular deposits may also be noted in cryoprecipitates and deposit not only in the kidney but also in other tissue (356). The differential diagnosis for glomerular microtubules includes immunotactoid glomerulopathy, although this process usually has much more well-defined and longer microtubules (refer to Chapter 23). By EM, cryoglobulinemic MPGN frequently has numerous macrophages in capillary lumens and infiltrating capillary walls and the mesangium. These macrophages often have numerous large secondary phagolysosomes.

The mainstay of therapy for HCV-associated glomerulonephritis, including cryoglobulinemic MPGN, is interferon (standard or pegylated) combined with ribavirin (30,352). In cases nonresponsive to interferon, corticosteroid and cyclophosphamide can be used (30). Monoclonal antibody to B cells (anti-CD20, rituximab) has been shown to be helpful in refractory cases (30,352). In patients with nephrotic proteinuria and/or progressive renal failure, combined antiviral and immunosuppressive therapies are the treatment of choice. Rituximab is preferred to cyclophosphamide because the former is better tolerated and at least as efficient as the latter. During the acute phase, plasmapheresis and steroid pulses can be used. Needless to say, prospective, controlled, and randomized studies are needed to establish evidence-based guidelines to treat HCV-related glomerulonephritis (30).

The precise role of HCV in the pathogenesis of MPGN remains to be determined. The demonstration of a beneficial response to interferon treatment, with a decrease in proteinuria and clearance of HCV RNA, suggests the etiologic role of HCV in the pathogenesis of this renal disease. Isolated reports of successful immunohistochemical localization of HCV antigens in renal tissue have been published (357). HCV RNA has been localized to tubular epithelial and capillary endothelial cells of HCV-infected patients with various patterns of injury (358). Likewise, HCV RNA and core protein have been shown in glomeruli and tubules isolated with laser capture microdissection in HCV-infected patients with various patterns of renal injury including MPGN type I (359). Chronic infection with HCV may lead to persistent stimulation of innate immunity and adaptive immune response (352), which stimulates the production of anti-HCV antibodies and monoclonal rheumatoid factor. The rheumatoid factor binds to immunoglobulins producing type II cryoglobulins, which then deposit in the glomeruli (32,33). Studies (360) have shown that HCV core and nonstructural protein 3 triggers inflammatory pathways via Toll-like receptor 2 (TLR2), which may affect viral recognition and contribute to the activation of the innate immune system. In addition, mesangial cell TLR3 (recognizing double-strand RNA of viral origin) mRNA expression was elevated in HCV-associated GN, thereby modulating chemokine/cytokine release and affecting cell proliferation and apoptosis (361,362). Similarly, it has been shown that TLR3 expression is up-regulated in patients with HCV-associated GN, and the overexpression of

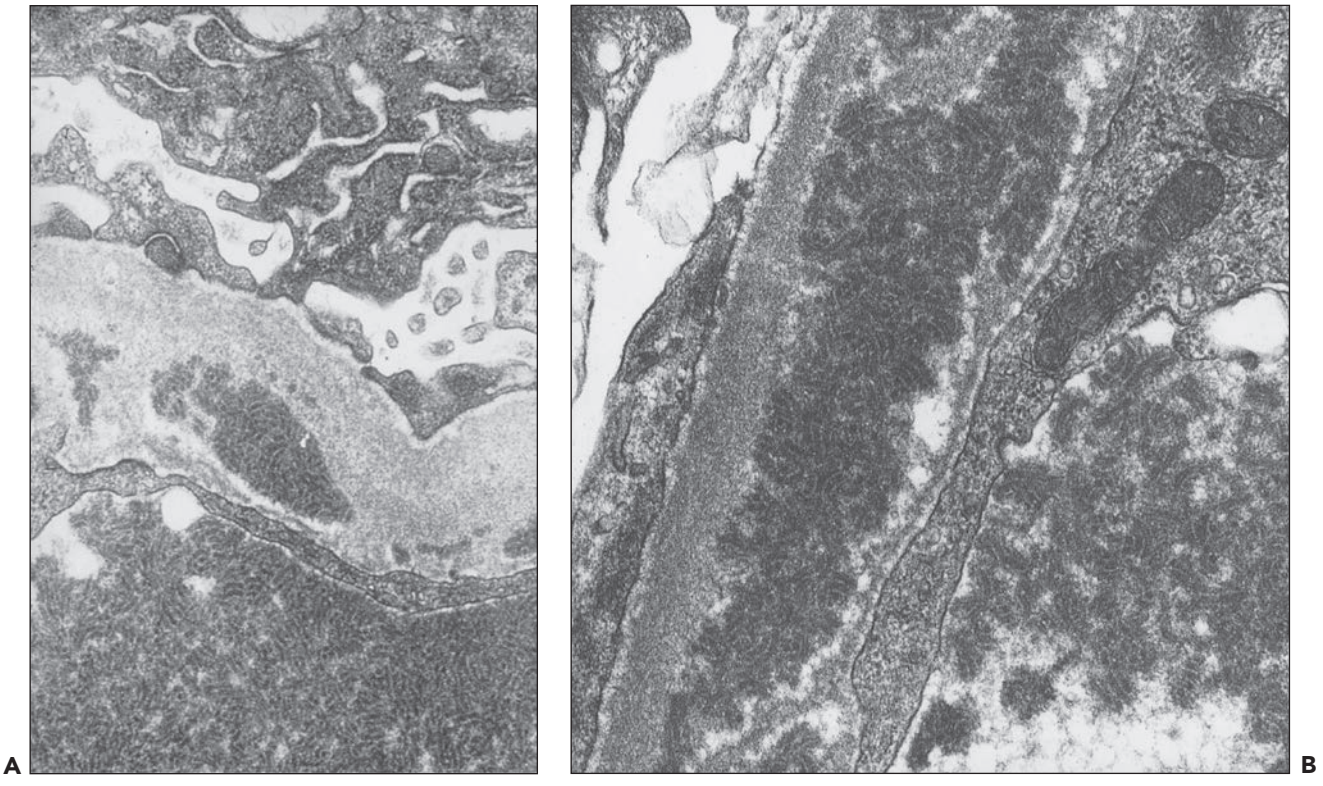

FIGURE 8.27 Hepatitis C–associated cryoglobulinemic glomerulonephritis. A & B: There are subendothelial and intraluminal electron-dense deposits with a microtubular substructure. Note the short parallel stacks of microtubules. The intramembranous deposits correspond to hyaline thrombi by light microscopy. (Uranyl acetate and lead citrate; **A:** x12,500; **B:** x25,000.)

TLR3 is associated with reduced renal function and enhanced proinflammatory cytokine production (363).

There is a high prevalence of HCV in patients on dialysis (364). HCV is also the leading cause of non-A and non-B hepatitis among renal allograft recipients. Transmission of HCV by renal transplantation of an HCV-infected donor kidney has been confirmed. Although renal transplantation is an effective therapy for HCV-positive patients, studies suggest that both graft and patient survival are lower for HCV-positive patients when compared with those of HCV-negative patients (364–366). HCV patients had more acute rejection, a higher degree of proteinuria coupled with elevated creatinine, and a greater likelihood of chronic allograft nephropathy and transplant glomerulopathy. Roth et al. (365) have described the development of de novo MPGN in five HCV-infected kidney recipients despite immunosuppression.

Hepatitis B Infection

Membranous glomerulopathy is the best-known renal complication of hepatitis B antigenemia, which arises with or without clinically apparent chronic hepatitis (21–23). There have been, however, many reports of MPGN in patients with chronic hepatitis B virus (HBV) infection (23,24). Adults and children with typical MPGN type I have a significantly higher carrier rate of hepatitis B surface antigen (HBsAg) than the normal population in many countries. For example, in a study of 46 adult patients with MPGN type I in Hong Kong by Chan et al. (25), 20% of the patients tested showed positive results for HBsAg (twice the incidence in the general population), although these authors found no difference in cumulative renal survival between those patients with HBsAg and those without. Other studies have not demonstrated an association of MPGN with the HBsAg carrier state (24).

Hepatitis B–associated renal disease is more common in children than in adults and in male than in female. Patients with renal disease most commonly show initial signs of severe proteinuria (often the nephrotic syndrome) and microscopic hematuria. Hypertension and renal insufficiency is noted in about half and one fifth of patients, respectively. Serum complement levels (C3 and C4) are often depressed, and CICs may be present. HBsAg and antibodies to hepatitis B core antigen (HBcAg) are usually present in the serum but not always. Patients often have no history of clinical hepatitis in spite of having elevated transaminase levels. Liver biopsy often shows either chronic active or chronic persistent hepatitis, although cirrhosis can be present. On rare occasions, acute fulminant hepatitis may be present.

Some of HBsAg-associated glomerulonephritis is quite characteristic of MPGN type I or IIIB, whereas other has different patterns of proliferative glomerulonephritis or membranous glomerulopathy. In some cases, HBsAg, HBeAg, and HBcAg have been found in glomeruli, and the detection of covalently closed circular DNA in renal tissue has been reported (23). In one series of 15 children diagnosed as having MPGN, HBsAg was identified in the glomeruli in 12; 10 of the children had HBsAg in the blood, and 12 had circulating antibodies to HBcAg (26). None of these children had clinically apparent liver disease. Ultrastructural studies showed glomerular subendothelial or mesangial deposits. IF findings consisted of mesangial IgG, IgM, IgA, and C3 in all glomeruli.

Such patients had several of the features of MPGN type I, but the IF findings were somewhat dissimilar to the typical MPGN type I. Stratta et al. (27) described the case of an adult patient with chronic active hepatitis with several anomalous features; these included deposits identified by EM confined to the mesangial regions and C3 restricted to the mesangial areas, as seen by IF. IgG and IgM were noted in a glomerular subendothelial position. Hepatitis B antigen was demonstrated in the mesangial regions. One study described the transformation of HBsAg-related membranous nephropathy to mixed membranous nephropathy and MPGN (MPGN type IIIB) with crescents (28).

HBsAg can be found in the glomeruli, blood, and immune complexes, and anti–hepatitis B surface antibody can be identified in the CICs (367). Antibody to HBsAg has been eluted from renal tissues in a patient with MPGN; in this patient, HBsAg was identified in the glomeruli and the CICs were shown to contain HBsAg and anti–hepatitis B surface antibody. HBV DNA and RNA have been detected in glomerular and tubular epithelial cells (368). On two occasions, improvement in renal function coincided with a marked increase in serum HBsAg levels and elevation of CIC levels, suggesting that extreme antigen excess may inhibit glomerular deposition of immune complexes (367).

The pathogenesis most likely involves glomerular mesangial and subendothelial trapping of CICs that are at least in part composed of HBV antigens (23,24). These HBV-containing immune complexes (mainly HBsAg and anti-HBs) presumably localize in the glomerulus either as a result of deposition of CICs or owing to local in situ immune complex formation. There is some in vitro and in vivo evidence in humans that HBV can directly infect the mesangial cell and possibly other resident glomerular cells (24). The HBV genotype may also play a role in the pathogenesis of glomerulonephritis. The association between the clearance of HBeAg and the remission of proteinuria suggests that HBeAg may be involved in the pathogenesis (23). However, it is also possible that the HBV antigens are not pathogenetically related and that the immune deposits develop by another virally induced mechanism, such as autoimmunity. Thus, there still remains the possibility that HBV infection and the glomerular process are pathogenetically unrelated. In addition, genetic factors may also play a role (369). It has been shown that MHC class II allele DRB1*1302 was associated with protection against persistent HBV infection among both children and adults in the Gambia (369). More investigation is needed to determine the exact mechanism(s) of action.

The role of antiviral therapy, such as alpha and beta interferon, has not been studied in a large-scale controlled protocol. Studies have shown that antiviral and immunosuppressive combination therapy can reduce proteinuria in adult hepatitis B–associated glomerulonephritis without affecting HBV replication or liver and kidney functions (370,371).

Other Infections

Many forms of chronic infectious disease in addition to HCV and HBV are associated with MPGN, especially type I and type IIIB (see Table 8.2). Persistent indolent bacterial infections, especially staphylococcal infections, are the most common. Glomerulonephritis secondary to endocarditis and infected ventriculoatrial shunts often manifests as MPGN type I and are discussed in detail in Chapter 10. *Staphylococcus epidermidis* is the most common organism (approximately 75% of all shunt infections) responsible for glomerulonephritis associated with infected ventriculoatrial shunts. More than 150 cases have been reported, and the histologic picture resembles that of MPGN type I (11). IF revealed deposits with a predominance of IgM (84%), IgG (66%), and C3 (94%). The clinical abnormalities disappear when the infected shunts are replaced, in contrast to the typical progression of idiopathic MPGN type I.

Nephropathia epidemica is a mild form of hemorrhagic fever with renal syndrome caused by Puumala Hantavirus. Morphologically, the kidney usually reveals acute tubulointerstitial nephritis with very mild nonspecific mesangial changes in glomeruli. In two separate reports, Mustonen et al. (36,37) described a total of 12 patients who developed microscopic hematuria and nephrotic syndrome during the convalescent phase of an otherwise typical acute febrile nephropathia epidemica. Renal biopsies showed MPGN type I in 10 patients, 5 of whom disclosed significant neutrophil infiltration in the glomeruli. IF showed granular staining along the capillary walls of C1q, C3, IgG, and IgM. A remission of the nephrotic syndrome was observed in nine patients, with only one entered into end-stage renal failure. Heavy glomerular deposits of C1q and C3 as well as hypocomplementemia are consistent with activation of the classical complement pathway. Genetic factors may also play a role since three of five patients were HLA-B8 and/or HLA-DR3 positive, which is significantly greater than the frequency of those alleles in the general population.

Lyme disease is a multisystem disorder caused by the tick-transmitted spirochete *B. burgdorferi*. MPGN type I has been described in few patients with Lyme disease (17,18). Infection caused by *B. burgdorferi* is known to induce MPGN in dogs (342).

α_1-Antitrypsin Deficiency

Various patterns of immune complex–mediated glomerulonephritis have been observed in patients with α_1-antitrypsin deficiency; MPGN type I has been seen most often. For example, the cases of three children with α_1-antitrypsin deficiency (protease inhibitor type ZZ) have been described; they all died from cirrhosis and, at autopsy, were found to have MPGN type I (67). Oliguria, hematuria, and abnormal renal function tests were noted during life. Light microscopic examination showed an MPGN-like pattern. Electron and immunofluorescence microscopy was performed on only one patient in this series; glomerular subendothelial and mesangial deposits were visible by EM. IF studies showed granular capillary wall staining for IgG, IgA, IgM, C3, and C4. α_1-Antitrypsin was detected in the glomerular capillaries; it was not detected in the glomeruli of patients with MPGN who did not have this deficiency or in children with chronic liver disease and no deficiency. The role of α_1-antitrypsin deficiency in the onset of glomerular lesions is controversial. Ineffective inhibition of proteolytic enzymes by reduced levels of α_1-antitrypsin may cause damage in tissue other than lungs. It has been suggested that abnormal PiZ protein may act as an antigen, leading to the formation of CICs and renal injury (68). The presence of abnormal PiZ protein in the subendothelial region of the GBM coupled with reversal of nephrotic syndrome and renal function after liver transplantation in a 23-year-old woman with severe α_1-antitrypsin deficiency supports the above hypothesis (68).

Neoplasia and Monoclonal Gammopathy

The MPGN type I is associated with many forms of neoplasia. Solid organ cancers associated with MPGN include esophageal, gastric, lung, kidney, and bladder, to name a few (45–51). However, the most frequently associated neoplasms are B-cell neoplasms, as well as other B-cell dyscrasias that produce nephritogenic monoclonal immunoglobulin. Cases of MPGN type I and type III have been reported in the context of MGUS, low-grade B-cell lymphoma, lymphoplasmacytic lymphoma, chronic lymphocytic leukemia, and multiple myeloma (43,372–374). In a retrospective single-center study of 68 patients who had MPGN type I without apparent autoimmune or chronic infectious process, 28 (41%) of whom had evidence of monoclonal gammopathy determined by serum and/or urine electrophoresis (43). In another retrospective study (372), authors described an entity of proliferative glomerulonephritis associated with monoclonal IgG deposition. On light and electron microscopy, the lesion mimics immune complex–mediated GN, 57% of which have an MPGN pattern. On IF microscopy, the deposits stain for a single light chain isotype and a single heavy chain subclass, most commonly IgG3 k. Importantly, if staining for light chains is not performed routinely, there is no way to distinguish this MPGN caused by monoclonal IgG from immune complex–mediated MPGN type I. Approximately 30% of patients had a detectable serum M-spike, but the rest do not. Most patients present with nephrotic-range proteinuria and hematuria with or without renal insufficiency.

MPGN with monoclonal immunoglobulin deposits should be differentiated from immunotactoid glomerulopathy with monoclonal immunoglobulin and from "monoclonal immunoglobulin deposition disease," both of which can have an appearance by light microscopy that is similar to MPGN. Immunotactoid glomerulopathy typically has longer better defined microtubules by EM, no hyaline thrombi by light microscopy, and no cryoglobulins in the serum. MIDD can be caused by light chains (usually kappa), heavy chains (usually truncated gamma), or both. By light microscopy, MIDD usually has more nodularity than MPGN (see Fig. 8.23A); by IF microscopy, more linear staining for the immunoglobulin (see Fig. 8.23B); and by EM, granular rather than microtubular deposits (see Chapter 23).

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CHAPTER 9

H. Terence Cook • Matthew C. Pickering

C3 Glomerulopathies, Including Dense Deposit Disease

C3 glomerulopathy is a recently introduced term (1) that encompasses glomerular disease characterized by the accumulation in the glomeruli of C3 or its metabolites without significant deposition of the early components of the classical pathway of complement activation, C1q and C4, and with minimal or no immunoglobulin. On electron microscopy (EM), there are electron-dense deposits corresponding to the C3 deposits seen on immunohistochemistry. The deposition of C3 with little or no immunoglobulin and without classical pathway complement activation imply uncontrolled activation of the alternative pathway of complement. Recent work has elucidated the mechanism by which this occurs in many cases. C3 glomerulopathy, thus defined, is distinct from forms of thrombotic microangiopathy that may also be associated with alternative pathway activation because in those cases complement activation is on the renal endothelium and is not associated with well-defined deposits on EM. C3 glomerulopathy also is distinct from glomerulonephritis caused by immune complex accumulation in glomeruli that contain immunoglobulin as well as complement, often including classical pathway components such as C4 or C1q. As described in more detail in the following sections, the morphology seen by light microscopy is variable and includes mesangial proliferation, a membranoproliferative pattern, endocapillary proliferation, and crescentic glomerulonephritis.

It is possible to subclassify C3 glomerulopathy based on differences of morphology as seen by light microscopy and EM (Table 9.1) or by etiology; for example, some cases are caused by an underlying gene mutation and others by autoimmune processes. Perhaps, the simplest distinction in terms of morphology is on the basis of the appearance of the electron-dense deposits seen on EM. In some cases, these have a very dense osmiophilic appearance (Fig. 9.1) leading to the designation as dense deposit disease (DDD), whereas in other cases, the deposits do not show this appearance and are designated C3 glomerulonephritis (C3GN). We therefore discuss C3 glomerulopathy in terms of these two categories while recognizing that the distinction is not always clear cut and that there is overlap of pathogenesis.

DENSE DEPOSIT DISEASE

In 1963, Berger and Galle (2) described a type of glomerulonephritis with unique, extremely osmiophilic electron-dense deposits in the glomerular basement membranes (GBMs) as the major identifying characteristic (see Fig. 9.1). Since that time, many additional reports of DDD have appeared (3–18). Because DDD often has light microscopic features of a membranoproliferative glomerulonephritis (MPGN), it has also been referred to as MPGN type II. However, it is clear that many cases do not have an MPGN pattern on light microscopy, and therefore the name DDD is to be preferred. In some series, it has accounted for up to a third of cases of MPGN although the frequency compared to type I MPGN in most series is much lower. Appel et al. (19) published an excellent review on DDD in 2005.

Clinical Presentation

DDD has a prevalence of 2 to 3 per million population and is primarily a disease of children and young adults (11,15,17,19). However, in a 2009 series from New York, 39% of the adult patients were over 60 years of age (16). It affects males and females equally in many cohorts although some studies have shown a female predominance (15,16). The clinical picture is not distinctive, and it is not possible to distinguish DDD from

TABLE 9.1 Pathologic classification of C3 glomerulopathy

C3 glomerulopathy
Dense deposit disease (DDD) (formerly membranoproliferative GN type II)
Membranoproliferative GN pattern (type II)
Mesangioproliferative or proliferative GN pattern
C3 glomerulonephritis (C3GN)
Membranoproliferative GN pattern (types I and III)[a]
Mesangioproliferative or proliferative GN pattern

[a]Note that membranoproliferative GN types I and III may be either the result of a C3 glomerulopathy or an immune complex–mediated glomerulonephritis (see Chapter 8).

immune complex MPGN type I on clinical grounds alone (5,7,10,19,20).

At presentation, almost all patients have proteinuria (6,16,18) usually with hematuria (16–18). Nephrotic-range proteinuria is present in two thirds of the patients (15,16), and full nephrotic syndrome in 12% to 65% in different series (5,8,15–17,21). In a large series of 98 patients from North America (18), the commonest symptoms leading to health care referral were hematuria (42.9%) and peripheral (37.8%) and facial (31.6%) edema. About one fifth of these patients (21.4%) did not suspect a problem, and in this group, signs of kidney disease were detected as part of a routine annual examination. A number of patients have initial signs and symptoms of acute nephritic syndrome; this presentation is found in 16% (21) to 38% (7) of patients. There may be episodes of acute nephritis (gross hematuria, edema, hypertension) or renal insufficiency that are reversible and show complete clinical subsidence (7). Renal insufficiency is common at presentation (6,16) and is more common in adults (16). Hypertension is commonly found either at clinical onset or during the course of the disease (18).

The clinical onset of DDD is preceded by acute infection, often an upper respiratory tract infection, in approximately one half of the patients (5–7,16). Elevated antistreptolysin O (ASO) titers were noted in 21% to 45% of patients with infective episodes (5,6,21); therefore, some were perhaps related to group A streptococcal infection.

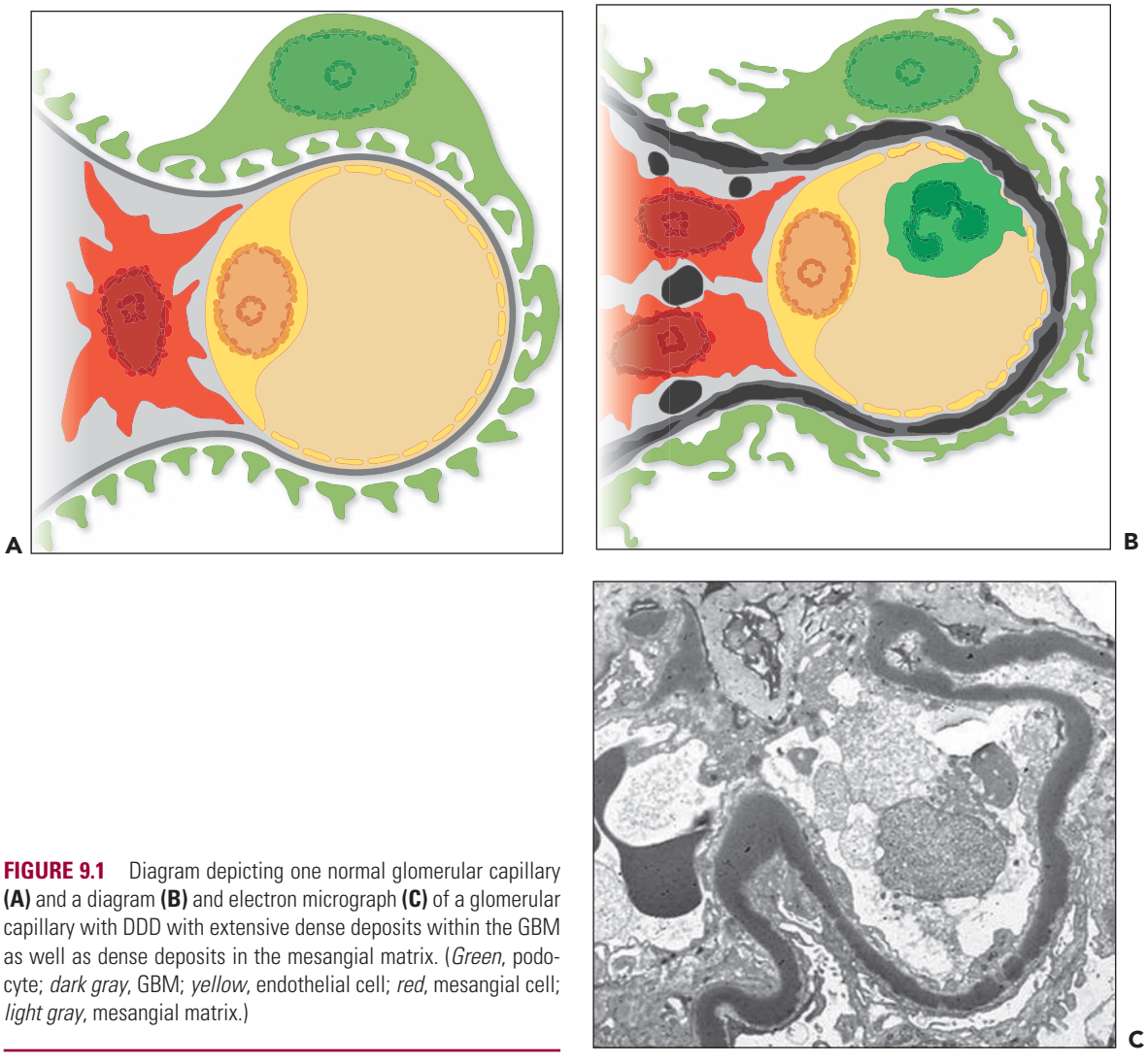


FIGURE 9.1 Diagram depicting one normal glomerular capillary **(A)** and a diagram **(B)** and electron micrograph **(C)** of a glomerular capillary with DDD with extensive dense deposits within the GBM as well as dense deposits in the mesangial matrix. (*Green*, podocyte; *dark gray*, GBM; *yellow*, endothelial cell; *red*, mesangial cell; *light gray*, mesangial matrix.)

Persistently, low serum levels of C3 are found in most patients (approximately 80%) (6,22), whereas fluctuating levels are found in others. In the series reported by Nasr et al. (16), the entire pediatric group had low C3 levels but significantly fewer of the adults (41%). In contrast to MPGN type I, serum levels of the early components of the classic pathway (C1q and C4) are usually normal. These complement profiles suggest that the complement is activated in DDD primarily through the alternative pathway, whereas MPGN type I arises through the classic and alternative pathways. Most patients with DDD are positive for serum C3 nephritic factor (C3NeF), an autoantibody directed against C3bBb, the convertase of the alternative pathway of complement activation. In more than 50% of patients, serum C3NeF persists throughout the clinical course (23). However, C3NeF is not a specific serologic marker because it also occurs with MPGN type I, lupus nephritis, and poststreptococcal glomerulonephritis, although less frequently. Its role is discussed further in the section dealing with pathogenesis.

Patients with DDD may also develop ocular drusen (24–26). These are lipoproteinaceous deposits of complement-containing debris within the Bruch membrane beneath the retinal pigment epithelium. This pathology is similar to age-related macular degeneration (AMD), but in contrast to AMD, drusen in DDD occur at an early age and may be found in the second decade of life. The long-term risk for visual problems is 10%. There is no correlation between the severity of the disease in the kidney and that in the eye.

A small minority of patients with DDD have acquired partial lipodystrophy (APL), a condition with symmetrical loss of adipose tissue from the face, arms, and upper portions of the trunk (27–30). APL is often accompanied by low levels of serum C3, normal serum levels of the early components of the complement, and the presence of C3NeF in the serum (27,28,31–33). Misra et al. (27) reported that approximately 83% of APL patients have low C3 levels and polyclonal C3NeF and that approximately 20% go on to develop MPGN.

Recently, an intriguing familial association has been shown between DDD and type 1 diabetes mellitus. In a series of 98 patients from North America, 16% reported at least one family member with type 1 diabetes, which is far greater than expected on the basis of the prevalence of type 1 diabetes in the general population (18). The significance of this observation remains to be determined.

Pathologic Findings

Light Microscopy

Glomeruli

DDD is defined by the presence of dense osmiophilic transformation of the GBM on EM (see Fig. 9.1), and on light microscopy, the morphology is variable (see Table 9.1). Previous reports have emphasized the membranoproliferative form of the disease, designating this as MPGN type II, and this makes it difficult in older reports to assess the full range of histologic appearances. While it is clear that a membranoproliferative pattern of glomerular injury with increased lobulation, mesangial expansion, and capillary wall thickening with segmental double contours is common, a range of other patterns of glomerular involvement also occur (Figs. 9.2 to 9.7). At one end of the spectrum, the glomeruli may show only mesangial expansion and hypercellularity. In some cases, the glomeruli show prominent endocapillary hypercellularity with segmental neutrophil infiltration (sometimes called exudative pattern). In others, large numbers of crescents may be present, warranting the diagnosis of crescentic glomerulonephritis. Walker et al. (34) collected 69 cases of DDD from centers in North America, Europe, and Japan. They identified four distinct histologic patterns on light microscopy: membranoproliferative (25%), mesangial proliferative (45%), crescentic (18%), and acute proliferative and exudative (12%). Crescentic GN was defined as more than 50% crescents. Two of their cases could not be further classified. In the Columbia series of 32 cases (16), the frequencies were MPGN (44%), mesangial proliferative (28%), endocapillary proliferative (19%), and crescentic

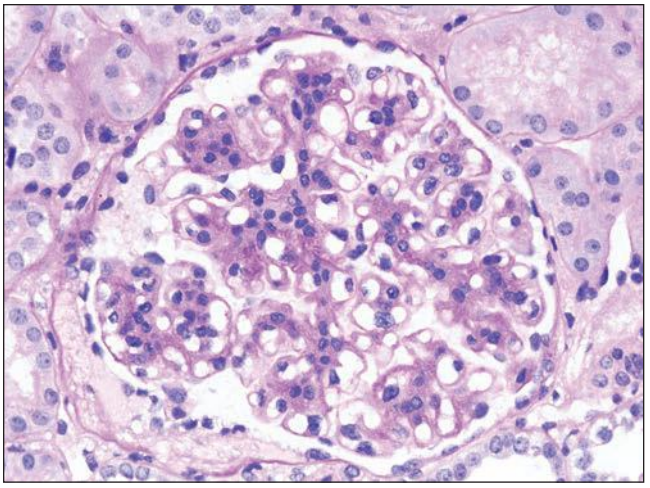


FIGURE 9.2 Glomerulus from a patient with DDD showing mesangial hypercellularity. (PAS.) (Courtesy of Dr. Patrick Walker.)

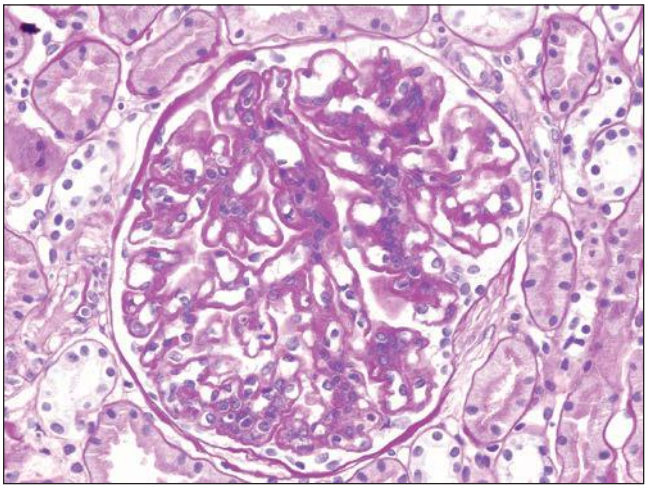


FIGURE 9.3 Glomerulus from a patient with DDD showing mesangial hypercellularity and a ribbon-like thickening of the glomerular capillary wall corresponding to the deposits seen by EM. (PAS.) (Courtesy of Dr. Patrick Walker.)

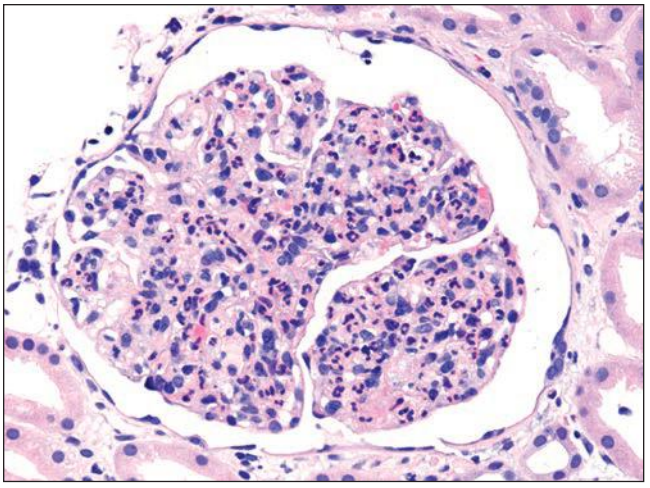


FIGURE 9.4 Glomerulus from a patient with DDD showing an endocapillary proliferative pattern with many neutrophils within capillary lumens. (H&E.) (Courtesy of Dr. Patrick Walker.)

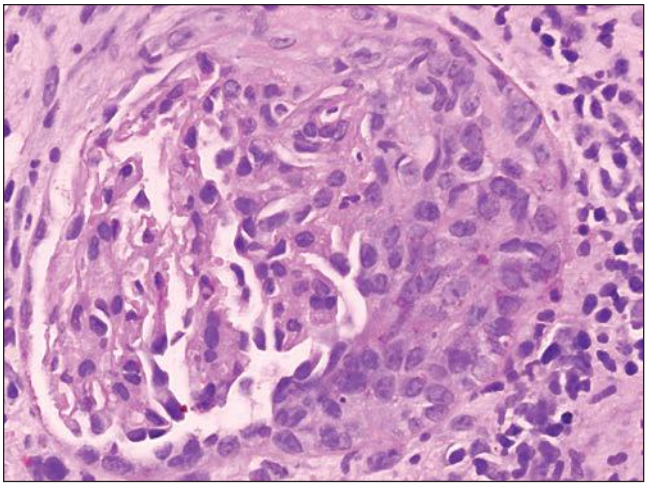


FIGURE 9.6 Glomerulus from a patient with DDD showing a cellular crescent. (PAS.) (Courtesy of Dr. Patrick Walker.)

GN (9%). These reports emphasize that fewer than 50% of cases of DDD have an MPGN morphology. Focal crescents are common in patients without full-blown crescentic GN (16,34).

The GBM dense deposits are recognized on light microscopy as thickening of the GBMs by ribbon-like glassy intramembranous deposits. They stain strongly with eosin and appear somewhat refractile (hyaline). They are intensely periodic acid-Schiff (PAS) positive (see Fig. 9.3), and the trichrome stain shows them to be fuchsinophilic (red) although this reactivity varies among specimens. These glomerular intramembranous deposits appear dark blue with toluidine blue in 0.5- or 1.0-µm plastic-embedded sections. With methenamine silver staining, the intramembranous deposits are not as argyrophilic as the GBM and are somewhat brownish (6,35). Thus, the intramembranous nonstaining deposit is often bordered on each side by a thin, silver-positive GBM (36). A double-contour appearance of the glomerular capillary wall is noted in approximately half of the patients. The glomerular intramembranous deposits may stain with the fluorochrome dye thioflavin T (Fig. 9.8) (9,37).

The glomerular intramembranous deposits vary greatly in size and number, and it is this feature that determines the extent of the glomerular capillary wall thickening. In typical cases, diagnosis may be suspected by light microscopy although EM may be needed to establish the presence of diagnostic deposits with certainty. In some biopsies, PAS- and trichrome-positive mesangial deposits are evident. EM often reveals mesangial deposits that cannot be identified by light microscopy. Deposits are also noted in the basal lamina of the Bowman capsule and the tubular basement membranes

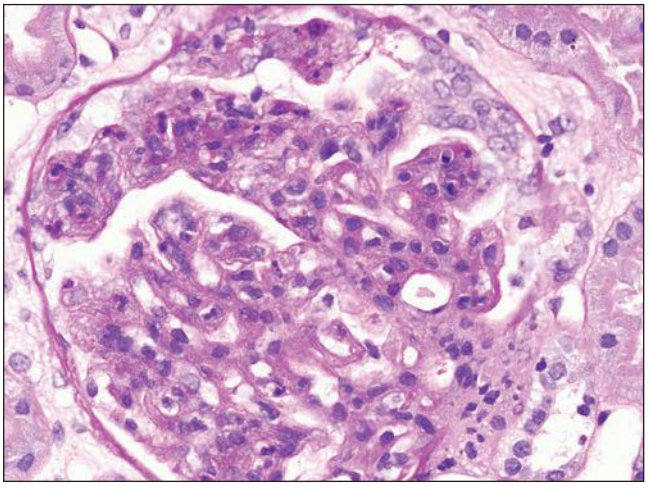


FIGURE 9.5 Glomerulus from a patient with DDD showing prominent segmental hypercellularity with endocapillary hypercellularity and a small cellular crescent. Some capillary walls show a double-contour appearance. (PAS.) (Courtesy of Dr. Patrick Walker.)

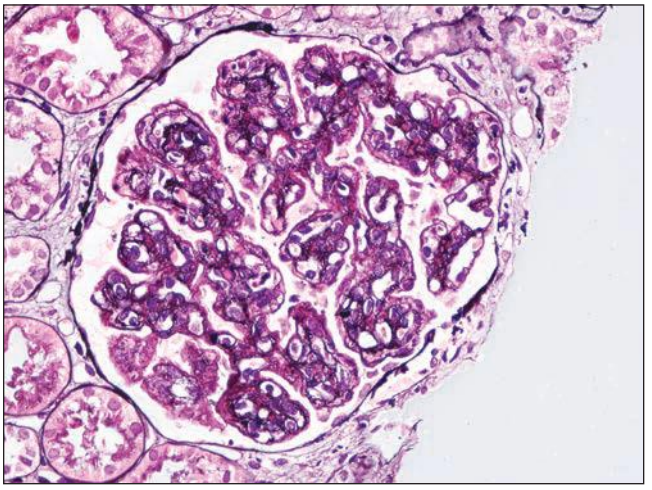


FIGURE 9.7 Glomerulus from a patient with DDD showing MPGN patterns. There are mesangial increase and capillary wall double contours. (Jones methenamine silver.)

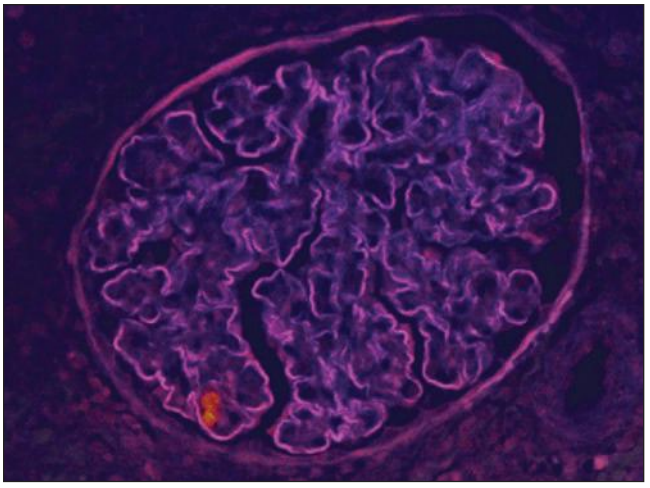


FIGURE 9.8 Glomerulus from a patient with DDD showing the staining of the capillary wall dense deposits with thioflavin T. (Thioflavin T stain.) (Courtesy of Dr. Patrick Walker.)

(TBMs) of both proximal and distal tubules (Fig. 9.9) (38); the extent of this extraglomerular involvement is quite variable.

As renal disease progresses, the glomeruli undergo sclerosis, but even in advanced cases, it is usually possible to see the characteristic intramembranous dense deposits by EM. In the Columbia series, segmental glomerulosclerosis was significantly more common with the MPGN pattern of GN and also in adults compared with children (16).

Tubules

The tubular epithelium may display either hyaline droplets (evidence of glomerular filtration of protein) or vacuolation. The same type of deposit noted in the GBM may be identified along the proximal and distal TBMs (38) (see Fig. 9.9). With progression of glomerular sclerosis, there are tubular atrophy and interstitial fibrosis.

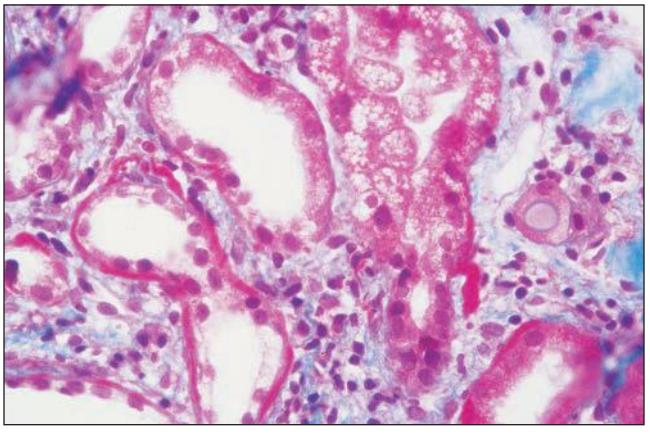


FIGURE 9.9 Focal band-like fuchsinophilic (*red*) deposits in the tubular basement membranes corresponding to the dense deposits seen by EM. (Trichrome, ×400.)

Blood Vessels

Intimal thickening of the arteries becomes evident as the disease progresses, probably secondary to hypertension. Electron-dense deposits may be identified in a few interstitial capillaries and arterioles (6,39).

Interstitium

Foam cells are sometimes present, indicative of the nephrotic syndrome with substantial hypercholesterolemia and lipiduria. Interstitial fibrosis appears as renal failure develops.

Immunohistochemistry

The invariable finding in DDD is the presence of C3 in the glomeruli (5,6,16,34,39–41). Intense staining for C3 is noted along the glomerular capillary walls and often in the glomerular mesangial regions (Fig. 9.10). The immunofluorescence patterns have been variously described as linear, pseudolinear, smooth, ribbon-like, granular, or nodular. The C3 deposition is usually diffuse and global. The GBM staining may be continuous or discontinuous. The mesangial deposits may stain as scattered granules, coarse granules, spherules, or small rings. The early components of complement, C1q and C4, are usually absent, although occasionally C1q is found (16,34,42). One study (43) reported C4 in 9 of 13 patients when glomerular granular capillary wall staining was present. When there is staining for C1q or C4, it is less intense than C3 and may be focal and segmental (38). C3 may also be detected in the Bowman capsule and along the TBMs.

Kim et al. (40) have reported a characteristic staining pattern for C3. A double-linear appearance, referred to as "railroad tracks," was detected in the glomerular capillary walls, while numerous circular, unevenly stained structures termed *mesangial rings* were noted in the mesangial areas. Using phase-contrast and electron microscopy with a double-labeling antibody technique (rhodamine-conjugated anti-GBM and fluoresceinated anti-C3), these authors thought that the railroad tracks and the mesangial rings represented the deposition of C3 along the

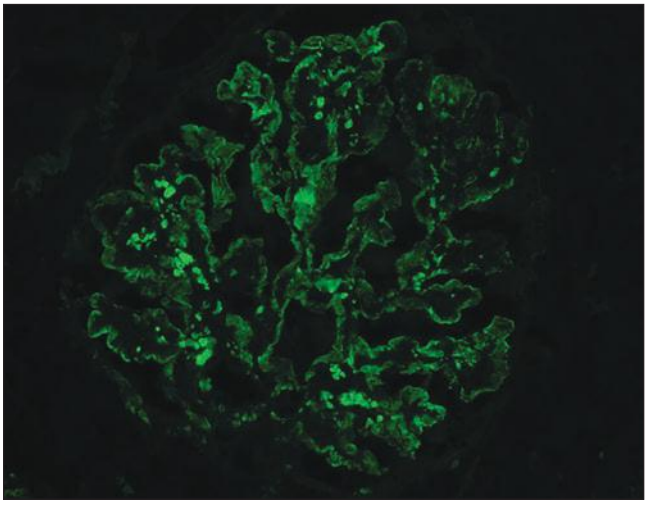


FIGURE 9.10 Immunofluorescence with antibody to C3c in a patient with dense deposits disease. There is staining of the glomerular capillary wall and also staining in the mesangium of spherical structures some of which have accentuation of staining at the edges (ring pattern).

margin, but not within the central portions, of the large intramembranous or mesangial deposits (40). However, our own unpublished data using immunoelectron microscopy showed staining of the dense deposit itself for C3 and C9. It may be that the pattern depends on the fragment(s) of C3 detected by the antibodies, and this is worthy of further study.

Immunoglobulins are usually absent or show only focal and segmental staining. If they are present, they often stain much less intensely than C3 and they are usually of the IgM type with a segmental distribution; IgG and especially IgA are less common (16,40). Joh et al. (38) suggested that IgG deposition in DDD is related to the glomerular subepithelial deposits visible on EM. Using a monoclonal antibody to a neoantigen of the C9 portion of the membrane attack complex (MAC) of complement, Falk et al. (44) performed immunofluorescence and immunoelectron microscopy to study the antigen distribution in renal biopsies of DDD. MAC and C3 were distributed along either side of the dense deposits within the GBMs and TBMs, around the circular mesangial deposits, and within the subepithelial deposits. In 12 biopsies from patients with DDD and an MPGN pattern, properdin staining was seen in 3 and was absent in 9 specimens (41), whereas Kim et al. (40) found properdin in a granular distribution in all 9 biopsies they examined and along the capillary wall in 5.

Electron Microscopy

EM led to the discovery of DDD, which is distinct from other forms of renal disease (2). The disease takes the name "dense deposit disease" from the characteristic ultrastructural appearance of the glomerular intramembranous deposits (Figs. 9.1 and 9.11). There have been many reports on the electron microscopic findings (4–6,9–11,16,34,36,38), and there is generally good agreement on the ultrastructural features. Confirmation of the diagnosis of DDD requires EM, although the diagnosis can be suspected with high confidence if the typical light microscopic and immunofluorescence microscopic features are observed.

The hallmark of DDD is the presence of dense osmiophilic deposits in the GBMs, basal lamina of the Bowman capsule, TBMs (mostly proximal but also involving distal tubules), and mesangial regions. Involvement of the glomerular capillary walls is variable. The deposits may replace the entire width of the lamina densa, whereas in patients with less extensive involvement, they occupy only part of the width. In the latter instances, the remnant or native GBM can be identified on one or both sides of the dense deposits. There may be fusiform segmental thickening of regions of the GBM or large, irregular masses of the dense deposits that cause considerable distortion of the GBM. Focal stretches of the glomerular lamina densa may not have dense deposits (Fig. 9.12).

The elongated or ribbon-like deposits in the GBM usually affect long stretches of many loops. In less severe cases, only a few loops are affected by shorter and narrower dense deposits. In some cases of mild involvement, the glomerular capillary wall deposits appear toward the inner (subendothelial) aspect of the GBM (38). Large glomerular subendothelial deposits are rare. In some cases, the deposits are found to be more prominent in the area of the GBM overlying the mesangium compared with the peripheral capillary loop GBM (16). In the mesangial proliferative form, dense deposits were more intermittent compared with the membranoproliferative form (34).

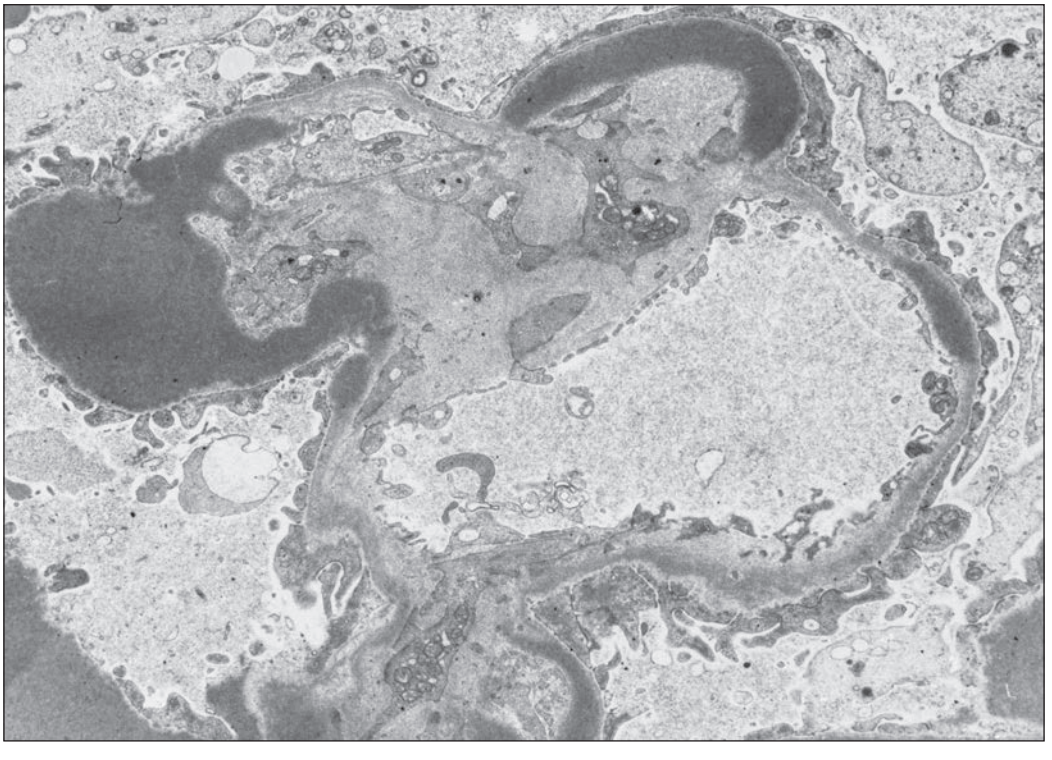


FIGURE 9.11 Dense deposits in the GBM. They are of a much greater density than the lamina densa and are usually elongated, as in this photo. (×3200.) (Courtesy of Dr T. Antonovych.)

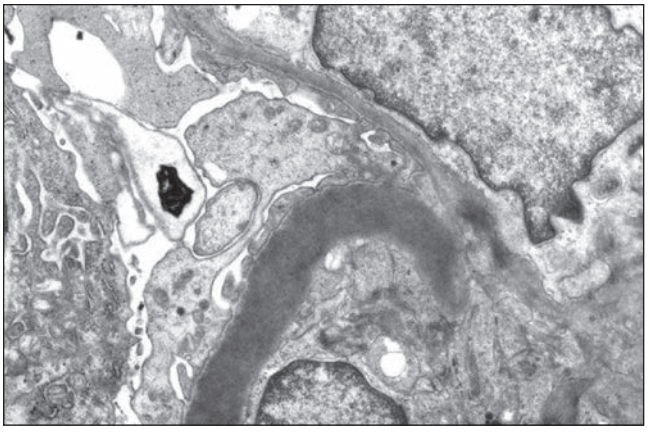


FIGURE 9.12 Electron micrograph showing the segmental distribution of the deposits that may be seen in DDD. In the low part of the picture, there is dense deposit occupying most of the thickness of the GBM, while in the upper part of the picture, no deposit is seen.

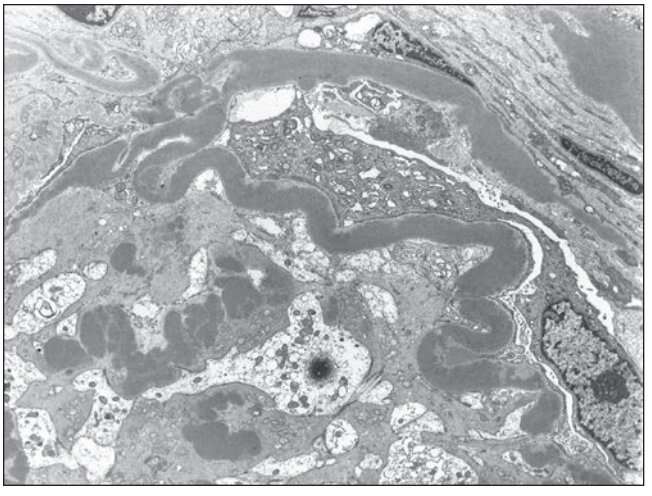


FIGURE 9.13 Electron micrograph from a case of DDD showing deposits in the GBM and typical nodular deposits in the mesangium.

The electron-dense deposits lack substructure, even at very high magnification. Although the deposits are quite dense, their density is accentuated several orders of magnitude after staining with lead or uranyl salts (36). Because their osmiophilia is so much greater than that of the lamina densa of the GBM, the deposits can readily be identified and distinguished from the lamina densa of the GBM, even if they are only focal and small. It has been suggested that the ultrastructural deposits are different from the finely granular discrete deposits that characterize the various forms of immune complex glomerulonephritis.

The mesangial regions may show several changes. There may be an increase in the number of cells in the mesangial regions, either mesangial cells or inflammatory cells or both. There also may be an increase in the amount of mesangial matrix, which may be so marked as to produce nodules. Electron-dense deposits are common in the mesangial regions (Fig. 9.13). Mesangial deposits are typically nongranular and dense like those of the GBM; they may be well circumscribed or large with vague margins. They often are more spherical or globular than typical immune complex mesangial dense deposits.

Many cases have subepithelial electron-dense deposits. In some cases, these appear to be subepithelial projections of the electron-dense material in the GBM, while in other cases they are identical to the typical hump-like deposits seen in postinfectious glomerulonephritis (Fig. 9.14). Subepithelial deposits are reported as being more common in adults than in children (16) and more common in endocapillary proliferative and crescentic disease than in the membranoproliferative pattern (34). West and McAdams (45) found subepithelial deposits adjacent to the paramesangial GBM in many patients with DDD and showed that their presence was strongly associated with hypocomplementemia at the time of biopsy.

Using scanning EM, Weidner and Lorentz (46) studied the three-dimensional appearance of GBMs rendered acellular by enzymatic digestion. When the findings from patients with DDD were compared with those of normal controls, the acellular GBM appeared rigid and thickened, with a coarsely granular or undulating surface that was punctuated by single or clustered crater-like deformities. These authors thought that this three-dimensional appearance was unique to DDD.

Electron-dense deposits may be noted along the basal lamina of the Bowman capsule, along the TBMs (Fig. 9.15), and in interstitial capillaries, arterioles, and small arteries (6,39). Dense deposits are commonly found in the Bowman capsule, although they may be quite focal and segmental. These deposits may or may not expand the Bowman capsule. Nasr et al. (16) found Bowman capsule deposits and TBM deposits in 44% and 50% of patients, respectively.

As noted above, a percentage of patients with DDD have drusen, deposits of lipoproteinaceous material in the Bruch membrane of the eye. Other extrarenal dense deposits have been sought using thioflavin T and EM in a number of patients with DDD, but they have been identified only in the basement membranes of the splenic sinusoids in two patients (47,48). No other organ system, such as the brain, heart, lung, liver, adrenal, or pancreas, was found to be involved in this and other studies.

Clinical Course, Prognosis, and Treatment

The overall long-term prognosis for patients with DDD is poor. In a series of 44 children (6), only one patient experienced remission. End-stage renal disease (ESRD) develops in most patients although the time to end stage is variable. In the series of children just noted, 10 of 44 progressed to end stage in 20 months from diagnosis and another 5 by 10 years. In a series of 98 patients from North America, 50% of the patients progressed to end stage within 10 years of diagnosis with young females having the greatest risk for renal failure (18). Servais et al. (17) found 41% of the patients progressed to end stage in a mean time of 10 years.

The presence of nephrotic syndrome at presentation predicts a poorer outcome in several series (6,10,13,15) although not in all (16). Lu et al. (18) found no effect of age at diagnosis on risk of progression to end stage, whereas in the series from Columbia (16), which included 14 children and 18 adults, the older patients had a significantly worse outcome. In the series described by Servais et al. (17), adults were more likely to

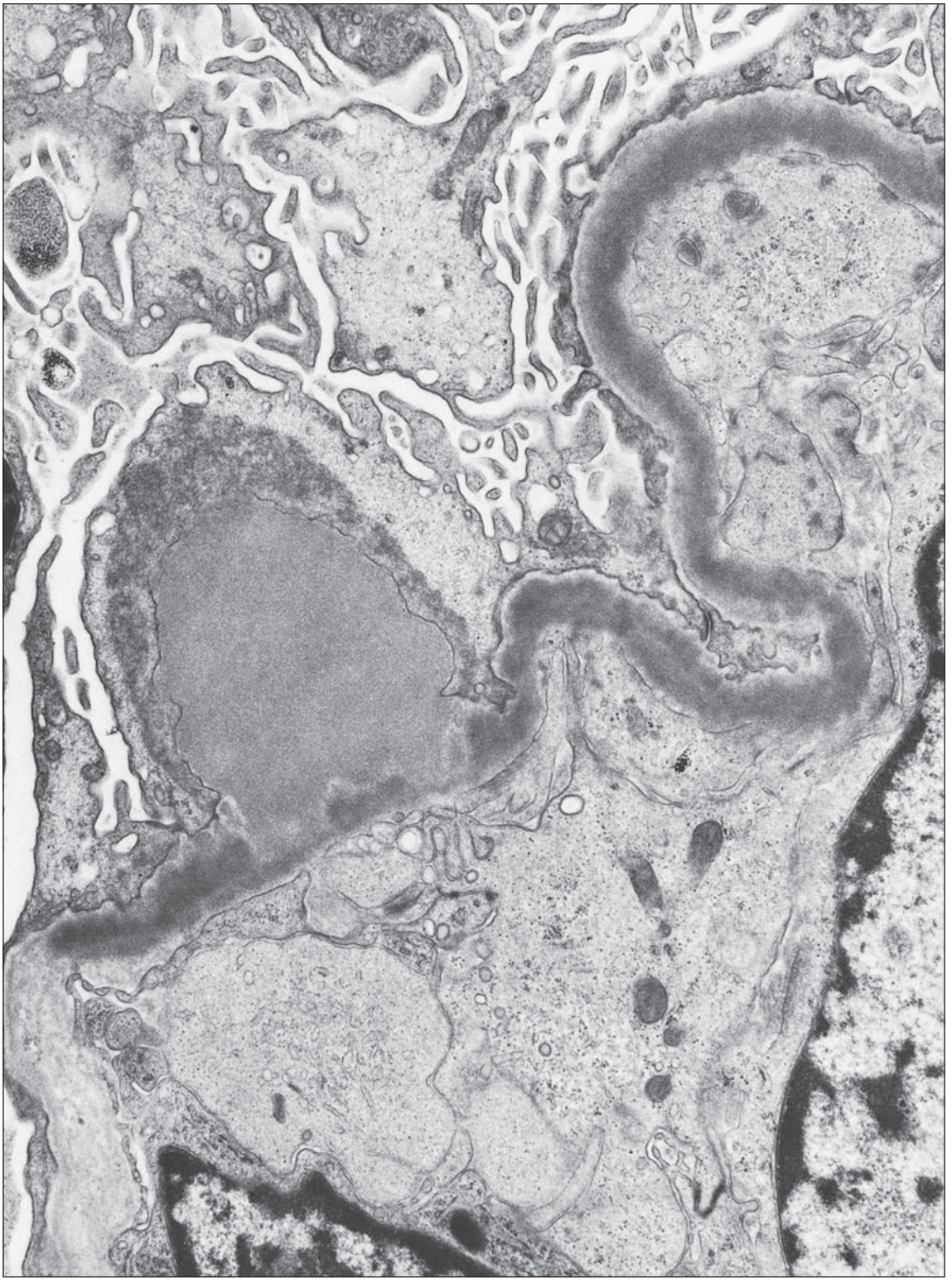


FIGURE 9.14 Electron micrograph of a glomerulus from a patient with dense deposit disease. This segment of a glomerulus shows a large, discrete, subepithelial deposit (hump) in addition to the dense intramembranous deposits. There is marked effacement of the glomerular visceral epithelial cell foot processes over the hump. (×15,516.) (Courtesy of Dr. Richard Sibley.)

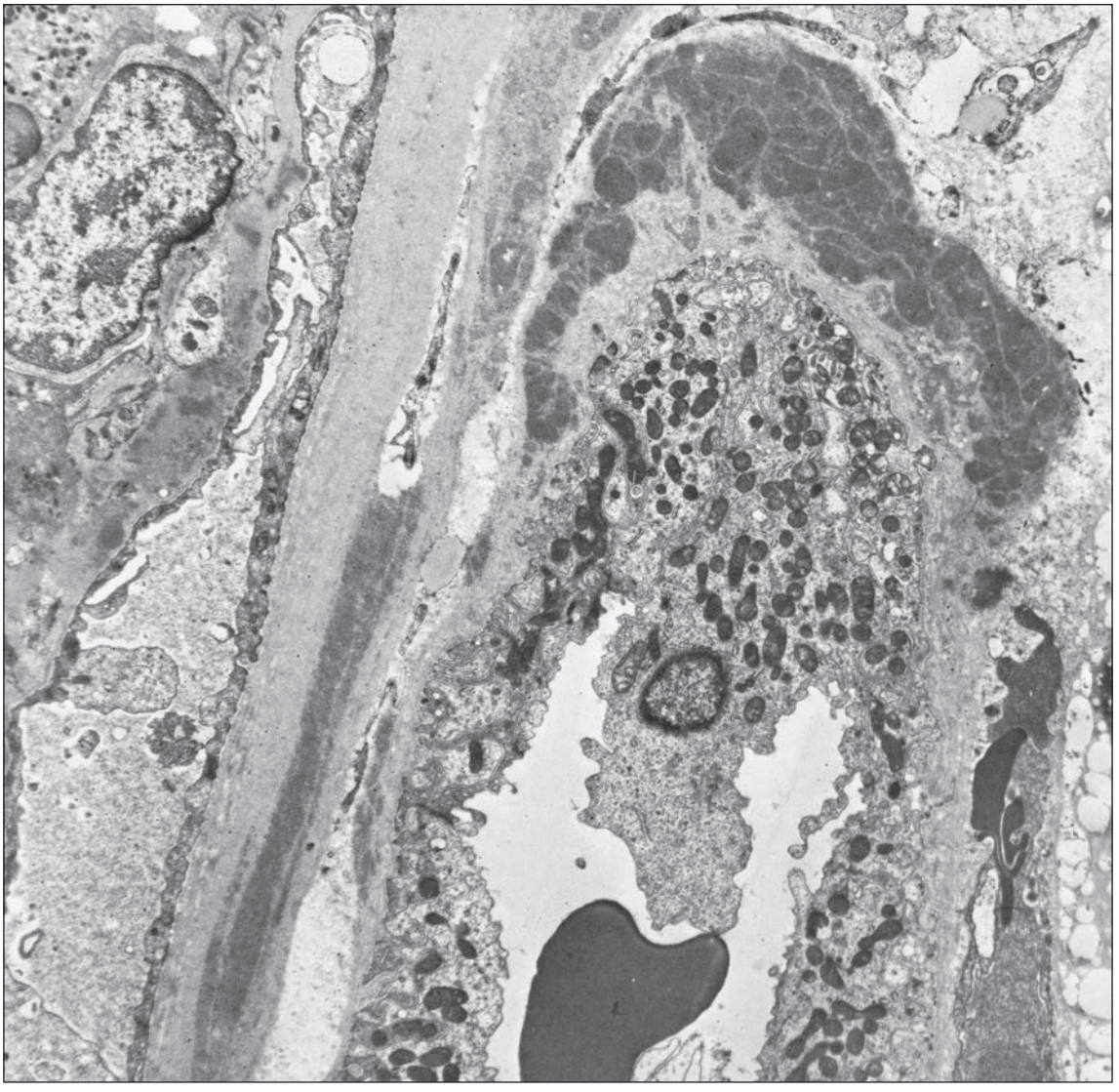


FIGURE 9.15 Extraglomerular deposits are frequently identified in biopsies showing dense deposit disease. Note the discrete and large electron-dense osmiophilic deposits in the basal lamina of the Bowman capsule (left) as well as in the tubular basement membrane. (Uranyl acetate and lead citrate; ×4620.) (Courtesy of Dr. Conrad L. Pirani.)

suffer from a rapid decline in renal function. Histologic factors predictive of outcome have varied between series. In several series, cellular crescents on biopsy at the time of diagnosis (15) have been associated with a poorer prognosis (6,11,13,15). However, Nasr et al. (16) found no correlation between crescents and ESRD, which they attributed to the fact that patients with more crescents were significantly more likely to have received immunosuppressive therapy. In that study, the presence of subepithelial humps and the presence of arteriosclerosis were predictors of ESRD.

The optimal treatment for DDD remains undefined in part because of its rarity, the lack of large prospective randomized clinical trials, and, at least until recently, a lack of knowledge about etiology and pathogenesis. Treatments that have been tried include renin-angiotensin blockade, corticosteroids and other immunosuppressants, anticoagulants and antithrombolytics, and plasmapheresis or plasma exchange. As pointed out by Appel et al. (19), the choice of therapy is usually made empirically or in desperation.

The most commonly used medications are ACE inhibitors and oral corticosteroids (18). In a cohort of 134 patients with MPGN type 1, DDD, and C3GN (17), the use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers was associated with better renal survival but not the use of immunosuppressive agents. However, the effect on the dense deposit patients alone was not stated. A randomized placebo-controlled trial of 80 children with MPGN, including 14 with DDD, demonstrated that alternate-day prednisone improved outcome in this heterogeneous group but not in those with DDD specifically (49). In the series of Nasr et al. (16), 14 patients received immunosuppression. The regimens included steroids in all patients, and three also received calcineurin inhibitors, and two received mycophenolate mofetil. There was a trend toward benefit in patients on immunosuppression

that did not reach statistical significance. There was a significant benefit of combined therapy with immunosuppression and renin-angiotensin blockade compared with either alone. McEnery and McAdams (50) described regression of DDD in six children treated continuously with an alternate-day prednisone regimen. All showed signs of reduction of glomerular mesangial hypercellularity and widening of the glomerular capillary lumens. A change was noted in the position of the dense deposits, from the lamina densa to the lamina rara interna of the GBM, in four patients. There was also a reduction in the prevalence of deposits in three children, with a virtual absence of deposits in two. Kher et al. (51) likewise found regression of the dense deposits in a child treated with immunosuppression and anticoagulant therapy. There are case reports of the effectiveness of plasmapheresis (52–54) but no controlled trials.

C3 deposition in glomeruli may be associated with activation of C5 and generation of the anaphylatoxin C5a and the MAC C5b-9. Therefore, it may be that inhibition at the level of C5 could inhibit, at least in part, glomerular injury in DDD. Eculizumab is a humanized monoclonal antibody that binds with high affinity to C5. In an open-label, nonblinded study, it was given to six adult subjects with C3 glomerulopathy all of whom had a renal biopsy within 6 months of enrolment (55). Three patients had DDD, including one with recurrence in a renal allograft, and three had C3 glomerulopathy without dense deposits (C3GN), including two with allograft recurrence. After 12 months of treatment, two subjects with DDD showed significantly reduced serum creatinine and one achieved marked reduction in proteinuria. Of the patients with C3GN, one showed reduction of serum creatinine and one showed histopathologic improvement with stable laboratory parameters. Elevated levels of serum MAC normalized on therapy. Examination of repeat biopsies showed reduction of active glomerular proliferation and neutrophil infiltration consistent with blockade of the synthesis of the chemotactic C5a (56). There was no significant alteration of immunofluorescent staining for C3 or C5b-9. Interestingly, all biopsies after eculizumab treatment showed staining for IgG and kappa light chains consistent with binding of monoclonal eculizumab in the glomeruli. The long-term consequences of this are unknown.

C3 GLOMERULONEPHRITIS

While DDD is recognized by the presence of glomerular C3 on immunohistochemistry and characteristic osmiophilic deposits indicative of DDD, other forms of C3 glomerulopathy have been less clearly defined until recently. There have been occasional reports of patients with isolated C3 deposition (57–60), in some cases with deposits on EM. In addition, it was recognized that patients with MPGN may have deposition of C3 without immunoglobulins or components of the classical pathway of complement activation (61) implying alternative pathway activation. However, it was the publication of a series of cases by Servais et al. (62) that drew attention to the importance of recognizing the presence of C3 in the absence of immunoglobulin as a defining feature of a distinctive category of glomerular disease. This led directly to the proposal to recognize these cases as forms of C3 glomerulopathy regardless of the underlying morphology (1), thus alerting the clinician to the importance of searching for an underlying abnormality of the complement system in these patients.

As noted earlier, C3 glomerulopathy is further categorized as DDD or C3GN (see Table 9.1). Morphologically, most C3GN cases show either a mesangial proliferative or membranoproliferative pattern. The recognition of C3GN has resulted in reconsideration of the significance of finding MPGN by light microscopy on biopsy. Whereas in the past there has been an emphasis on the morphology of biopsies with MPGN, with recognition that those showing DDD are a special category, there is now general acceptance that the most important feature in a biopsy with MPGN type I is whether there is substantial immunoglobulin indicative of immune complex deposition or predominantly isolated C3 (63). Type III MPGN can be similarly divided, with many cases of type III of Burkholder falling into the immune complex category and many cases of type III of Strife falling into the C3GN category.

Clinical Presentation

The forms of C3 glomerulopathy without dense deposits represent a heterogeneous group in terms of pathogenesis and clinical course. There are a range of mutations that have been found in these patients in genes that code for proteins involved with the alternative pathway of complement. There are two examples of familial forms of the disease where specific cosegregating mutations have been demonstrated—CFHR5 nephropathy (64), an autosomal dominant form of glomerulonephritis endemic in Cyprus, and a familial MPGN from Ireland (65).

Servais et al. (17) have reported the clinical features in 56 patients with C3 glomerulopathy without dense deposits (C3GN) and compared them with 29 patients with DDD and 49 patients with immune complex MPGN type 1. The mean age at diagnosis for C3GN was 30, which was significantly higher than for DDD; 25% of patients were below 16 years of age. Twenty-seven percent of patients with C3GN had nephrotic syndrome at presentation as compared with 38% of patients with DDD and 65% of patients with MPGN type I. Approximately two thirds of the patients with C3GN had microhematuria at presentation and about one third had elevated blood pressure. At presentation, 40% of the C3GN patients had low C3 levels in the circulation. C3NeF was found in 45% of patients, which was significantly fewer than in DDD (86%). The genetic abnormalities found in these patients are discussed in the section on pathogenesis. In a series of 12 patients from the Mayo clinic (66), the age at presentation varied from 8 to 73 years. Recent studies have drawn attention to cases of C3 glomerulopathy where the initial clinical presentation and histologic features, including subepithelial hump-like deposits, were suggestive of postinfectious glomerulonephritis. However, the hematuria and proteinuria did not resolve leading to the subsequent diagnosis of C3GN (67,68).

CFHR5 nephropathy is a familial form of C3 glomerulopathy without dense deposits that occurs in patients of Cypriot descent (64). It shows autosomal dominant inheritance due to a mutation in the complement factor H (CFH)–related protein 5 gene (*CFHR5*). The mutation results in a duplication of exons 2 and 3 of the gene. Athanasiou et al. (69) analyzed 91 patients with this mutation from 16 families. The major clinical feature in young patients with the mutation was hematuria, and overall microscopic hematuria was present in 90% of patients. Twenty

percent of patients reported episodes of macroscopic hematuria often associated with upper respiratory tract infection. Proteinuria became more common with increasing age and was seen in 80% of males and 20% of females over the age of 50. Impaired renal function was more common with increasing age, particularly in men, and of 18 patients who reached ESRD, 78% were male. Interestingly, nearly all the male patients who reached end stage had a history of episodes of macroscopic hematuria in childhood or adolescence. The cause for the striking gender difference in outcome is unclear.

Another familial form of C3 glomerulopathy without dense deposits in which a specific mutation has been found was originally reported as a familial MPGN type III (70). The disease showed linkage to chromosome 1 (71) and has now been shown to cosegregate with a mutation involving the genes coding for CHF-related proteins 1 and 3 forming a hybrid gene (65). The condition is inherited in an autosomal dominant fashion. There was variation in the clinical progression with one member of the family presenting at age 4 with steroid-unresponsive nephrotic syndrome progressing to proteinuria at age 10, whereas his father developed nephrotic-range proteinuria at the age of 51, 12 years after donating a kidney to his son.

Pathologic Findings

Light Microscopy

Glomeruli

The defining features of C3GN are the presence of C3 on immunohistochemistry and deposits on EM. As with DDD, the light microscopic features are variable. Glomeruli may show mesangial proliferation, membranoproliferative features, endocapillary hypercellularity, and variable crescent formation (Figs. 9.16 to 9.19). At present, we do not know how the different morphologic features relate to the underlying genetic or functional abnormalities of complement activation. In the series of 56 cases from France, 71% of biopsies showed a membranoproliferative pattern with mesangial proliferation, increased mesangial matrix, capillary wall thickening, and a double-contour appearance of the capillary walls (17). In 29% of cases, there was no capillary wall thickening or mesangial proliferation, and these were associated with only mesangial

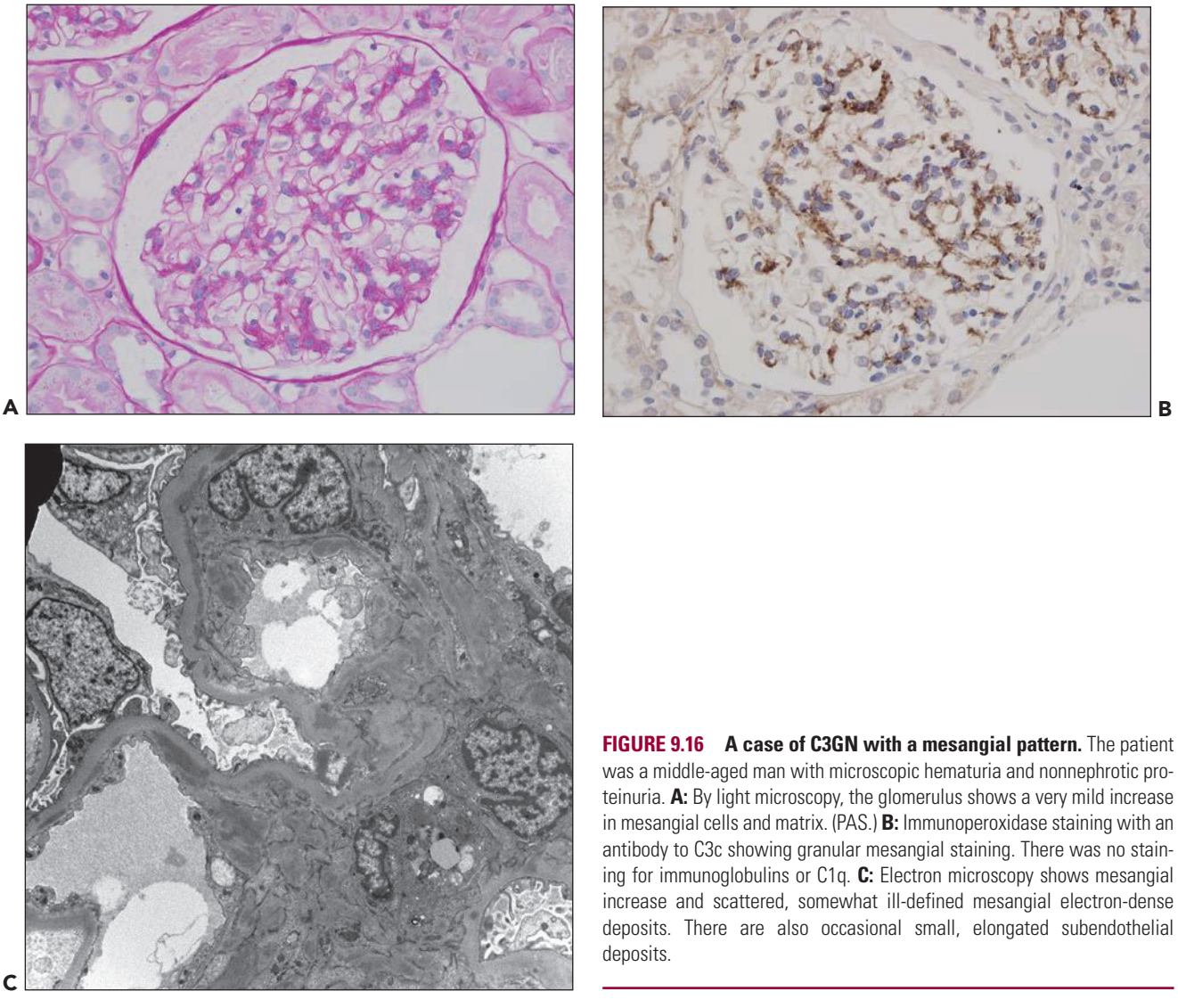
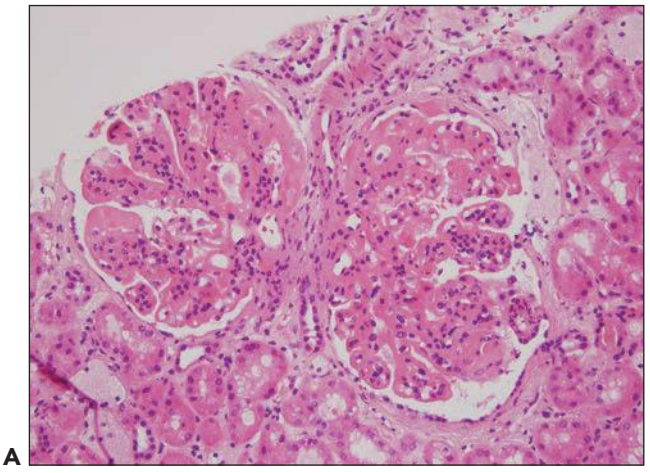


FIGURE 9.16 A case of C3GN with a mesangial pattern. The patient was a middle-aged man with microscopic hematuria and nonnephrotic proteinuria. **A:** By light microscopy, the glomerulus shows a very mild increase in mesangial cells and matrix. (PAS.) **B:** Immunoperoxidase staining with an antibody to C3c showing granular mesangial staining. There was no staining for immunoglobulins or C1q. **C:** Electron microscopy shows mesangial increase and scattered, somewhat ill-defined mesangial electron-dense deposits. There are also occasional small, elongated subendothelial deposits.



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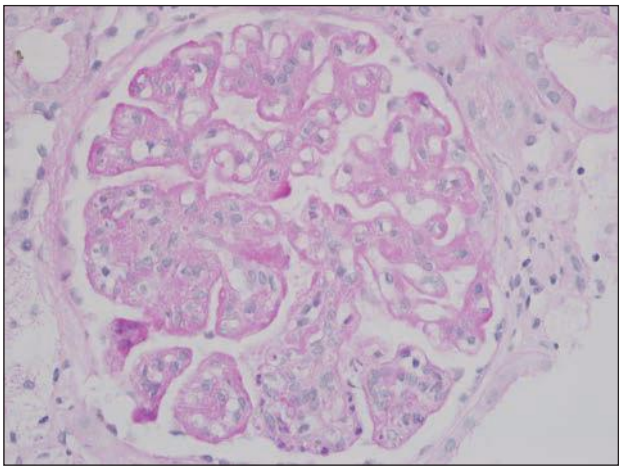

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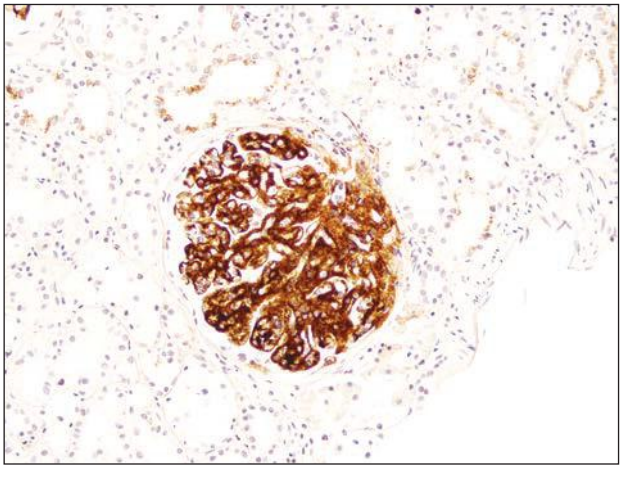

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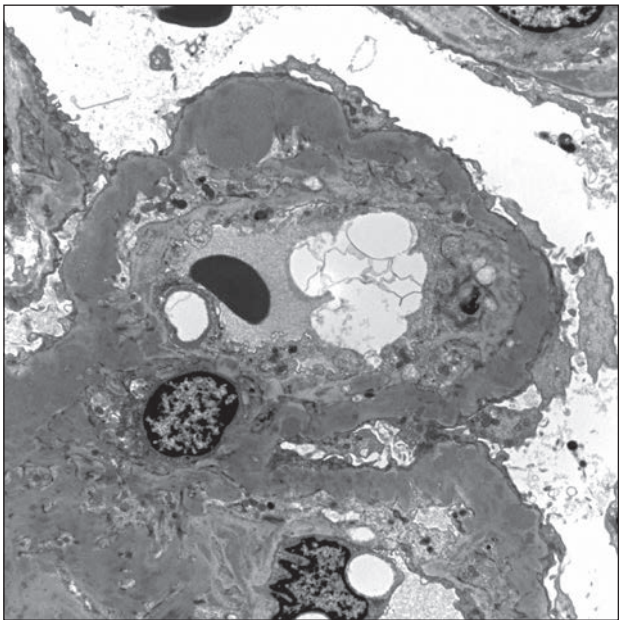

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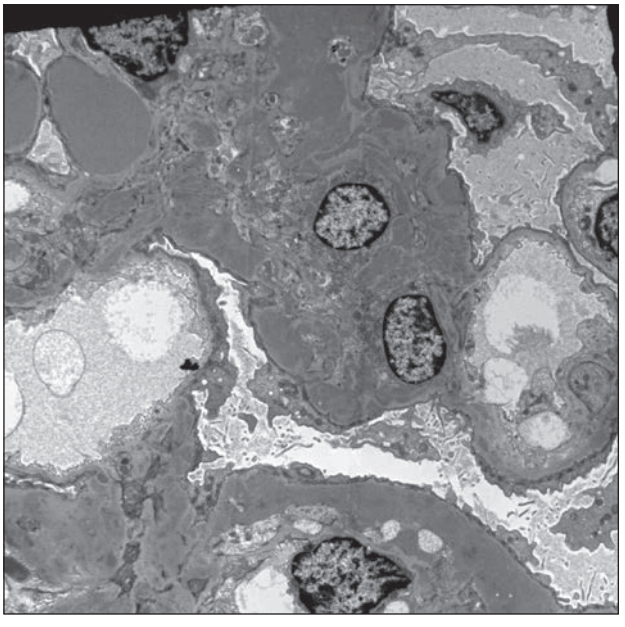

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FIGURE 9.17 A case of C3GN with a membranoproliferative pattern. The patient was a young woman with a 6-year history of recurrent nephrotic syndrome. Serum C3 was low. **A:** Light microscopy shows enhanced glomerular lobulation, increased mesangial cells and matrix, and capillary wall thickening. (H&E.) **B:** Light microscopy showing increased mesangial matrix and cells, and capillary wall thickening with double contours. A few neutrophils are seen in the glomerulus in the lower part of the picture. (PAS.) **C:** Immunoperoxidase staining with an antibody to C3c showing strong mesangial and capillary wall staining. There was no staining for immunoglobulins or C1q. **D:** Electron micrograph showing marked thickening of the glomerular capillary wall by electron-dense material. In general, the deposits appear less sharply defined than typical immune complexes. **E:** Electron micrograph showing an expanded mesangium occupied by electron-dense deposits. At the upper left, there is a subepithelial hump-like deposit.

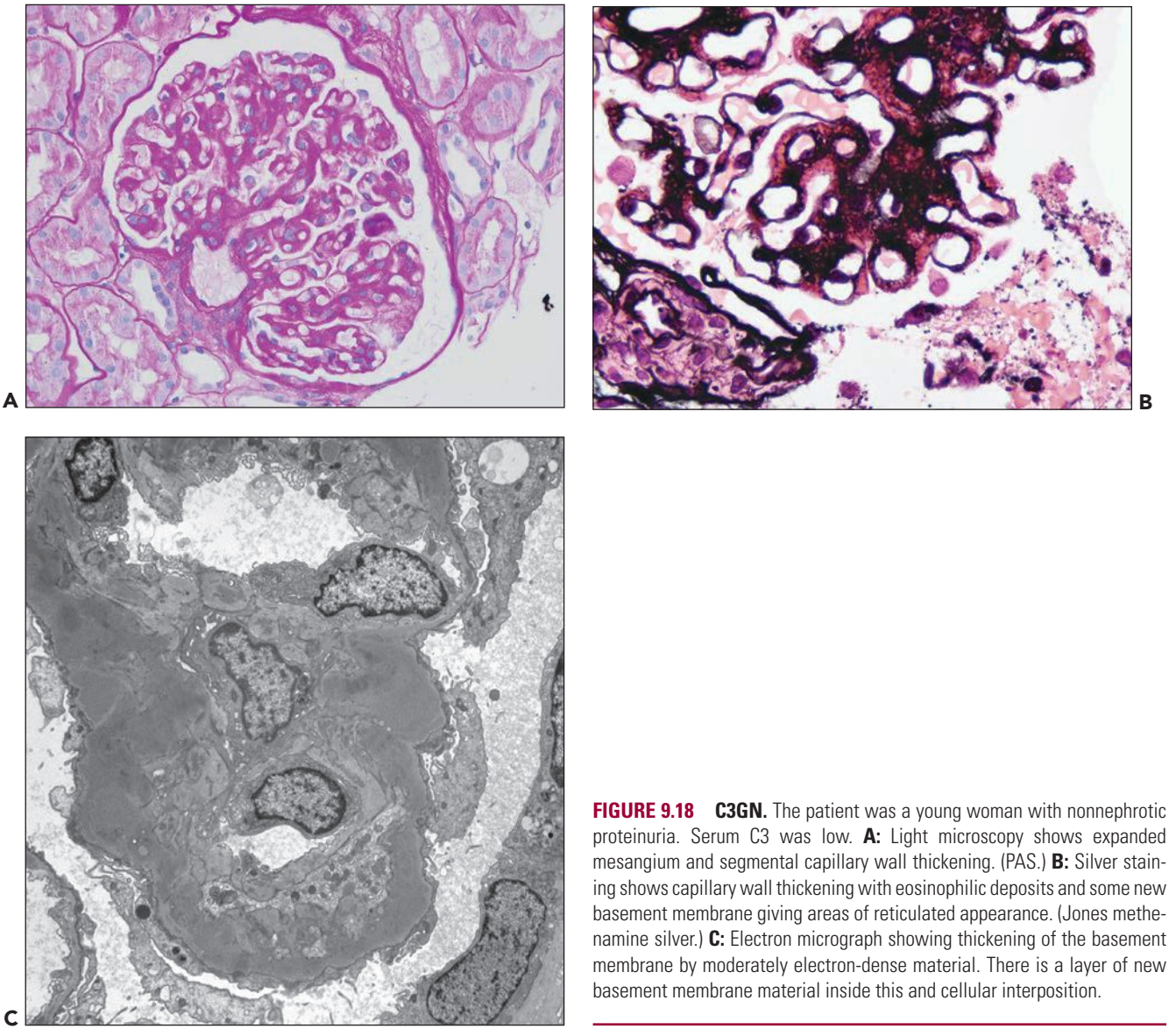


FIGURE 9.18 C3GN. The patient was a young woman with nonnephrotic proteinuria. Serum C3 was low. **A:** Light microscopy shows expanded mesangium and segmental capillary wall thickening. (PAS.) **B:** Silver staining shows capillary wall thickening with eosinophilic deposits and some new basement membrane giving areas of reticulated appearance. (Jones methenamine silver.) **C:** Electron micrograph showing thickening of the basement membrane by moderately electron-dense material. There is a layer of new basement membrane material inside this and cellular interposition.

and subepithelial deposits without subendothelial deposits. Crescents were seen in 10 patients. In 10 patients from the Mayo clinic, 8 showed a membranoproliferative pattern and 2 showed diffuse endocapillary proliferative glomerulonephritis with influx of both mononuclear cells and neutrophils (66).

We have seen a number of cases of CFHR5 nephropathy. In many cases, the glomeruli either are normal or show mild mesangial changes on light microscopy with slight mesangial expansion and mesangial hypercellularity (Fig. 9.20). Later, capillary walls show segmental thickening with double contours. As disease progresses, there is development of segmental and global glomerulosclerosis.

Tubules, Interstitium, and Blood Vessels

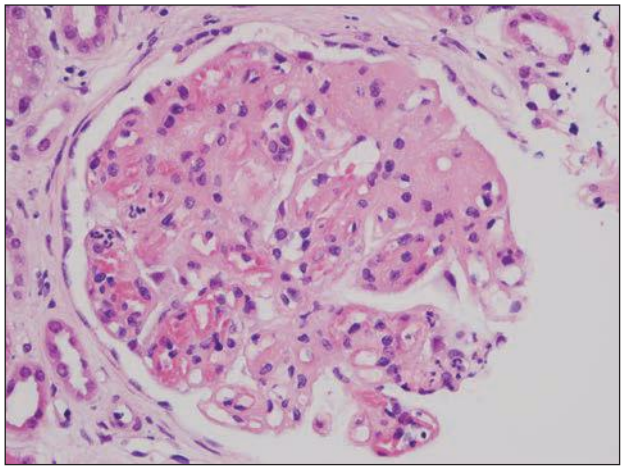
No specific features have been described. In patients with persistent heavy proteinuria collections of foam cells may be seen in the interstitium. Tubular atrophy and interstitial fibrosis appears to parallel the development of glomerulosclerosis.

Immunohistochemistry

The defining feature is the presence of C3 in glomeruli with little or no immunoglobulins (see Figs. 9.16, 9.17, and 9.20). At the present time, it is not clear how much immunoglobulin staining can occur in C3GN before the alternative diagnosis of immune complex glomerulonephritis is more likely. In C3GN with a membranoproliferative pattern on light microscopy, there are usually prominent capillary wall and mesangial deposits of C3. In some cases, the capillary wall deposits may have a distinct granular appearance. In some biopsies, the C3 staining is mainly mesangial. C3 staining on the TBMs was found by Sethi and Fervenza in 2 of 10 cases (66).

Electron Microscopy

The deposits of C3 seen by immunohistochemistry correspond to electron-dense deposits on EM (see Figs. 9.16 to 9.19). In some cases, these deposits have very similar appearances to those



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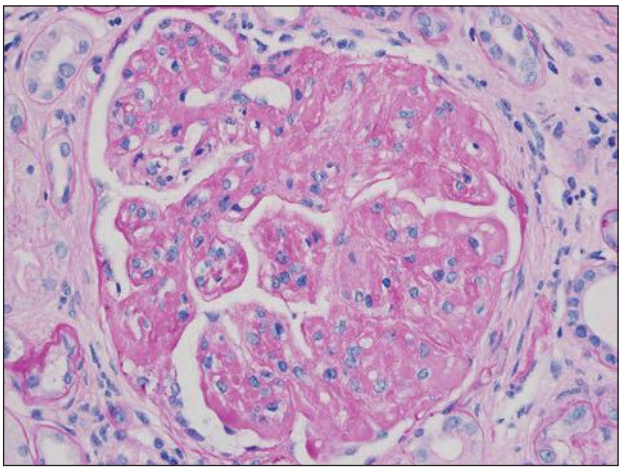

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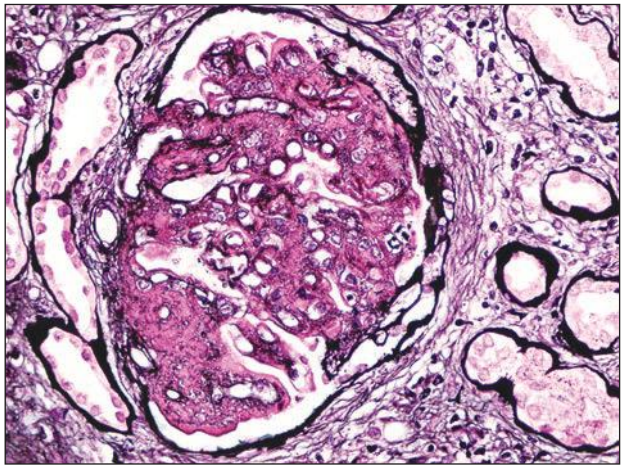

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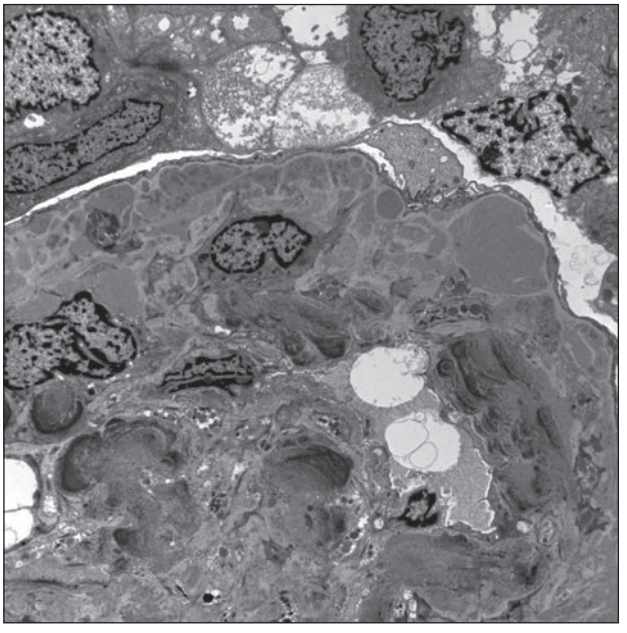

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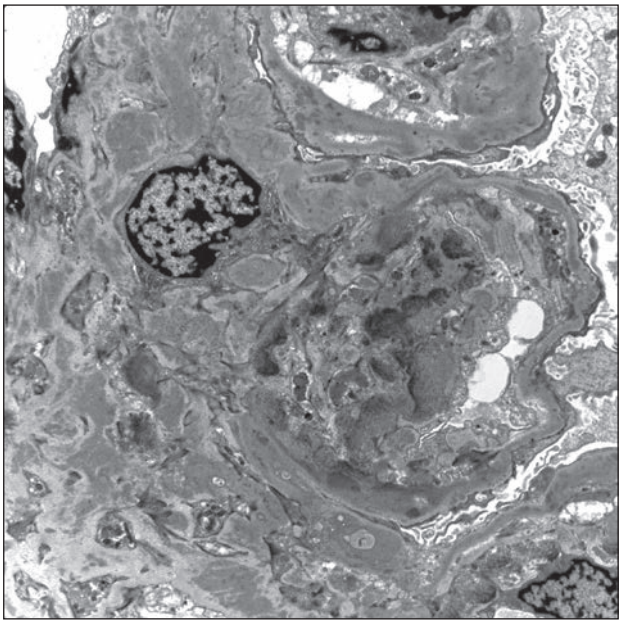

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FIGURE 9.19 **C3GN.** The patient was a young man with acute renal failure and nephrotic syndrome. Serum C3 was low. **A:** Light microscopy shows marked increase in mesangial matrix and capillary wall thickening. Some capillary lumens are lined by granular eosinophilic material. (H&E.) **B:** The glomerulus showing marked mesangial increase and capillary wall thickening. (PAS.) **C:** Silver staining shows extensive deposition of silver-negative eosinophilic material in the mesangium and capillary walls. **D:** Electron micrograph showing marked thickening of the GBM with widespread electron-dense deposits separated by thin strands of basement membrane material. Around the capillary lumen, there are curvilinear deposits of more electron-dense material corresponding to the granular eosinophilic material seen in **panel A**. **E:** Electron micrograph showing mesangial expansion with multiple mesangial electron-dense deposits. As in **panel D**, there are deposits of more electron-dense material beneath the endothelium.

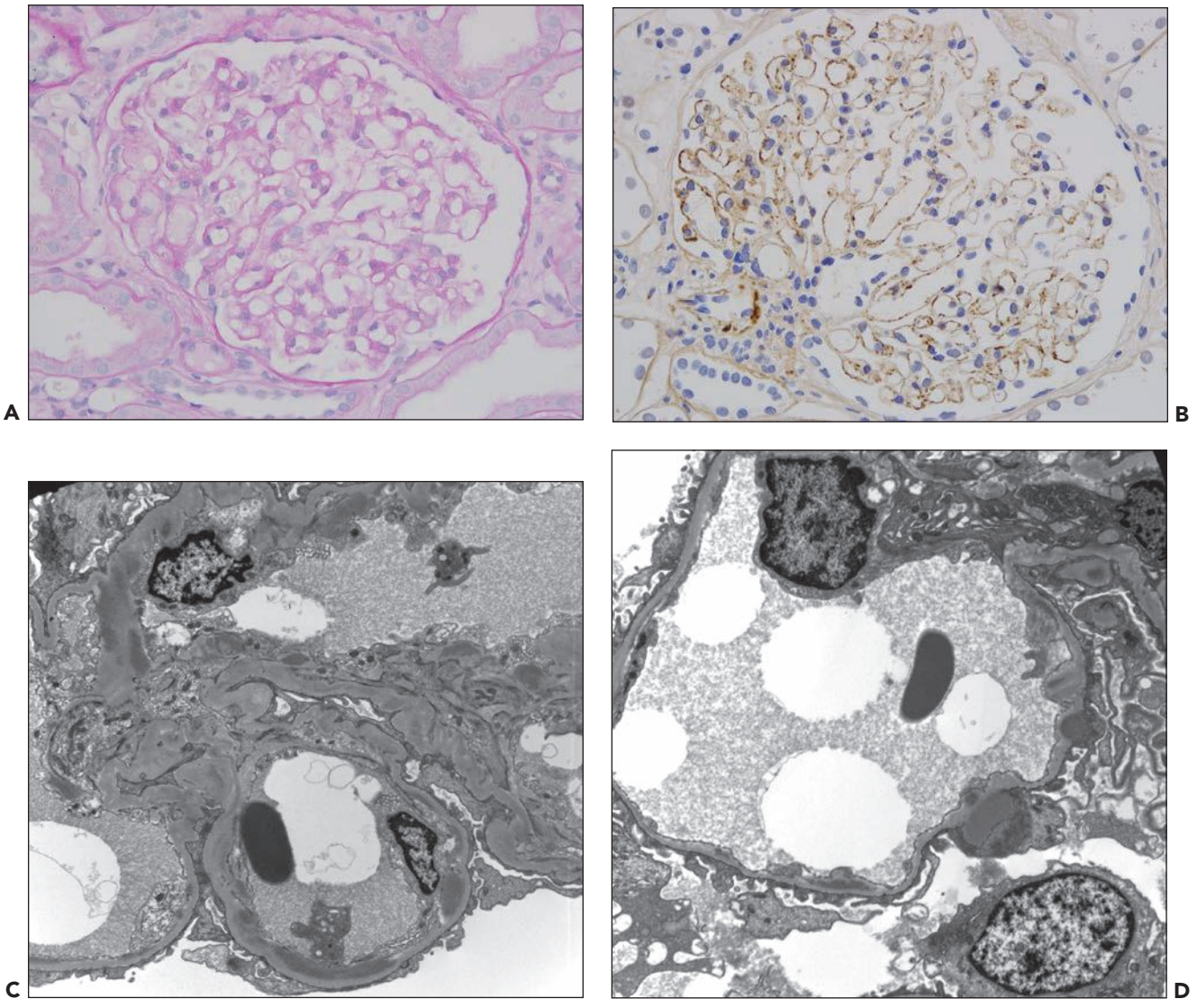

FIGURE 9.20 Biopsy from a patient with CFHR5 nephropathy. A: Light microscopy showing a morphologically normal glomerulus. (PAS.) **B:** Immunoperoxidase staining with an antibody to C3c showing fine granular capillary wall staining. There was no staining for immunoglobulins or C1q. **C:** Electron micrograph showing prominent elongated subendothelial electron-dense deposits and scattered mesangial deposits. **D:** Electron micrograph showing small, elongated subendothelial electron-dense deposits and two subepithelial deposits.

seen in typical immune complex glomerulonephritis, whereas in other cases, they may be less sharply defined. In some cases, they resemble the intramembranous deposits of DDD but with less dense osmiophilic appearance. Occasional cases of C3 glomerulopathy have substantial overlapping features of DDD and C3GN that make subcategorization difficult.

It is not clear at present how the site and appearance of the deposits relate to the underlying genetic and functional abnormalities although some associations are apparent. Patients with CFHR5 nephropathy form a homogeneous group in terms of pathogenesis, and the biopsies we have seen in these cases show similar appearances on EM (Fig. 9.20). The deposits appear similar in density to typical immune complexes. Characteristically, there are segmental elongated deposits on the endothelial side of the basement membrane. They may be associated in areas with a new layer of basement membrane beneath the endothelium. There are usually discrete mesangial deposits and scattered small subepithelial deposits that may have adjacent projections from the GBM. Similar features may be seen in other patients without the typical genetic defect of CFHR5 nephropathy.

In other cases of C3GN, the deposits may be less dense and less sharply demarcated than typical immune complex deposits. In some cases, they appear to replace areas of the basement membrane without clearly defined borders. Similar changes may be seen in the mesangium. In some cases, we have seen complex thickening of the basement membrane with multiple electron-dense deposits separated by material of similar density to the basement membrane (see Fig. 9.19D). These appearances are similar to those that were described by Strife

as subtype of MPGN type III, thus indicating that at least some cases of C3GN have a pathologic phenotype of MPGN type III of Strife.

In all cases, subepithelial deposits may be present. Some of these appear to be subepithelial projections of intramembranous deposits, while others have the appearance of typical subepithelial humps as seen in postinfectious glomerulonephritis (see Fig. 9.17E). It is tempting to speculate that the latter may be related to infectious exacerbations of the disease.

The group of West has emphasized the importance of subepithelial deposits located on the paramesangial GBM overlying the mesangium. They found such deposits commonly in patients with an MPGN pattern of glomerulonephritis and isolated C3 deposition but much less frequently in patients with typical immune complex MPGN type I.

In patients from an Irish family with hereditary glomerulonephritis associated with a hybrid *CFHR*1/3 gene, there were discrete subepithelial and subendothelial deposits on EM (Fig. 9.21).

Clinical Course, Prognosis, and Treatment

The clinical course and prognosis of patients with C3GN is not well defined as the condition has only recently been recognized as a distinct entity and previously many of the patients would have been included in cohorts of cases classed as MPGN or DDD. However, it is clear that there is a wide variation in outcome depending on the underlying etiology and it will be important in future to relate outcome to the pathology, serology, and genetics in individual patients. In the French series of 56 patients with C3GN (17), progression to ESRD was similar to that of MPGN type 1 and DDD with an overall 10-year survival of 63.5%. In a group of 10 patients with C3GN in their native kidneys (66), there was a range of clinical outcomes with one patient progressing to dialysis within 3 months of presentation and another with stable renal function for 23 years. In CFHR5 nephropathy, there is a major difference in outcome between men and women (69); in carriers of the *CFHR5* mutation aged over 50 years, 80% of men and only 21% of women developed chronic renal failure. The cause for this sex difference is unknown.

There are no controlled trials of treatment of C3GN. As described in the section on treatment of DDD, there is an open-label study in which three patients with C3GN were treated with eculizumab (55). One of the patients with C3GN showed reduction of serum creatinine and one showed histopathologic improvement with stable laboratory parameters. Further studies will be needed to define the role of C5 inhibition in this disease.

PATHOGENESIS OF C3 GLOMERULOPATHY

There is extensive evidence that C3 glomerulopathy is associated with abnormal complement regulation (dysregulation). DDD is typically associated with a failure to control the activation of the alternative pathway in the circulation, and this is reflected in low circulating levels of C3. In many cases of C3GN, there is no reduction in plasma C3 levels despite glomerular C3 accumulation. These cases may be due to a local defect in handling C3 deposits within the local environment of the glomerulus. The pathogenesis of C3 glomerulopathy will be discussed in the context of the complement system, genetic and acquired complement abnormalities, and experimental models of C3 glomerulopathy.

The Complement System

The complement system comprises over 30 proteins either circulating in plasma or on cell membranes. It plays a central role in inflammation in the response to pathogens and also the clearance of apoptotic cells and cell debris. Complement activation occurs through the classical, lectin, and alternative pathways (Fig. 9.22). Activation of these pathways results in the generation of an enzyme complex (C3 convertase) that cleaves C3, generating fragments termed C3a, an anaphylatoxin, and

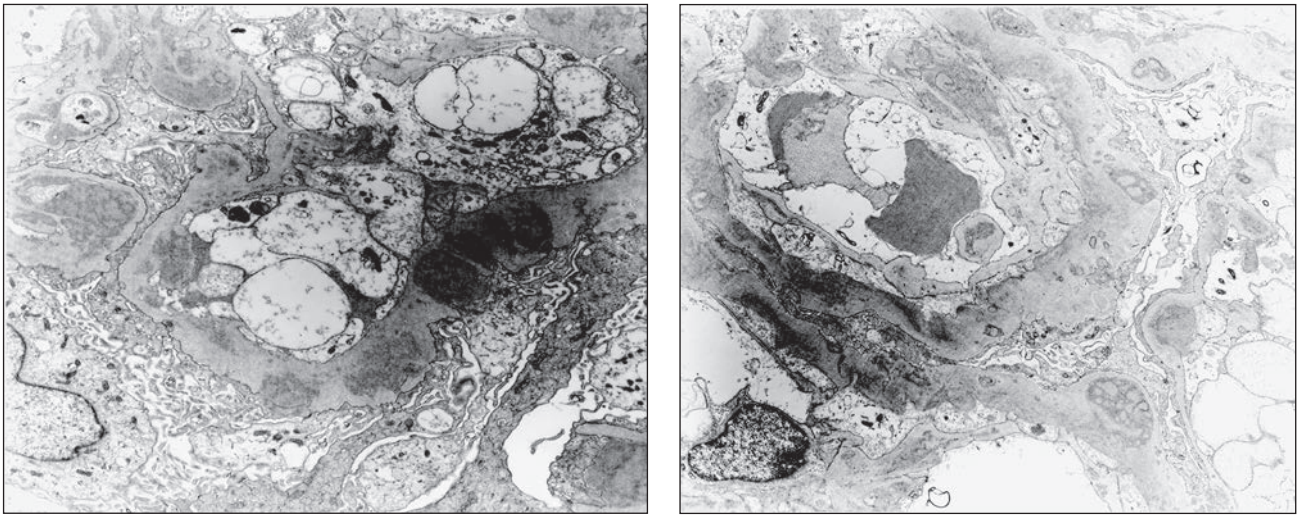

FIGURE 9.21 Electron micrographs from a case of hereditary C3GN associated with a hybrid CFHR1/3 gene. There are multiple large subendothelial and subepithelial electron-dense deposits. (Courtesy of Dr. Anthony Dorman.)

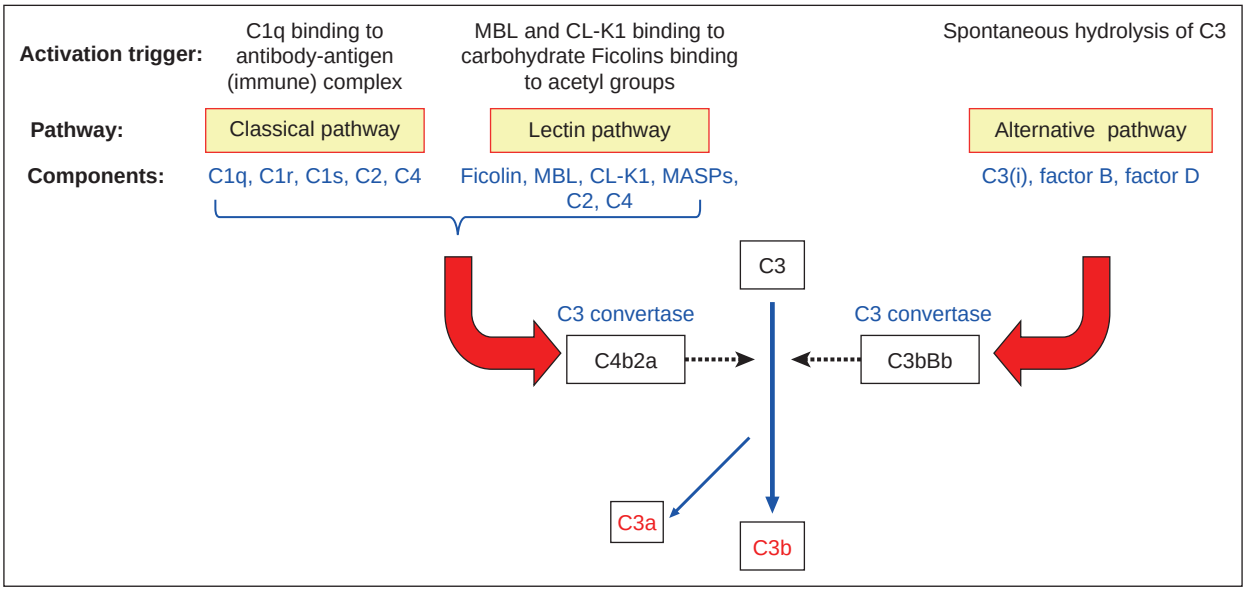

FIGURE 9.22 Complement activation. Complement is activated through three pathways that converge on C3. The activating triggers of each pathway are outlined. Note that C4 is one of the activation proteins of the classical pathway. Therefore, in immune complex disease where there is increased classical pathway activation, C4 levels are typically reduced with or without a reduction in C3 levels. Only rarely is isolated reduction in C3 seen, and this usually indicates abnormal activation of the alternative pathway. Activation of each pathway results in the generation of enzyme complexes that can cleave C3. These are termed C3 convertases and comprise C3bBb (alternative pathway C3 convertase) and C4b2a (classical and lectin pathway C3 convertase). Enzymatic cleavage of C3 generates C3b (see Fig. 9.23) and C3a (anaphylatoxin). MBL, mannose-binding lectin; MASP, MBL-associated serine protease; CL-K1, human collecting kidney 1.

C3b, a potent opsonin. Rapid amplification of C3b is achieved through a positive feedback loop (termed the C3b amplification loop) that can generate millions of C3b molecules within minutes. Through the binding of an additional C3b molecule, C3 convertases become capable of cleaving complement C5 (C5 convertases). This generates C5a, an anaphylatoxin, and C5b, which, through the sequential interaction with complement C6, C7, C8, and C9, generates the MAC. The biologic effector functions of complement are depicted in Figure 9.23.

The classical pathway is activated by immune complexes and the lectin pathway by carbohydrate and acetylated groups. The alternative pathway is unique in that activation occurs continuously at low levels in the circulation. This is a consequence of spontaneous hydrolysis in plasma of an internal thioester bond in complement C3. Hydrolyzed C3 (C3i) interacts with factor B, another complement plasma protein. The factor B within C3iB is cleaved by the serine protease factor D resulting in a C3 convertase (C3iBb). This complex cleaves C3 to C3b, which, in the same manner as C3i, interacts with factors B and D to form a C3 convertase (C3bBb). The result is continuous generation of C3b. Regulatory proteins act at multiple steps within the activation cascade to appropriately modulate effector functions. These regulators comprise soluble and membrane-bound proteins (Fig. 9.24). Because of the spontaneous activation of the alternative pathway and potency of the C3b amplification loop, regulation of these pathways is particularly important. Both pathways are regulated by complement factor I (CFI) and complement factor H (CFH).

CFI is a serine protease that cleaves C3b sequentially to iC3b and C3d. Unlike C3b, iC3b and C3d cannot form C3 convertases, so the CFI-mediated cleavage of C3b stops further C3b activation. In complete CFI deficiency states, the spontaneous activation of the alternative pathway and subsequent C3b amplification proceed unhindered and secondary severe C3 depletion develops. Importantly, CFI is only able to cleave C3b in the presence of a cofactor. These include CFH and the membrane-bound proteins, CD46 (membrane cofactor protein), and complement receptor 1 (CR1, CD35).

CFH is an abundant single-chain glycoprotein predominantly made in the liver. In common with other complement regulators encoded within chromosome 1, it is composed of protein subunits of approximately 60 amino acids, termed short consensus repeat (SCR) domains. CFH regulates C3 activation in three ways: (a) It blocks the formation of alternative pathway C3 convertases by binding to C3b thereby inhibiting interaction between C3b and factor B, (b) it promotes the spontaneous dissociation of these convertases, and (c) it acts as a cofactor for the CFI-mediated cleavage of C3b to iC3b. CFH acts as an important regulator in plasma. Like complete CFI deficiency, complete CFH deficiency results in uncontrolled C3b generation and secondary severe C3 deficiency. An important difference is that, in CFH deficiency, uncontrolled generation of C3b, iC3b, and C3d is possible, whereas, in CFI deficiency, generation of iC3b and C3d by CFI cannot occur.

CFH also regulates C3 activation along renal endothelium. Optimal interaction of CFH with endothelial surfaces requires interaction with both C3b and polyanions. To understand the molecular pathogenesis of CFH in renal disease, it is important to appreciate that (1) its C3 regulatory functions reside within the first four amino-terminal SCR domains and (2) optimal surface recognition requires the terminal two

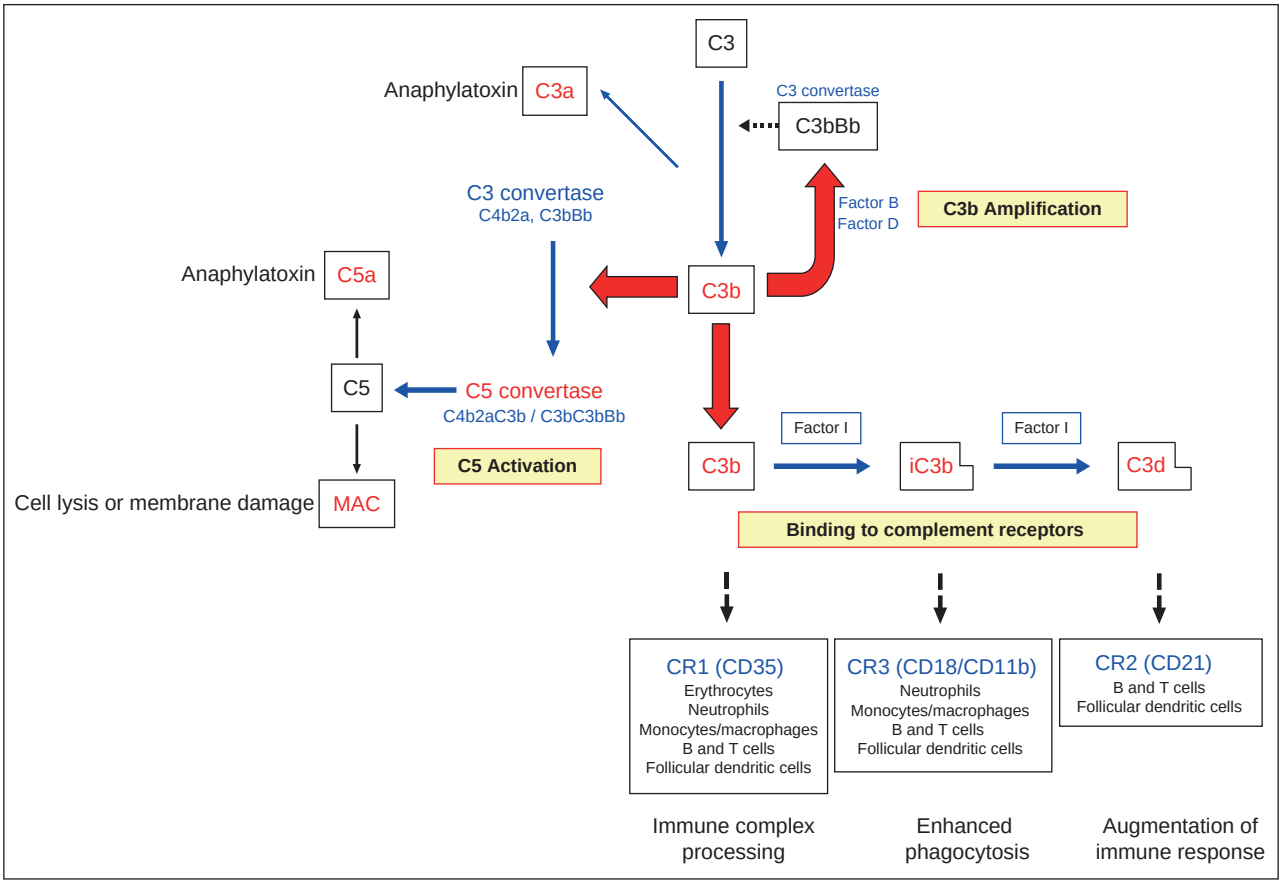

FIGURE 9.23 Complement effector functions. Complement is part of the innate immune response. Functions include the physiologic removal of tissue-bound and soluble immune complexes, enhanced phagocytosis through the production of opsonin (C3b), augmentation of the immune response, anaphylatoxin production (C3a, C5a), and direct damage to surfaces through the production of the MAC. C3b generated through the activation pathways (see Fig. 9.22) is a potent opsonin, and its generation can, through a positive feedback loop, be rapidly amplified. C3b can trigger activation of C5 that results in the production of C5a (potent anaphylatoxin) and the MAC. Further enzymatic cleavage of C3b by the enzyme factor I results in the sequential generation of iC3b and C3d. These fragments interact with cellular receptors, thereby facilitating phagocytosis and immune responses, respectively. CR1–3, complement receptor 1–3; MAC, membrane attack complex.

carboxyl SCR domains (Fig. 9.25). The implication, and what is observed, is that it is possible for molecular defects to impair these functions selectively. Mutations that selectively affect C3 regulation domains are associated with C3 glomerulopathy, whereas those that affect surface recognition domains are associated with atypical hemolytic uremic syndrome (Fig. 9.26).

There are five genes adjacent to the *CFH* gene that encodes structurally similar proteins termed CFH-related proteins. Across the *CFH-CFHR* locus are multiple regions of sequence homology that, through recombination events, predispose to structural variation such as partial and whole-gene deletion and/or duplications (Fig. 9.27). The most common variant is combined deletion of the *CFHR1* and *CFHR3* genes (Δ*CFHR3-1*) that is present in homozygosity in 5% of Caucasian populations. Less frequent is deletion of the *CFHR1* and *CFHR4* genes (Δ*CFHR4-1*).

Recent studies have begun to unravel the biologic functions on the CFHR proteins. Until recently, these proteins were thought to have complement regulatory activity. For example, in vitro studies showed that CFHR1 can inhibit C5 activation (72) and CFHR5 can inhibit C3 activation (73). However, these actions were defined using nonphysiologic concentrations of protein and were markedly inefficient when compared to CFH. Recently, it has become clear that, unlike CFH, these proteins have no complement regulatory activity at physiologic concentrations. For example, CFHR4 has no intrinsic complement regulatory activity but is able to act as a platform for convertase assembly in vitro thereby actually promoting complement activation (74). Similarly, CFHR1, CFHR2, and CFHR5 are able to bind to activated C3 (C3b) but not impair C3 convertase formation (75). This led to the hypothesis that these proteins compete with CFH for binding to C3b. If CFH binds, C3b is inactivated preventing further complement activation. Conversely, if CFHR1, CFHR2, or CFHR5 binds to activated C3b, this prevents CFH binding while enabling C3 convertase formation, enabling complement activation to continue. Since these CFHR proteins are devoid of intrinsic complement regulatory activity, this activity has been termed CFH deregulation (75). A further exciting insight was the finding that CFHR1, CFHR2, and CFHR5

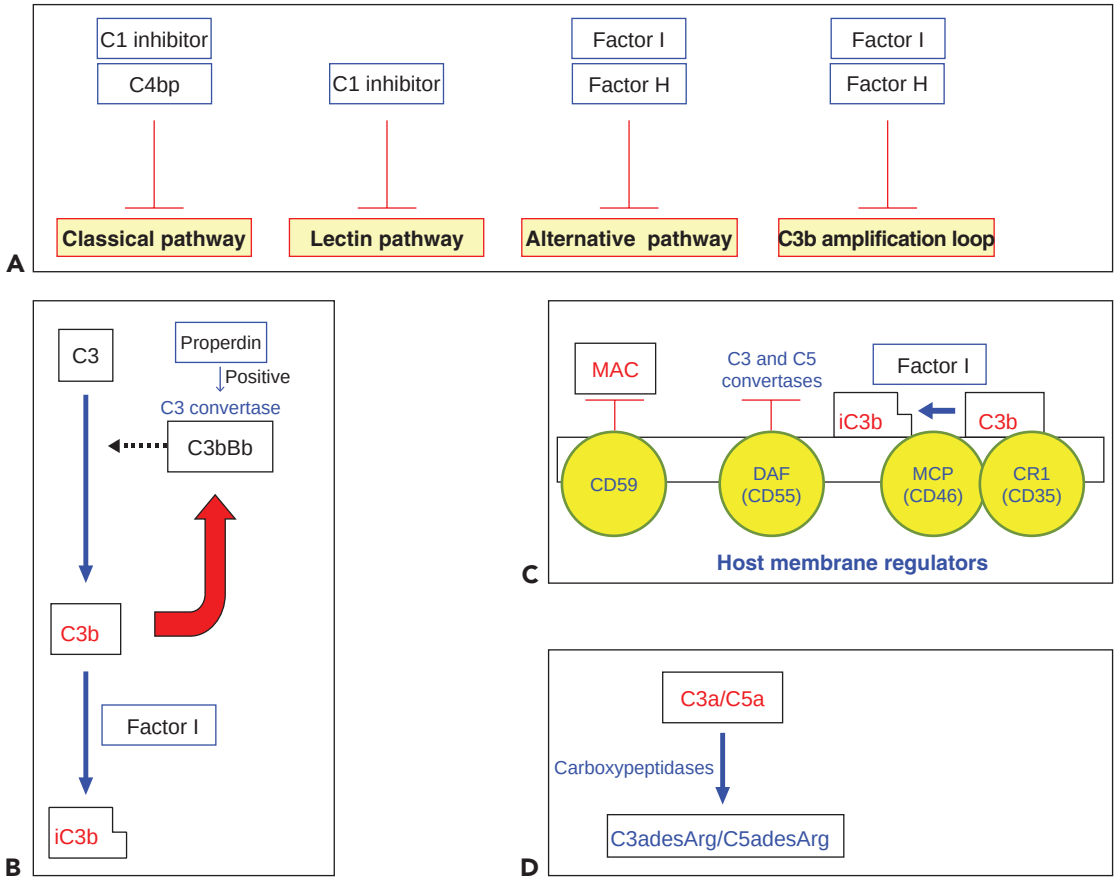

FIGURE 9.24 Complement regulation. Complement is regulated by proteins that act at different stages in the activation cascade and that may be soluble or membrane bound. **A:** Soluble regulators of the activation pathways. Note that factor H and factor I are negative regulators of the alternative pathway and the C3b amplification loop. C4bp, C4-binding protein. **B:** Properdin is a positive regulator of the alternative pathway C3 convertase. The spontaneous decay of the convertase is reduced in the presence of properdin. Enzymatic conversion of C3b to iC3b by factor I prevents further C3b generation since unlike C3b, iC3b cannot interact with factor B. **C:** Membrane-bound complement regulators include CD59, which negatively regulates the membrane attack complex, DAF, which enhances ("accelerates") the spontaneous decay of C3 and C5 convertases, and proteins that act as cofactors for the conversion of membrane-bound C3b to iC3b by factor I. These include MCP and CR1. MAC, membrane attack complex; MCP, membrane cofactor protein; CR1, complement receptor 1; DAF, decay-accelerating factor. **D:** The anaphylatoxins are inactivated by carboxypeptidases.

possess a common dimerization motif located within the first two amino-terminal SCR domains. This motif would predict not only homodimers (CFHR1-CFHR1, CFHR2-CFHR2, CFHR5-CFHR5) but also heterodimerization (CFHR1-CFHR2, CFHR2-CFHR5, CFHR1-CFHR5). Some of these species have been identified both in vitro and in vivo but further studies will be needed to determine both their relative abundance and activity in vivo. Early evidence suggests that dimerization enables these proteins to effectively compete with CFH for surface-bound C3b. This competition may be particularly important under conditions of high flow such as the renal microvasculature.

The existence of Δ*CFHR3-1* and Δ*CFHR4-1* polymorphisms implied that the biologic functions of CFHR1, CFHR3, and CFHR4 are nonessential. In fact, Δ*CFHR3-1* is associated with protection from AMD (76) and IgA nephropathy (77). If, as the evidence now suggests, these proteins are deregulators of CFH, the protective role of Δ*CFHR3-1* may be a result of reduced deregulation (i.e., less interference with the complement inhibitory actions of CFH). This remains to be proven.

Genetic and Acquired Disorders of Complement

DDD is strongly associated with factors that enhance activation of circulating C3 through the alternative pathway and C3b amplification loop (see Fig. 9.26) (17,78,79). These comprise both genetic and acquired factors and can be grouped into those associated with CFH dysfunction and those that enhance C3 convertase formation. CFH dysfunction includes (a) complete CFH deficiency (79), (b) mutations selectively targeting the C3 regulation domains (80), and (c) autoantibodies that selectively target the C3 regulation domains (81). In complete CFH deficiency, the secondary C3 deficiency that ensues is severe. Plasma C3 may drop under the limit of detection. Functional complement assays that test the ability of each pathway to lyse red cells or to opsonize surfaces with C3b typically show complete absence of activity. Factor B, an alternative pathway component that is consumed during activation, is also

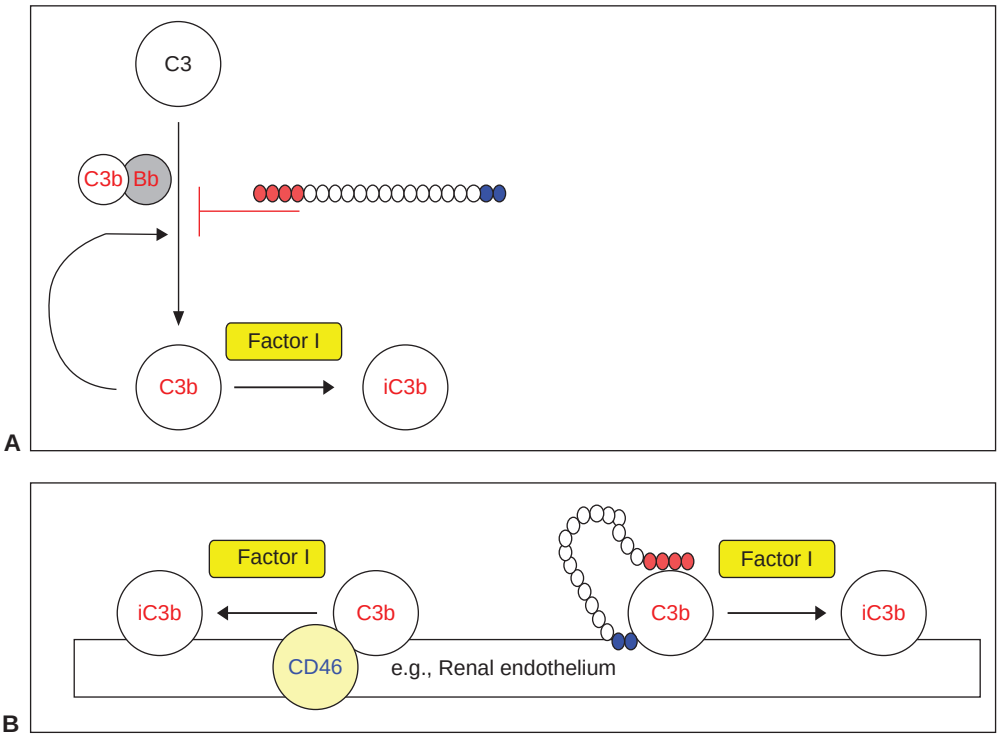

FIGURE 9.25 Regulation of factor H and C3 activation within plasma **(A)** and along surfaces **(B)**. Factor H comprises 20 subunits termed SCR domains. The amino-terminal four SCR domains (*red*) mediate complement regulation in the fluid phase. The terminal two carboxyl domains (*blue*) are important for its interaction with surface-bound C3b. This interaction requires binding to both C3b and surface polyanions. The localization of C3 regulation and surface recognition actions to these domains means that it is possible for mutations within SCR domains to selectively impair these functions (see Fig. 9.26).

reduced. In many but not all reports, C5 and other terminal pathway components are also reduced. Fluid-phase dysregulation also occurs when the regulatory domains are selectively inhibited by either mutations or autoantibodies.

Factors that enhance C3 convertase formation include gain-of-function mutations in C3 (82) and stabilizing autoantibodies to either factor B (83) or the C3 convertase, the latter defined as C3NeFs (78,84,85). C3NeFs are heterogeneous and include those that are associated with selective depletion of C3 (properdin independent) and those that deplete C3 and C5 (properdin dependent). Properdin is a positive regulator of the C3 convertase. It interacts with C3bBb to increase its half-life. Studies have shown that properdin-independent nephritic factors are the most common seen in DDD patients (84). A gain-of-function C3 mutation in a family with DDD was shown to selectively enhance plasma C3 activation by generating a C3 convertase that was resistant to inactivation by CFH (82). Importantly, the abnormal convertase was inactivated normally by the membrane-bound regulator, decay-accelerating factor (DAF, CD55). This elegant study provided powerful evidence that fluid-phase dysregulation, not the inability to regulate along surfaces, is sufficient alone to initiate DDD.

Complement Activation in C3 Glomerulopathy

How does uncontrolled plasma C3 with or without C5 activation result in C3 glomerulopathy? Evidence from animal models (discussed below) suggests that the C3 activation products accumulate within the glomeruli and initiate renal injury. This explanation is consistent with the recurrence of DDD in renal transplants, the failure to demonstrate that GBM can activate complement directly even when CFH is removed, and the failure to detect C3NeF (immunoglobulin) in association with glomerular C3.

These factors are not specific to DDD. For example, C3NeFs are also seen in MPGN type 1 (17) and in C3GN (17). Furthermore, gain-of-function C3 mutations (characterized at the protein but not genetic level) were described in two families with C3 glomerulopathy without dense deposits (86,87). One was described as MPGN type III (86) and the other showed mesangial expansion but with capillary wall deposits (87). In one series of C3GN of 56 patients, mutations in *CFH* (n = 7), *CFI* (n = 3), and *MCP* (n = 1) were detected (17). The relationship between mutations and phenotype is complex. The renal phenotype is almost certainly influenced by additional common genetic susceptibility factors and environmental triggers. The CFH Y402H polymorphism (88) and C3 haplotype (88) are associated with DDD, and a CD46 haplotype is associated with C3GN (17). The difficulty with these associations is that they derive from a candidate gene approach in small numbers of patients so whether they represent true associations is unclear. Environmental triggers such as throat infections exacerbate renal injury in CFHR5 nephropathy and CFH deficiency.

In many cases of C3GN, plasma C3 depletion is not present, and it must be concluded that the accumulation of C3 within the glomeruli in these circumstances derives from abnormal activation or clearance within the kidney. Important clues come from the characterization of the genetic basis of two examples of familial C3GN (64,65). In both of these reports, abnormal structural variation was seen within the CFHR locus in the absence of the known causes of CFH dysfunction; that is, there was no evidence of mutations or autoantibodies affecting CFH (see Fig. 9.25). In familial C3GN endemic in Cypriot individuals (CFHR5 nephropathy), the mutation was an internal duplication affecting the *CFHR5* gene. From recent structural insights into CFHR5, it is evident that this mutation results in duplication of the dimerization motif (see above).

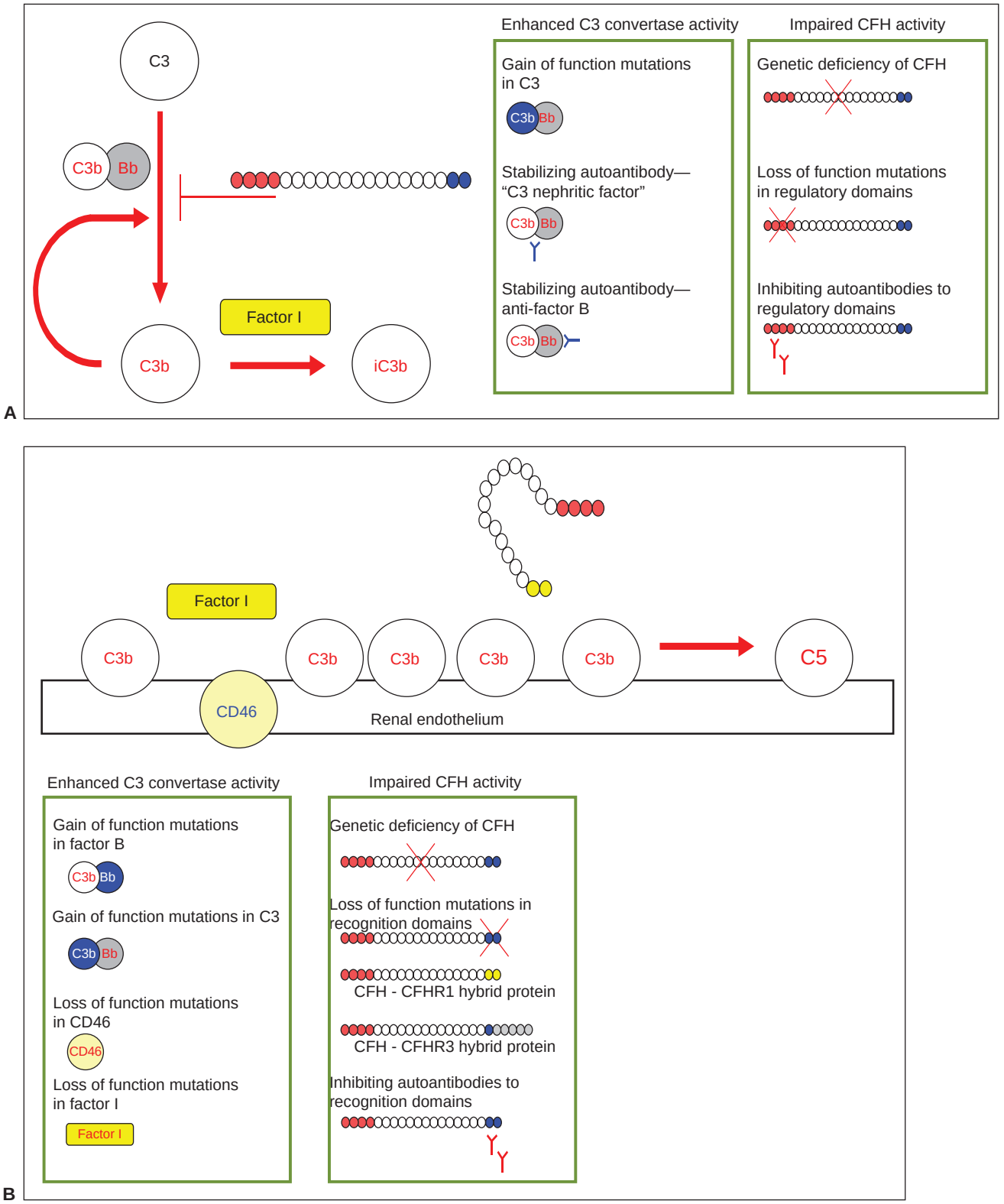

FIGURE 9.26 Pathophysiology of C3 glomerulopathy. In C3 glomerulopathy, abnormal C3 regulation may be mediated by mutations or autoantibodies that either enhance the stability of the C3 convertase or impair the actions of factor H. This may occur within plasma (fluid phase) or along surfaces. **A:** In DDD, there is enhanced activation of C3 in the fluid phase. Causes include factor H mutations and autoantibodies that selectively target the C3 regulatory domains (see also Fig. 9.25). **B:** In atypical hemolytic uremic syndrome, there is abnormal activation of C3, and hence C5, along the renal endothelium. Causes include factor H mutations and autoantibodies that selectively target the surface recognition domains (see also Fig. 9.25 and for the hybrid genes, Fig. 9.27). The role of abnormal surface activation in C3 glomerulopathy (e.g., activation along the GBM or within the mesangium) and the role of abnormal CFHR proteins in familial C3 glomerulopathy are not fully understood but may be related to factor H deregulation (see text).

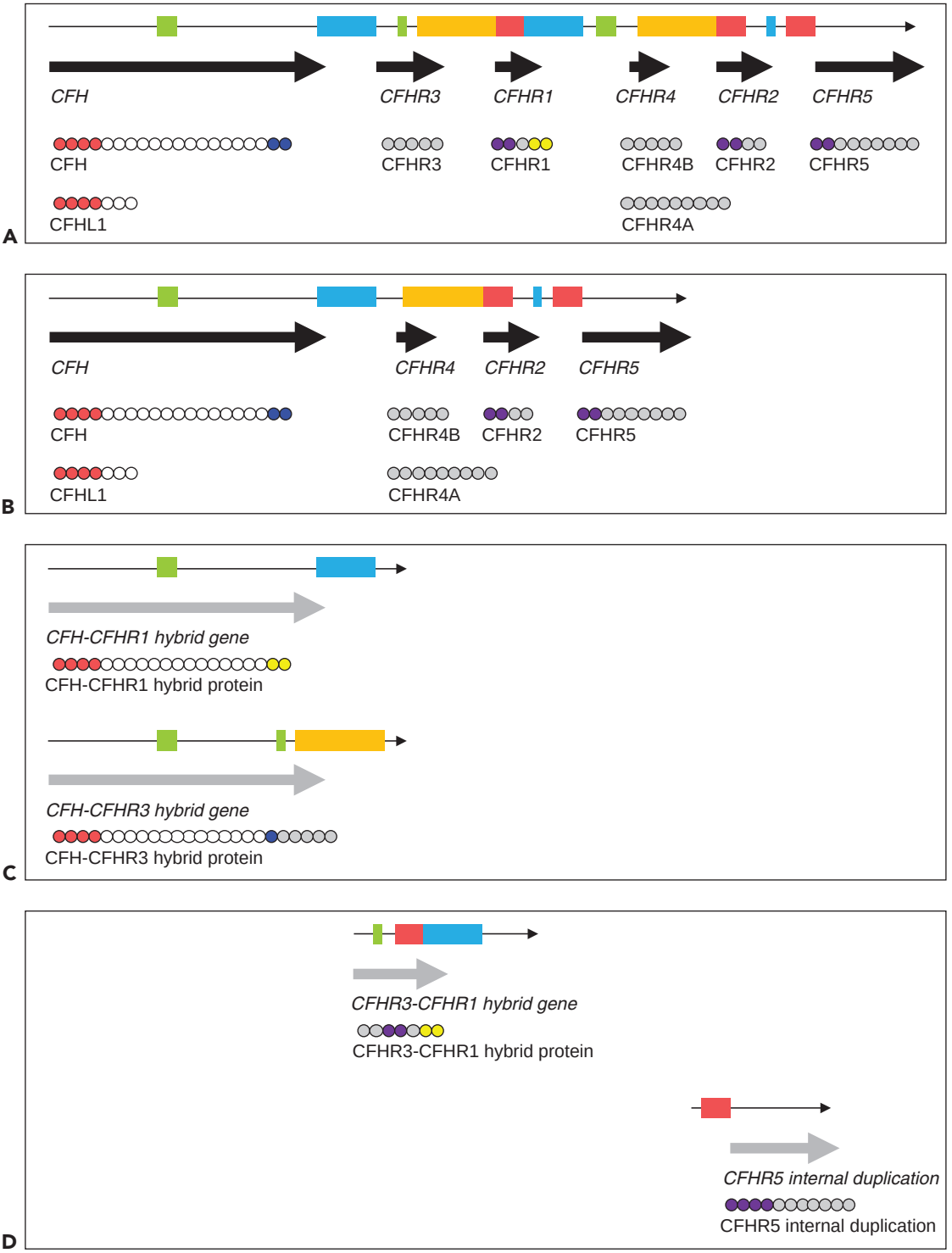

FIGURE 9.27 The CFH-CFHR family. This protein family is encoded by a group of genes (*arrows*) in chromosome 1, and this region contains areas of high sequence similarity (long homologous repeats, denoted by colors above gene *arrows*). **A:** The family comprises factor H and five proteins termed factor H–related proteins. All are composed of SCR domains. The C3 regulatory domains in CFH (*red*) are not found in the CFHR proteins but are present in an alternative splice product of the CFH gene termed CFH-like protein 1 (CFHL1). The biologic role of CFHL1 is unknown. The first two amino domains of CFHR1, CFHR2, and CFHR5 (*purple*) are identical. **B:** Recombination between areas of sequence similarity is common at this locus. Most frequent is deletion of both the CFHR1 and CFHR3 genes, which is a frequent copy number polymorphism. Individuals that are homozygous for this polymorphism have complete absence of CFHR1 and CFHR3. **C:** Rare rearrangements within this locus can result in disruption of exons encoding the surface recognition domains of factor H. These include the hybrid CFH-CFHR1 and CFH-CFHR3 genes. **D:** Rare rearrangements associated with familial C3 glomerulopathy include those that occur within the CFHR locus and hence do not disrupt the CFH gene. They include an internal duplication of the CFHR5 and a hybrid CFHR3-1 gene.

This led to the hypothesis that the resultant abnormally large protein would, through enhanced avidity, potently deregulate CFH. Enhanced CFH deregulation has been shown using serum containing all CFHR1, CFHR2, and CFHR5 (wild type and mutant) proteins from individuals with CFHR5 nephropathy (75). In the second family of Irish ancestry (70), the mutation resulted in a hybrid *CFHR3-1* gene that was present in addition to the normal copies of the *CFHR3* and *CFHR1* genes (65) (see Fig. 9.26). Enhanced CFH deregulation has also been shown in these individuals, a finding thought to be a consequence of increased CFHR protein number in those affected (75). Therefore, it appears that in both of these familial diseases, the effect of different CFHR mutations is to enhance the ability of CFHRs to deregulate the activity of CFH within the glomerulus leading to enhanced alternative pathway activation and glomerular C3 deposition.

Evidence From Animal Models

Animal models have been of central importance in understanding the mechanisms by which deficiency or mutations of CFH lead to glomerular injury. A lethal form of C3 glomerulopathy, described as porcine MPGN type II, occurred in a strain of pigs with a mutation in the *CFH* gene that prevented secretion of the protein (89–92). The pigs had undetectable CFH in circulation. The glomerular lesion was characterized by MPGN. Immunofluorescence microscopy showed deposition of C3 along the glomerular capillary walls that started in utero. The earliest light microscopic changes were seen at 4 days when there was mild mesangial hypercellularity and increased glomerular neutrophils. Subsequently, glomeruli developed marked capillary wall thickening and mesangial proliferation. On EM, there were electron-dense deposits initially on the subendothelial side of the GBM that gradually progressed to occupy more of the thickness of the GBM. The pigs developed renal failure with a median survival of 37 days. No pathology was evident in other tissues examined. When a normal pig kidney was transplanted into a CFH-deficient pig, C3 appeared in the transplant kidney within 24 hours, demonstrating that CFH synthesis by the kidney is unable to prevent disease (93). Administration of weekly plasma infusions to affected piglets in order to replace CFH improved survival and reduced the severity of glomerulonephritis (91). The CFH-deficient pig strain has now been eradicated.

A targeted deletion of *CFH* was subsequently developed in mice, and this model has allowed in-depth analysis of the mechanisms of glomerular C3 deposition and also provides a model in which potential therapies can be tested. Mice lacking CFH have uncontrolled activation of the alternative pathway in the circulation and hence very low levels of circulating C3 (94). From the earliest time point examined—2 days of age—there is linear C3 deposition on capillary walls by immunofluorescence, and this pattern persists throughout the life of the mice. Initially, no immunoglobulin is seen; although at 6 months of age, there is faint staining for IgG. On EM, there is electron-dense material deposited on the GBM. Initially, this begins as a thin layer of electron-dense material on the endothelial side of the basement membrane, but as the mice age, the electron-dense deposits become more pronounced and appear intramembranous. Scanty deposits are seen in the mesangium, but, notably, there are no deposits seen in the Bowman capsule or in the TBM. By light microscopy, mice develop MPGN with mesangial expansion and hypercellularity, capillary wall thickening, and segmental double contours. The clinical course is dependent on the genetic background, but in the initial report, there was 23% mortality by 8 months. No glomerular deposition of C3 was seen in CFH-deficient mice crossed with mice lacking factor B, demonstrating that C3 activation depended on the formation of the alternative pathway C3 convertase containing factor B.

CFH-deficient mice thus represent a good model of human C3 glomerulopathy with low C3 levels, capillary wall C3 deposition, and progressive MPGN. They have features similar to DDD, but there are notable differences—in particular, the deposits are not seen in the Bowman capsule and TBMs, and even in old mice, the deposits never show the typical very osmiophilic appearance seen in humans. However, the latter difference may simply reflect the huge difference in life span of mice and humans. It is noteworthy that a report of human factor H deficiency in two brothers described the disease as "atypical" DDD and drew attention to the absence of deposits on the Bowman capsule or TBMs (95).

The CFH-deficient mice have been used to explore further the mechanisms of C3 deposition and glomerular injury in CFH deficiency. The role of complement component C5 has been studied by crossing the CFH-deficient mice with mice lacking C5. In the absence of C5, mice still developed capillary wall electron-dense deposits and MPGN, but there was reduction in glomerular hypercellularity accompanied by reduction in serum creatinine levels and mortality (96). This suggests that, while it would not be expected to prevent the development of GBM deposits, chronic inhibition of C5 activation in humans with C3 glomerulopathy associated with CFH dysfunction may be beneficial by reducing the glomerular inflammatory response. Whether this would also be applicable to CFH-sufficient individuals with DDD is not clear.

Further insights into mechanisms of C3 glomerulopathy have come from mice deficient in factor I (97). These mice develop uncontrolled activation of the alternative pathway because there is failure to metabolize C3b to iC3b. Like humans with factor I deficiency, they develop depletion of circulating C3 and factor B (98). C3 deposits are found in the glomeruli, but, unlike CFH-deficient mice, the deposits are in the mesangium and associated with nodular mesangial expansion, but no capillary wall deposits are seen. The mice are therefore a model of human mesangial proliferative C3 glomerulopathy. Intriguingly, if mice lacking CFH are crossed with factor I–deficient mice, they are protected from capillary wall C3 deposition and MPGN and develop glomerular lesions identical to those seen in mice lacking just factor I. These data show that in the setting of CFH deficiency, factor I is required for the deposition of GBM C3 to develop with morphologic changes of MPGN. These animal data suggest that plasma C3b targets the mesangium, while plasma C3b metabolites, most likely iC3b, target the GBM. The implication is that in situations where GBM C3 is present, strategies that sequester C3b metabolites in the circulation may be therapeutically beneficial.

CFH-deficient mice have an increased susceptibility to renal injury following the induction of experimental nephritis (94,96). This exaggerated response was evident in young animals prior to the development of light microscopic changes of MPGN, suggesting that it is the complement dysregulation rather than preexisting renal disease that renders these

animals susceptible to nephrotoxic agents. Administration of a sheep nephrotoxic antibody led to an increase in capillary wall C3 deposition and markedly enhanced neutrophil infiltration compared to wild-type animals. This abnormal response to heterologous nephrotoxic nephritis was absent in CFH-deficient mice with deficiency of C5 but persisted in animals with combined deficiency of CFH and C6 indicating that it was the production of C5a not the formation of the MAC that was responsible for enhanced glomerular neutrophil response in this model. Furthermore, administration of an anti-mouse C5 antibody to CFH-deficient mice prior to the induction of heterologous nephrotoxic nephritis prevented both glomerular neutrophil accumulation and proteinuria. These data indicate that, in the setting of CFH dysfunction, (a) the threshold for renal injury is significantly lowered following exposure to a complement-activating nephrotoxic insult and (b) C5a production is a major mediator of renal injury in this setting.

What is the relevance of these observations to human C3 glomerulopathy? In DDD, it is known that patients may remain stable clinically for long periods. However, relapses associated with acute inflammatory changes within the kidney often result in a significant decline in renal function or threaten transplant kidney survival. Moreover, during rapidly progressive disease, all glomerular deposits, including paramesangial deposits, react strongly with anti-C5 antibodies (41), suggesting that C5 activation is a particularly important component of renal injury during acute inflammatory episodes. These observations suggest that anti-C5 therapy could be effective in preserving renal function during disease flares in human C3 glomerulopathy.

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CHAPTER 10

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Acute Postinfectious Glomerulonephritis and Glomerulonephritis Caused by Persistent Bacterial Infection

Bacterial infection outside the kidney can lead to glomerulonephritis either after the infection has been cleared, in which case the glomerulonephritis is appropriately called postinfectious glomerulonephritis, or while the active, persistent infection is still ongoing, in which case the terminology of postinfectious glomerulonephritis is obviously incorrect and the glomerulonephritis is best designated as glomerulonephritis associated with active/persistent bacterial infection. From the clinical point of view, it is relevant to differentiate these two forms of bacterial infection–related glomerulonephritis because, in postinfectious glomerulonephritis, antibiotic treatment is not necessary and immunosuppressive medications can be given. In contrast, if a bacterial infection is still active, the glomerulonephritis should be treated primarily with antibiotics, and immunosuppression should be avoided. If the previous or ongoing infection is known to the clinician and pathologist, the diagnosis is usually easy. However, in real-life situations, it is common that patients with bacterial infection–related immune complex glomerulonephritis do not display obvious clinical symptoms of infection at the time the glomerulonephritis is diagnosed. Such subclinical infections may be easily overlooked, and if the slightest suspicion for an underlying infection emerges, the pathologist has to raise this possibility to avoid immunosuppressive treatment before the infection can be safely excluded (1). There are several publications in the literature where postinfectious glomerulonephritis is defined

quite liberally and include cases of glomerulonephritis with a preceding infection, but the infection is still present. Such cases include glomerulonephritides associated with staphylococcal infection (see section on Glomerulonephritis associated with staphylococcal infections). However, if we consider a glomerulonephritis following an infection postinfectious, then even HIV-associated nephropathy or hepatitis C–related cryoglobulinemia could be considered postinfectious glomerulonephritis, which would clearly be inaccurate. In our opinion, poststreptococcal glomerulonephritis is the best example for postinfectious glomerulonephritis. Most other infection-related glomerulonephritides are not postinfectious; they are associated with ongoing infection.

This chapter deals first with acute postinfectious (poststreptococcal) glomerulonephritis, which is the type of glomerulonephritis that follows infections. The incidence of poststreptococcal acute glomerulonephritis (PSAGN) is declining in well-developed countries, but it used to be the most common and the most studied form of acute postinfectious glomerulonephritis. Therefore, it is described first in this chapter. In spite of the declining incidence of PSAGN, it is important to discuss it in detail, because the extensive studies on this glomerular disease provide invaluable insight into the pathogenesis of acute glomerulonephritis, in general, and the disease is still prevalent in many parts of the world. Major additions have been made to the section on *Staphylococcus aureus* infection–associated glomerulonephritis, which is now emerging as the most common form of "infection-related glomerulonephritis" in the United States, especially in the elderly, debilitated and diabetic population (2–4). The remainder of the chapter describes glomerulonephritis that accompanies persistent bacterial infections such as infective endocarditis, deep-seated abscesses, and infected ventriculoatrial shunts inserted for the relief of hydrocephalus.

ACUTE POSTSTREPTOCOCCAL GLOMERULONEPHRITIS

Historical Perspective

Acute glomerulonephritis has long been known to follow certain acute infections. Although Hippocrates, more than two millennia ago, described the occurrence of back pain and gross hematuria leading to oliguria or anuria (5), it was Wells (6) who noted bloody urine in patients with scarlet fever and postscarlatinal anasarca. Bright (7), too, noted the association with scarlatina and described the finding of blood in the urine and swelling of the face in what were probably attacks of PSAGN.

> According to Bright:
> The history of this disease, and its symptoms, is nearly as follows: a child or adult is affected with scarlatina or some other acute disease; or has indulged in the intemperate use of ardent spirits for a series of months or years: he is exposed to some casual cause or habitual source of suppressed perspiration: he finds the secretion of his urine greatly increased, or he discovers that it is tinged with blood; or, without having made any such observation, he awakes in the morning with his face swollen, or his ankles puffy, or his hands oedematous.

Bright further observed that, with or without treatment, the patient's urine lost its "red particles" and that the swelling subsided, although in some instances, he recorded that the patient returned at a later time with what we would now regard as chronic renal failure.

With the introduction of microscopic examination of the kidney over the ensuing decades, it became apparent that changes took place in the glomeruli, and Langhans (8) described a category of Bright disease with glomerular inflammation. Schick (9) commented on the similarity of the latent period in serum sickness to that of acute glomerulonephritis.

The first major clinicopathologic treatise on renal disease appeared in 1914 with the publication of the work of Volhard (the clinician) and Fahr (the pathologist), *Die Brightsche Nierenkrankheit* (10). They classified Bright disease into various categories, including inflammatory diseases of the glomerulus. Longcope (11,12) recognized two general forms of glomerulonephritis, the first of which was associated with preceding bacterial infections and had a quick recovery and a good prognosis (acute glomerulonephritis). Ellis (13) also distinguished two types of glomerulonephritis. Type 1 nephritis, usually seen in young patients, was characterized by an abrupt onset, constitutional symptoms, gross hematuria following infection, and a high recovery rate; this condition corresponded to the first type described by Longcope (11).

Scarlet fever was noted to be associated with acute glomerulonephritis in the late 1800s and early 1900s, and it soon became apparent that there was a common association with a previous infection of group A streptococcus (GAS). Varying attack rates of acute glomerulonephritis were noted in patients with scarlet fever, and a greater attack rate of nephritis was found in children compared with adults. These varying rates were probably largely dependent on the strain of *Streptococcus* causing the infection. Ophüls (14), as early as 1917, had suggested that only certain strains of streptococci appeared to have a nephritogenic capacity.

Nephritogenic Strains and Epidemiology

Most cases of acute glomerulonephritis seen worldwide are caused by the *streptococcus,* without the clinical signs and symptoms of scarlet fever. In colder northern climates, most cases of acute glomerulonephritis follow upper respiratory tract infections, such as pharyngitis or tonsillitis, but cases also can follow skin infections, especially in warmer climates (15–17). Most cases of PSAGN are caused by group A streptococci, which are also responsible for rheumatic fever. Although rare cases of concomitant rheumatic fever and PSAGN have been noted (18,19), there are many differences between the epidemiology of acute glomerulonephritis and rheumatic fever. A likely explanation for the different patterns is that only certain (nephritogenic) strains of group A streptococci lead to acute glomerulonephritis (20–26). Types 12, 4, and 1 are more likely to cause acute glomerulonephritis after throat infections than other types (25,26). Type 12 is especially common as a strain leading to acute glomerulonephritis. However, even with the same type of streptococcal organism, there are differences in the attack rate. Siegel et al. (27) showed that only 1 of 58 patients with well-documented type 12 streptococcal infection progressed to acute glomerulonephritis; this was a convincing demonstration that not all strains of type 12 are nephritogenic. The attack rate (variably defined and detected) with certain nephritogenic strains ranges from 1% to 33% of patients (28,29). Differences in the host, such as different immune responses, abnormalities in the alternate complement pathway activation, could lead to

this variability. Of all children infected with the various strains of streptococci, it appears that less than 2% show clinically obvious signs of acute glomerulonephritis.

Acute glomerulonephritis resulting from skin infections is not uncommon, especially in warm climates (16,17,22,30–34). Streptococcal infections of the throat are more common in the winter and early spring, whereas streptococcal pyoderma or impetigo tends to occur in temperate climates in the late summer and early fall (34). The same seasonal pattern is found for acute glomerulonephritis. When skin infections lead to acute glomerulonephritis, certain serotypes of streptococci are isolated more commonly than others; streptococcal M types 49, 42, 2, 57, and 60 seem to be predominant, and types 49, 42, and 2 are particularly potent (34). The nephritogenic strains from the throat and skin show, in general, comparable attack rates of glomerulonephritis (34). However, type 49 infections of the skin have quite different attack rates of acute glomerulonephritis (24%) than type 49 that appears in the throat (5%) (34). Frequently, the same bacteria are found in the throat and the skin; in these instances, the skin infection typically precedes that in the throat (35).

Many of the important early observations on the epidemiology of acute postinfectious glomerulonephritis were made on the Red Lake Indian Reservation in Minnesota, where outbreaks of acute glomerulonephritis occurred in 1953 and again in 1966 (35,36). A study of the second epidemic (both caused by type 49) showed that all cases occurred in children too young to have been infected in the first epidemic (35) because of the lack of type-specific immunity. Epidemic outbreaks tend to occur in closed communities (20,36,37) or in highly populated areas in which poor hygiene, malnutrition, anemia, and parasites are common (17,20,22,38–40). PSAGN epidemics related to skin infections may be associated with outbreaks of scabies (38). Some epidemics in certain communities tend to recur and are separated by 5 to 7 years (17,20).

From the 1940s to the mid-1980s, the incidence of the suppurative and nonsuppurative complications of group A β-hemolytic streptococcal infections, such as glomerulonephritis and rheumatic fever, all but disappeared in the United States and throughout much of Europe (41,42). However, in 1987, the first of several outbreaks of rheumatic fever was reported (43). The concern about these infections increased when the outbreaks were followed by severe systemic streptococcal illnesses, invasive skin diseases, and a toxic shock–like syndrome (42). Despite these outbreaks and the continued prevalence of certain major nephritogenic strains (M type 12) (44), PSAGN has apparently continued the same sharp decline in incidence it had pursued before the mid-1980s. This decline is not thought to be caused by primary prophylaxis with penicillin but by a changing epidemiology of the disease that may stem from either changes in the nephritogenic potential of certain strains (e.g., M type 12) or changes in susceptibility of the host.

Roy and Stapleton (18) noted a changing perspective in the occurrence of PSAGN in one Tennessee hospital during the course of two decades. Although they noted a marked decline in the prevalence of PSAGN, they also noted a decline in urban patients and an increase in rural patients with PSAGN. In the last decade, they noticed a predominance of antecedent pharyngeal infection in children older than 6 years of age and a predominance of antecedent pyoderma in African American children (18). Postinfectious glomerulonephritis, however, continues to have a high incidence in other parts of the world, especially in areas with tropical climates, where skin infections are common, such as Africa (19), South America (20,38,39), the Caribbean (17), New Zealand (45), India, and in indigenous communities (Aborigines in Australia) (46). Incidence and prevalence of PSAGN in selected countries worldwide, based on biopsy studies published after 1985, are shown in Table 10.1 (68). A Kuwait study described 234 patients over a 9-year period, and these patients showed a high prevalence of certain nephritogenic strains (M types 12 and 49) (67). The possibility of reemergence of poststreptococcal glomerulonephritis in the United States and Europe cannot be excluded (41). In 1995, an epidemic outbreak was reported in Armenia following serious deterioration of the living conditions there. In this epidemic, most children had upper respiratory tract infections or scarlet fever preceding PSAGN, and only 13% of them had skin infections (40). There are two recent reviews describing the global burden of PSAGN/postinfectious glomerulonephritis worldwide, one from Bangkok, Thailand, and the other a collaborative work from the United Kingdom, Australia, and Canada (46,68). The calculations of incidence and prevalence of PSAGN are based on large population-based studies by Carapetis et al. (69) and Rodŕiguez-Iturbe et al. (70,71). Carapetis et al. calculated an incidence of approximately 24.3 cases per 100,000 person-years in children and 2 cases per 100,000 person-years in adults in the developing world versus 6 and 0.3, respectively, in the developed world. They calculated a prevalence of GAS disease of at least 18.1 million cases, with 1.78 million new cases each year and 517,000 deaths per year due to severe group A streptococcal (GAS) diseases (acute rheumatic fever, rheumatic heart disease, PSAGN, and invasive infections). There is significant global variation with the highest incidence of 239 per 100,000 in Australian Aborigines and the lowest incidence of 0.04 per 100,000 in an Italian study of people under the age of 60. Still all these statistical calculations are likely to be underestimations since they cannot account for the vast majority of subclinical disease that is thought to be 4 to 19 times more common than symptomatic disease. The estimates are even higher in the reports by Rodŕiguez-Iturbe et al. (70,71).

The epidemiology of postinfectious glomerulonephritis in the developed world is undergoing rapid changes. In the United States, most infection-related glomerulonephritis cases occur in adults, and staphylococcal infection–associated glomerulonephritis (usually not postinfectious) is more common than PSAGN (2,3). The type 2 diabetes "epidemic" and rapid increase in obesity substantially contribute to these changes (2,3,68).

General Properties of Streptococci, Antibody Formation, and Complement Changes

Streptococcus Pyogenes

Streptococcus pyogenes (GAS) produces many virulence-enhancing extracellular products and toxins, including erythrogenic toxin, DNase, hyaluronidase, streptokinase, NADase, proteinases, and the hemolysins streptolysin-O (oxygen labile) and streptolysin-S (oxygen stable). GAS is the etiologic agent of a number of suppurative infections, including pharyngitis, cellulitis, necrotizing cellulitis, scarlet fever, erysipelas, pyoderma, puerperal sepsis, toxic shock–like syndrome, and impetigo. Ferretti (72) reviewed the molecular basis of virulence and antibiotic

TABLE 10.1 Incidence and prevalence of PSAGN worldwide

Country	Ref.	Incidence	Prevalence	Period of study
Australia	(47)	7.33	0.16	1995 and 1997
Brazil	(48)	22.86	0.23[b]	1999–2005
China	(49)	13.25	0.04	1979–2002
Czech Republic	(50)	4.43	0.04	1994–2000
Denmark	(51)	7.54	0.14	1985–1997
France	(52)	0.6	0.15	1981–1985
Hong Kong	(53)	2.6	0.04	1993–1997
India	(54)	39.24	10.14[b]	1986–2002
Italy	(55)	37	0.06	1996–2000
Japan	(56)	25	0.02	1970–1980
Jordan	(9)	2.6	0.26	1993–1997
Korea	(57)	6	0.06	1973–1995
Macedonia	(58)	3.26	0.16[b]	1975–2001
Nigeria	(59)	0.9	0.04	1994–2003
Peru	(60)	4.82	0.06[b]	1985–1995
Portugal	(61)	2.67	1.01	1977–2003
Romania	(62)	7.7	0.12[b]	1995–2004
Saudi Arabia	(63)	25	0.11	1979–1983
Serbia	(64)	0.95	0.06[b]	1987–2006
Thailand	(65)	2	0.04[b]	2001–2004
Tunisia	(66)	44	0.41	1975–2005
USA	[c]	0.78	0.13[a]	1999–2006

[a]Data from children.

[b]Data from adults.

[c]Data provided by Dr Tray Hunley, Division of Pediatric Nephrology, Vanderbilt Children's Hospital, USA.

Estimates of the incidence and prevalence of postinfectious glomerulonephritis in selected countries, based on data from biopsy studies published after 1985 (68). Incidence is given as cases per year; prevalence is given as cases per 100,000 population.

resistance in GAS. Certain GAS organisms have surface receptors that bind selectively to the key fibrinolytic enzyme, plasmin (73). The bacterium-bound plasmin retains its enzymatic ability to cleave substrates and hydrolyze a fibrin clot, which may in part contribute to its tissue-invasive properties (73). GAS infection can be diagnosed and monitored with many laboratory procedures that detect the organism, its antigens, or its antibodies.

Conventional methods for the identification of viable organisms include finding β-hemolytic colonies on 5% sheep blood agar with a subsequent presumptive identification based on sensitivity to bacitracin on streptococcal-selective agar or hydrolysis of L-pyrrolidonyl-β-naphthylamide. Serologic procedures to identify *streptococcus* include latex agglutination, coagglutination, immunofluorescent antibody staining, and the Lancefield precipitin test, in which cell wall antigens must be extracted by heating or chemical treatment prior to testing. Throat cultures are a reliable method for finding GAS, but they have a long turnaround time (74).

Rapid methods for the detection of organism antigen directly from throat swabs include latex agglutination, coagglutination, and enzyme immunoassay (74,75). These rapid methods are truly helpful only if results are positive; negative results do not necessarily mean that the specimen collection site was free of *S. pyogenes*. In addition, cultures with fewer than 10 colonies (with false-negative rapid test results) have yielded positive serologic test results (i.e., a fourfold or greater rise in antibody titers). Therefore, small numbers of group A streptococci can be meaningful.

There is much information on the biologic characteristics of the streptococcal organism as well as the strains that lead to acute glomerulonephritis. Poststreptococcal glomerulonephritis is almost always caused by strains of the serogroup A; however, several well-documented outbreaks have been caused by group C organisms in patients with septic arthritis, pneumonia, and septicemia (76,77) and to group G streptococci (skin infections) (78). Milk-borne *Streptococcus zooepidemicus* infection from unpasteurized milk and cheese has been reported with septicemia and clinical evidence of PSAGN (39,79).

Streptococcal M proteins are dimeric, alpha-helical, coiled molecules on the surface of the bacteria and function as the major antiphagocytic factor. Despite differences in the amino acid sequences of different serotypes of the M molecules, there are certain regions that show important conserved architectures (80). Manjula et al. (80) demonstrated distinct differences within this conserved molecular architecture between nephritis-associated and rheumatic fever–associated strains; the functional significance of these differences is unclear. Historically, GAS vaccine development has focused on the N-terminus of the M protein. This has led to clinical trials of the 26-valent recombinant M protein vaccine; however, no vaccines using antigens

contained in the most conserved region of the M protein have yet been possible (81,82). Molecular typing of the M protein has been used to investigate the molecular epidemiology of GAS as well as group C and G streptococcal disease. A systematic review of the global distribution of GAS M types revealed that the epidemiology of GAS disease in Africa and the Pacific region seems to be different from that in other regions, particularly the United States and Europe. In Africa and the Pacific regions, there is more diversity of M types. The M types (including 1, 4, 6, and 12) that are more common in the high-income countries were found to be less common in Africa and the Pacific region. This has implications for the development of multivalent GAS vaccines. One vaccine may not provide good coverage worldwide (81). Nontypeable GAS organisms also have been cultured from patients with acute glomerulonephritis, which presumably represent unclassified nephritogenic strains (20). It is likely that multiple factors of the bacteria and the host contribute to the differences in the attack rates for different strains of streptococcal organisms. Numerous proteins/antigens were described that are characteristic of nephritogenic strains of streptococci. These nephritogenic proteins are discussed later in this chapter.

Antibody Formation

Both intracellular and extracellular antigens of the *streptococcus* stimulate the production of antibodies in the infected patient. Antibodies against the various streptococcal products are of great help in clinical medicine because their presence provides evidence of a preceding streptococcal infection, although probably not all are involved with conferring immunity. However, the specificity of these antibodies can be questionable. These antibodies include antistreptolysin O (ASO), antistreptokinase (ASK), antihyaluronidase (AH), antideoxyribonuclease-B (anti-DNase-B), antidiphosphopyridine nucleotidase (anti-DPNase), and anti–nicotinamide adenine dinucleotidase (anti-NADase). The "streptozyme" antibody test was introduced as a latex agglutination method in a kit intended to simultaneously measure antibodies to five streptococcal extracellular antigens (exoenzymes), including streptolysin, streptokinase, hyaluronidase, DNase, and NADase. It should be noted, however, that approximately 20% of healthy children have elevated streptozyme titers. Also, some investigators believe that the reliability of the streptozyme test is not as good as that of conventional methods for single-antibody determinations.

Two of the most useful antibody determinations in the evaluation of patients with recent streptococcal infections are the ASO and anti-DNase-B assays. The ASO assay is the best known and the one most frequently ordered. In one study (83), the ASO titer was greater than 160 units in 92% of patients with acute glomerulonephritis; ASK and AH titers were raised in less than 50%. The ASO titer is usually greater than 250 Todd units, and most patients have a threefold or greater rise. A rising titer provides the best proof of a streptococcal infection. The ASO titer begins to climb within a few days of infection and reaches a peak level after several weeks; as a rule, it then declines. However, the ASO titer does not increase in all patients with streptococcal infections; thus, the absence of a high titer does not exclude a streptococcal infection. This is especially true of patients with skin infections (pyoderma).

Conversely, the ASO titer can be modestly elevated in patients with nonstreptococcal disease, and up to one third of patients with other forms of nonstreptococcal glomerulonephritis may have mild elevations of ASO. Because the ASK or AH titer may be elevated when the ASO titer does not rise (as in skin infections), some researchers have suggested that a combination of all three tests is of advantage in diagnosing PSAGN. False-positive results are caused by β-lipoprotein in liver disease, some other bacteria, and oxidation of streptolysin O. False-negative results may be obtained after antibiotic treatment of the patient. AH and anti-DNase-B titers are commonly raised in patients with skin infections, more so than ASO, as indicated earlier. Anti-DNase-B testing is more sensitive than AH and is the test of choice in the investigation of skin infections. The anti-DNase-B titer remains elevated longer than the ASO titer. Zymogen is the precursor of cationic streptococcal proteinase (erythrogenic toxin B). Researchers in a multicenter study from South America concluded that detecting antibodies to streptococcal zymogen is superior compared with ASO and anti-DNase-B titers in the detection of PSAGN (84).

It is unusual for patients to experience a second attack of poststreptococcal glomerulonephritis. This finding is probably owing to the relatively limited number of nephritogenic strains of streptococci and to the acquisition of type-specific protective immunity to the serotype of *Streptococcus* that elicited the initial attack. Other factors probably contribute to the relative resistance to another nephritic attack, such as the presence of antibodies to the specific nephritogenic factor(s). Cross-reacting neutralizing antibodies may be directed at one potential factor but may cross-react with another (85). When second attacks occur (86), they are similar clinically and morphologically to the initial attack. Penicillin interferes with the production of both type-specific antibody and ASO when significant dosages are given (27). Experimental evidence in a rabbit model of poststreptococcal glomerulonephritis using viable group A streptococci suggested that penicillin therapy within the first 3 days of infection prevents the acute nephritic process (87).

Clinical and Laboratory Findings

PSAGN most commonly affects children and young adults, although no age group is exempt. Although the peak incidence is in the first decade of life, occurrence in older patients has been noted, particularly in the diabetic population (2,3,38,68,88,89). According to an epidemiologic study of the Italian Registry of Renal Biopsy, the incidence of PSAGN in the elderly is higher than in the adult general population (90). Haas et al. (91) reviewed 259 renal biopsies from elderly patients with acute renal insufficiency at the University of Chicago and found that 5.5% of them had some ultrastructural evidence of possible postinfectious glomerulonephritis. Males are affected more commonly than females, the ratio often being 2:1 (92). This ratio is in marked contrast to that for patients with rheumatic fever, which affects both sexes equally. The distribution of PSAGN glomerulonephritis is worldwide. In North America, it affects groups equally in the northern and southern parts, also in contrast to rheumatic fever. PSAGN may appear in either sporadic or epidemic form; children are the group most usually affected in the epidemic forms.

For diagnosis of "acute postinfectious glomerulonephritis," clear evidence that infection preceded the glomerulonephritis

is required. A preceding infectious episode (such as pharyngitis, tonsillitis, mastoiditis, peritonsillar abscess, otitis media, or pyoderma) is the sine qua non for clinical diagnosis of PSAGN (93,94). Skin infection also may lead to nephritis (13,16,17,22,31). This is most often associated with epidemics, particularly in humid warm climates. The offending organism is virtually always a GAS; types 12, 4, 1, and 49 appear to be the most typical nephritogenic types.

There is a delay, or latent (or gap), period between the streptococcal infection and the onset of signs and symptoms of acute glomerulonephritis. This period is usually 1 to 4 weeks (average 10 to 11 days) before the onset of the acute nephritic syndrome (hematuria, edema, hypertension, acute renal dysfunction). In general, the latent period is 1 to 2 weeks after a throat infection but may be longer (3 to 6 weeks) after a skin infection. Onset of signs and symptoms of nephritis at the same time as a respiratory tract infection (so-called synpharyngetic nephritis) is more likely to be immunoglobulin A (IgA) nephropathy than postinfectious glomerulonephritis.

The onset of clinical symptoms is typically abrupt. At the onset of clinical symptoms, the urine becomes dark, smoky, or Coke or coffee colored. Puffiness of the face or eyelids as a manifestation of edema is sudden and common; in some cases, there also may be edema of the legs and sacral region. Periorbital edema is characterized by prominence on awakening in the morning and a tendency to subside or decrease if the patient is up and about in the morning. Edema, as well as other features of circulatory congestion, such as dyspnea, cardiomegaly, and increased venous pressure, is the result of a defect in the renal excretion of sodium and water, although heart failure is also a factor both in children and older patients (95). The severity of edema in poststreptococcal glomerulonephritis is often disproportionate to the degree of renal impairment.

Compromise of the intraglomerular blood flow caused by glomerular endocapillary hypercellularity resulting in progressive encroachment on the patency of the glomerular capillaries, in part, leads to reduced blood flow that is manifested by low fractional excretion of sodium, low urinary sodium concentrations, and concentrated urine (96,97). This salt and water retention often results in dilutional anemia, hypertension, and edema. In patients with impaired cardiac function, this sodium retention may lead to pulmonary edema.

In patients with severe proliferative glomerulonephritis, progression of the lesion may result in oliguria or even anuria. This is particularly common in elderly patients with PSAGN. Oliguria may either be short lived or persistent, and it is possibly indicative of a severe form of glomerular disease (i.e., the crescentic glomerular form). Oliguria tends to be transient, with diuresis usually occurring within 1 to 2 weeks. Anuria is less common. During the onset of oliguria/anuria, proteinuria may actually diminish because of a decrease in the glomerular filtration rate (GFR) (98). With resolution of the glomerular inflammation, increasing proteinuria may parallel an increasing GFR or even precede it.

Hypertension occurs in half of the children (98) but is more common in adults, especially in elderly patients (99). It is usually transient with a rapid return to normal levels of blood pressure on normalization of the GFR, loss of edema, and normalization of the plasma volume. Plasma renin activity is usually low. Although hypertension is generally thought to be the result of sodium and water retention, studies by Parra et al. (100) have suggested that inhibition of the angiotensin-converting enzyme by captopril could be an effective short-term treatment of low-renin hypertension in this disease. However, hypertension may persist, and when it does, it indicates either progression to a more chronic stage (the likelihood of this happening is discussed later) or that the disorder is not acute postinfectious glomerulonephritis.

Hypertensive encephalopathy is noted in no more than 5% to 10% of patients. There is usually clinical improvement without any neurologic deficit. Despite sodium retention during the acute phase of PSAGN, investigators (101) have found increased plasma levels of atrial natriuretic peptide. This finding suggests unresponsiveness of the kidneys to atrial natriuretic peptide in this condition. The accompanying increased plasma levels of endothelin may also contribute to this condition (53,60). Endothelin-1 not only is a potent vasoconstrictor but also facilitates sodium reabsorption in the proximal tubule that results in increased blood volume. Patients with PSAGN have experienced successful pregnancies (48).

Subclinical forms of PSAGN are probably more usual than symptomatic disease (21,102–106). In a prospective study of 248 children with GAS infections, Sagel et al. (103) measured serum complement levels and ASO titers and performed urinalysis. They found that subclinical disease was almost 20 times more common than overt acute glomerulonephritis. Over a 6-week period, 54 children showed either transient depression of serum complement (19 children) or mild urinary abnormalities (proteinuria, hematuria, or leukocyturia—15 children) or both (20 children). All patients were asymptomatic, except for one who had edema; hypertension was present in half the patients. Renal biopsy was performed in 20 patients in whom depressed complement and urinary abnormalities were present, and a proliferative glomerular change, ranging from mild to severe, was noted. A granular glomerular immunofluorescence pattern for complement C3 was noted in 15 of the 20 biopsies.

Few patients may develop left ventricular dysfunction during the acute congestive and convalescent phases of PSAGN. This dysfunction may not be associated with hypertension or pericardial/pleural effusions (107). PSAGN rarely shows initial signs of pulmonary hemorrhage (108,109). PSAGN may be seen in alcoholics with or without cirrhosis (110). PSAGN has often been reported to be superimposed on diabetic nephropathy (Poststreptococcal and other infection-related glomerulonephritides superimposed on diabetic nephropathy, p. 412). A number of other diseases have been associated with PSAGN, but these case reports probably describe by chance associations.

Elevations in blood urea nitrogen (BUN) and serum creatinine levels reflect the decrease in GFR, and they are often noted during the acute stages. Lack of normalization of these values within several weeks or a few months suggests that one may not be dealing with a true case of acute postinfectious glomerulonephritis. Elderly patients have a higher rate of major elevations of serum creatinine (90,99). BUN and serum creatinine levels may remain elevated in those patients who have the crescentic form of postinfectious glomerulonephritis (111,112).

Proteinuria may be mild or so severe as to cause hypoalbuminemia and severe edema. Proteinuria is less than 3 g/24 hours in most cases. Nephrotic syndrome occurs in approximately 5% to 10% of patients (113); in one series (114), it was noted in 20%. Proteinuria usually disappears within 6 months and cleared with clinical healing in all but 4 of the 23 patients in the studies

of Jennings and Earle (115). Proteinuria may persist for longer periods, but complete clinical recovery has been noted after proteinuria has been maintained for as long as 26 months (115). McCluskey and Baldwin (114) described a well-documented case of one patient with disappearance of proteinuria after 6 years. Symptoms, including proteinuria, hypertension, and renal insufficiency, are more severe in adults and, in particular, in the elderly with postinfectious glomerulonephritis (2).

The urine of patients with PSAGN has a high specific gravity. The brown/smoky color is caused by hemolysis of erythrocytes that have penetrated the GBM and have passed into the tubular system. Both are particularly common in patients in whom urine volume is reduced. The urinary sediment has red blood cells, red blood cell casts, granular casts, and sometimes leukocyte casts. Microscopic hematuria often persists longer than proteinuria and may be present in patients in whom the disease has otherwise completely disappeared clinically (115). Hematuria may persist for as long as 18 months, and in a few patients, it persists for much longer periods, even up to 5 years. The presence of red blood cell casts is of great importance because they indicate that the bleeding is of glomerular origin. Such casts are best discovered in first early morning urine specimens studied by the physician shortly after voiding. Dysmorphic red blood cells are also indicative of glomerular disease. A report on 152 patients with PSAGN from Turkey indicates that microscopic hematuria is more common than gross hematuria in patients with severe systemic manifestations (defined by the authors as pulmonary edema, cardiac failure, and severe hypertension with signs of encephalopathy), and, in contrast, gross hematuria is more than three times more common than microscopic hematuria in patients with renal symptoms only (116).

Albuminuria and microhematuria can be detected in the interval between infection and nephritis in up to half the patients with streptococcal upper respiratory tract infections and are thought by some to be more likely to occur in patients who progress to acute glomerulonephritis. In renal biopsies taken shortly after the onset of infection, only mild focal hypercellularity of the glomeruli was noted (92). The serum albumin level is sometimes low because of the loss of albumin in the urine in those patients with severe proteinuria. The serum cholesterol level may be elevated in some children as well as adults.

As noted earlier, antibodies to various streptococcal products can be found in patients with acute glomerulonephritis and are used diagnostically to establish the presence of a preceding streptococcal infection. Comparisons of acute and subsiding titers are of importance clinically. A rise in serum titer of two or more dilution increments between the acute and the convalescent serum is usually considered significant regardless of the magnitude of the titer. The upper limit of the normal range varies with the season, geographic area, and age of the patient; thus, each laboratory should establish its own reference range. Patients who are treated with antibiotics early in the course of the infectious episode or elderly patients may not exhibit a significant rise in antibody titers; thus, the diagnosis may be difficult to make in the absence of positive cultures.

Anemia is commonly noted in the early stages. This feature is thought to be primarily a dilutional phenomenon as a consequence of the expanded extracellular fluid, although cases of hemolytic anemia (117) and hemolytic uremic syndrome have been reported (118–121).

Serum complement is decreased during the acute episode in almost all patients with PSAGN (52,65,118) and is considered evidence in favor of the diagnosis and of an antigen-antibody reaction. Serum complement levels usually return to normal within 6 weeks of the acute onset of the nephritis. In patients in whom the serum complement level is apparently normal, serial determinations will often show an increase during the recovery stage, suggesting that there was in fact a decrease associated with the glomerulonephritis. There is activation of both the classic and the alternative pathways of the complement cascade. Levy et al. (57) suggested that although both pathways are implicated in the early stages of the disease, continued C3 depression is probably through the alternative pathway. Serum complement abnormalities in PSAGN will be discussed more in detail later in this chapter (see Pathogenesis).

Pathologic Findings

As with most of the glomerulonephritides, our early knowledge of the pathology of acute glomerulonephritis was derived mostly from autopsy material. With the advent of renal biopsy, it became possible to compare the morphologic pattern of the glomerular involvement in the living patient with that seen in patients dying with glomerulonephritis. Renal biopsy studies have shown that the morphologic picture described from autopsy material is virtually identical to that found on renal biopsy. This is probably because death in patients with acute postinfectious glomerulonephritis was attributable to congestive heart disease, not to renal injury. Recently, fewer biopsies showing acute glomerulonephritis have been available, since the clinician (especially the pediatric nephrologist) is less likely to conduct a biopsy on a patient with classic or typical signs and symptoms of acute postinfectious glomerulonephritis.

Indications for considering renal biopsy in children with acute nephritic syndrome include (a) persistent severe (gross) hematuria longer than 1 month or persistent hypocomplementemia longer than 6 weeks, (b) progressive deterioration of the GFR, (c) hypertension persisting longer than 2 months, (d) extrarenal manifestations of systemic disease, (e) family history of renal disease, (f) age younger than 2 years, (g) onset of nephritis within 48 hours of pharyngitis (54,55), or (h) nephrotic syndrome (Table 10.2). The indications for renal biopsy in adults are not as clear but are probably more liberal because of the less common occurrence of PSAGN in the adult. A number of glomerular diseases may appear in a manner clinically resembling PSAGN, including C3 glomerulopathy (including dense deposit disease and C3 glomerulonephritis), membranoproliferative glomerulonephritis (MPGN), IgA nephropathy, IgA vasculitis (Henoch-Schönlein purpura), and renal-limited forms of anti-GBM (antiglomerular basement membrane) disease and ANCA (antineutrophil cytoplasmic autoantibody) disease. The most typical examples of disease processes masquerading as acute postinfectious glomerulonephritis in a child are C3 glomerulonephritis and MPGN, which may present with acute nephritis and hypocomplementemia.

Gross Appearance

The kidneys are symmetrically enlarged, generally 25% to 50% larger than normal. They are pallid in appearance, and the cut surfaces bulge because of interstitial edema. The main thickening is in the cortex. The glomeruli may stand out as reddish or gray translucent dots. The capsular and cut surfaces

TABLE 10.2 Atypical features that suggest a need for renal biopsy

Absence of evidence of streptococcal infection or immune complex disease
No rise in antistreptococcal antibodies
Normal serum complement level
Atypical early features
No latent period
Anuria
No improvement or continued decrease in GFR at 2 wk
Persistence of hypertension longer than 2 wk
Nephrotic syndrome
Atypical features during presumed recovery
Failure of normalization of GFR by 4 wk
Depression of serum complement level longer than 6 wk
Persistence of proteinuria longer than 6–8 mo
Persistence of hematuria longer than 18 mo

GFR, glomerular filtration rate.

Modified from Nash M. *Renal Biopsy in Medical Diseases of the Kidney.* New York: Postgraduate course, Department of Pathology, Columbia-Presbyterian Medical Center, 1989.

may have tiny red speckles caused by red blood cells in the lumens of the Bowman space and tubules.

Microscopic Findings

Glomeruli

Hypercellularity and Other Common Findings The glomeruli are all affected (diffuse involvement) and usually to an approximately equal degree (Figs. 10.1 to 10.3). The glomerular tufts are larger than normal, and the cells are more numerous. Many cell types contribute to the hypercellularity, including proliferating endothelial and mesangial cells from the tuft itself and influx of inflammatory cells, among them polymorphonuclear leukocytes and monocytes (Figs. 10.4 and 10.5). The extent to which native endocapillary cells contribute to the hypercellularity is a subject of debate and is discussed later. In most specimens with acute disease, polymorphonuclear leukocytes are the most easily identified cells and may be present in large numbers–hence the term *exudative glomerulonephritis* (although many of the neutrophils are marginated in the lumens of capillaries rather than exuding from the capillaries). In other cases, they are inconspicuous. It has been suggested by Jennings and Earle (115) that polymorphonuclear leukocytes may be more frequently found in biopsies performed shortly after the clinical onset of the disease. Obviously, as the acute inflammation resolves, the number of neutrophils will decline progressively. Occasionally, other inflammatory cells, such as eosinophils (59,98) and lymphocytes, are noted, but this is unusual. Necrosis in the glomerular tuft is rare (Fig. 10.6).

The individual lobules of the glomeruli are wider than normal and sometimes assume a clubbed appearance. The glomerular capillary lumina are often reduced by the hypercellularity so that erythrocytes may be difficult to see. The stalk region of the mesangium may be quite hypercellular (115). The glomerular capillary walls are generally not thickened, although there may

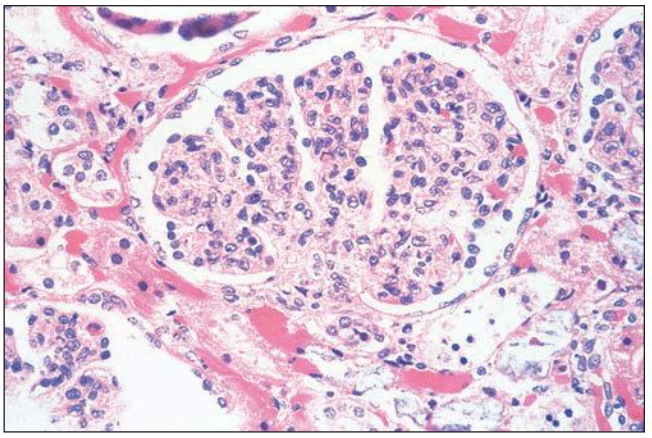
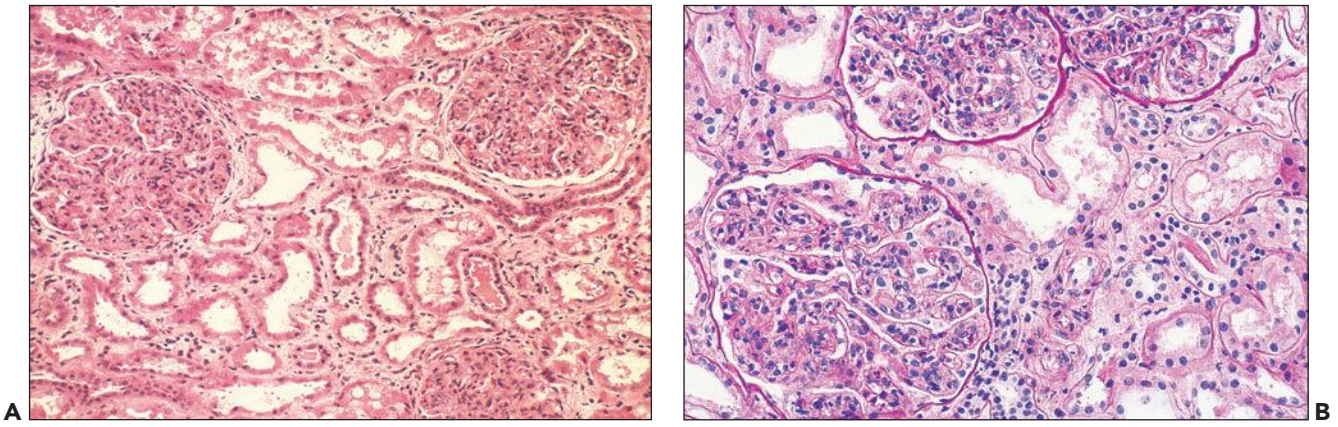


FIGURE 10.2 A glomerulus with endocapillary hypercellularity and closure of the glomerular capillaries. Because of the increased cellularity within each lobule, there is an accentuation of the lobularity. (H&E, ×400.)



A **B**

FIGURE 10.1 Three enlarged glomeruli show diffuse endocapillary hypercellularity with numerous neutrophils and closure of all the glomerular capillaries. The glomeruli are increased in size and cellularity. Although both (**A**) and (**B**) show very similar changes, the images were taken from biopsies of two different patients with PSAGN. (**A**, H&E, ×200.) (Courtesy of Dr. J. Charles Jennette.) (**B**, PAS, ×200.)

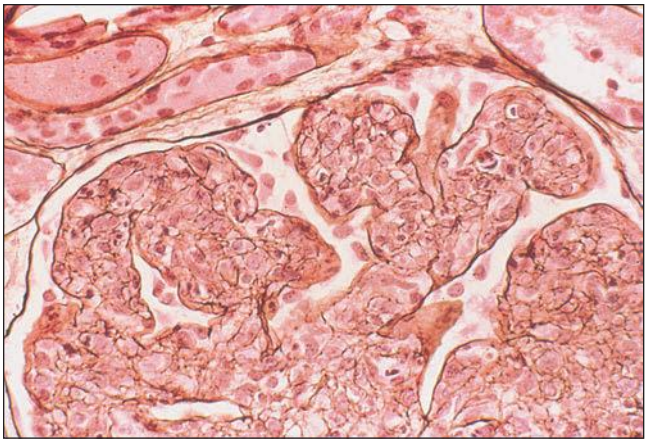


FIGURE 10.3 Silver stain of a glomerulus from a patient with PSAGN. Note that all the hypercellularity is confined within the glomerular tuft (endocapillary hypercellularity). (Jones silver methenamine, ×600.)

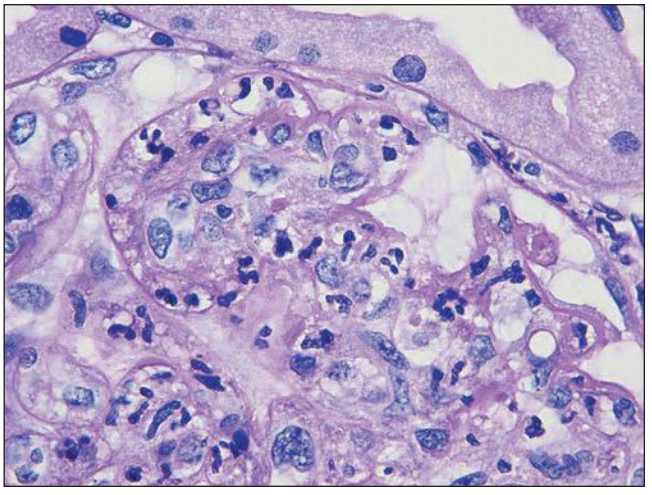


FIGURE 10.5 Acute diffuse proliferative glomerulonephritis with considerable infiltration of the glomerulus by neutrophils, which is common in acute postinfectious glomerulonephritis. (PAS, ×1000.)

sometimes be mild thickening visible on light microscopy. The combination of expansion of the lobules, hypercellularity of the tuft, and localized thickening of the glomerular capillary walls may produce a picture mimicking MPGN. Ultrastructural and immunofluorescence studies and clinical findings at the time of biopsy and follow-up allow easy separation of these morphologically and clinically distinct entities.

In some patients, it is possible, especially with the oil immersion lens, to detect tiny nodules on the epithelial side of the glomerular capillary wall. These nodules can be identified as fuchsinophilic dots with the trichrome stain (Masson or Mallory) either on thin (3-μm) sections or on 0.5-μm plastic-embedded sections stained with toluidine blue (Fig. 10.7). These minute structures correspond to the subepithelial deposits (humps) noted by electron microscopy. For optimum detection, it is important to study these renal biopsies with the oil-immersion lens and the trichrome stain because these small deposits may be overlooked on casual examination with the high-dry (40× or 60×) objective alone. Detection of those deposits by light microscopy is especially useful if there are no materials (i.e., glomeruli) for study by electron microscopy or immunofluorescence. Although the glomerulonephritis is diffuse (involving all or almost all glomeruli equally), there may be focal and segmental variability of the lesions among glomeruli, but this is unusual (Fig. 10.8).

In some patients, there may be crescent formation (2,66) or small adhesions (synechiae) (Fig. 10.9). In a few patients, crescent formation is so prominent that the term *crescentic glomerulonephritis* may be used, but usually only a small percentage of glomeruli are affected by crescents. The Bowman space may contain erythrocytes, which is evidence in a percutaneous renal biopsy that hematuria is caused by glomerular bleeding. Polymorphonuclear leukocytes also may be seen in the Bowman space.

Cell Types Both infiltrating leukocytes (neutrophils and monocytes) and proliferating glomerular cells (mesangial, endothelial, and epithelial cells) contribute to the glomerular

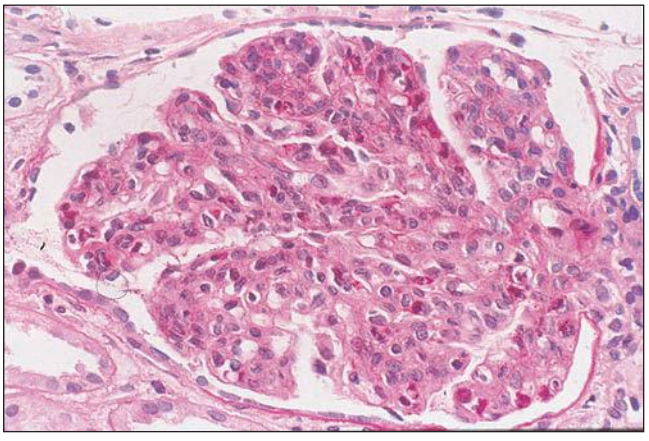


FIGURE 10.4 This glomerulus shows a broadening of the lobules, increase in cellularity with moderate numbers of neutrophils with segmented nuclei, and reduction of the capillary lumens. (PAS, ×400.)

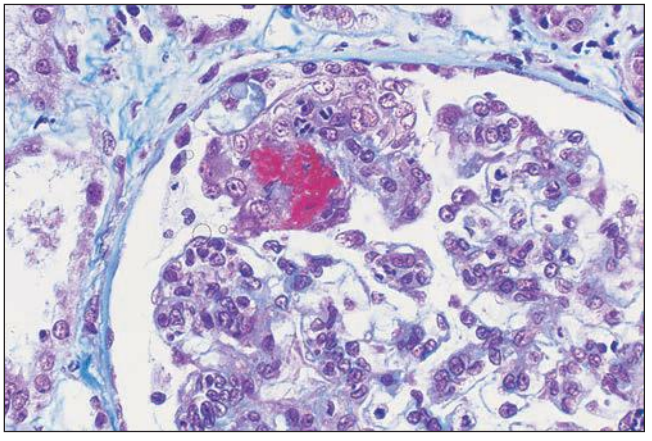


FIGURE 10.6 A glomerulus from a patient with clinically classic PSAGN. Note the focal segmental fibrinoid necrosis at approximately 10 o'clock as well as the endocapillary hypercellularity. (Masson trichrome, ×600.)

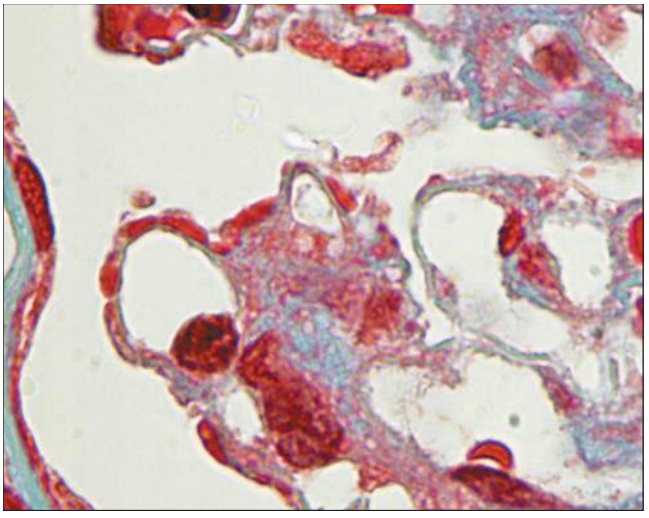


FIGURE 10.7 High magnification of a Masson trichrome–stained section from a renal biopsy with PSAGN. Note the fuchsinophilic (*red*) subepithelial deposits along the glomerular capillary walls at the periphery of the glomerular capillaries. (Masson trichrome, ×1000.)

hypercellularity. The old term *proliferative glomerulonephritis* implies that the increased cellularity is restricted to native glomerular cells, either endocapillary cells (endothelial or mesangial) or extracapillary cells (visceral and parietal epithelial cells). However, current evidence suggests that much of the glomerular hypercellularity (as well as some of the crescent formation in the Bowman space) stems from infiltrating leukocytes from the peripheral circulation. Langhans (8) initially proposed that the major cause of the cellular increase in the glomerular tuft was a proliferation of endothelial cells. This concept

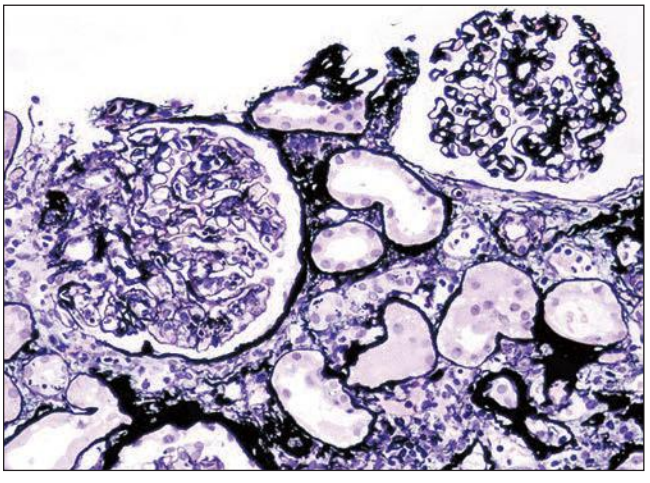


FIGURE 10.8 Renal biopsy from a patient with PSAGN. Most of the glomeruli showed global severe endocapillary hypercellularity such as the glomerulus on the left. An occasional glomerulus (the glomerulus on the right) showed only mild and/or segmental hypercellularity. Note that the glomerular capillaries in the glomerulus on the right are patent. (Jones silver methenamine, ×200.)

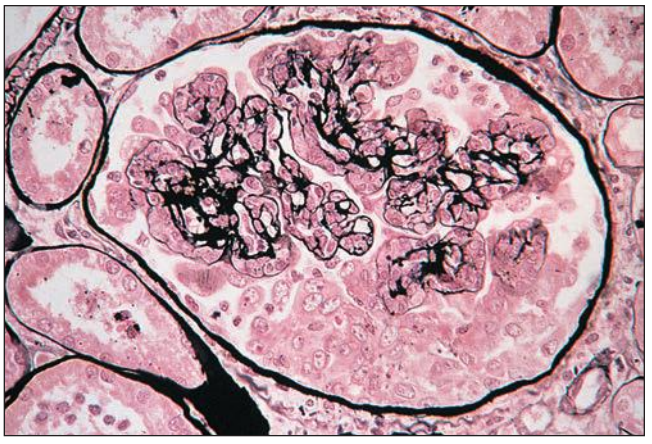


FIGURE 10.9 A glomerulus, with early crescent formation. Note that in the underlying glomerular capillary tuft, there is global increase in cellularity including polymorphonuclear leukocytes. (H&E, ×400.) (Courtesy of Dr. Vivette D'Agati.)

was responsible for the designation *endocapillary proliferative glomerulonephritis*.

Jennings and Earle (115) favored the notion that hypercellularity was owing to native intraglomerular cells because of the presence of mitotic figures in "cells inside and attached to the glomerular capillary basement membrane (by definition, endothelial cells)." These authors also used electron microscopy to strengthen their view and described cells in the resolving phases of the disease process that had inclusions of electron-dense material resembling GBM. They stated that such inclusions were not evident in mononuclear inflammatory cells (115). This argument, however, did not resolve the question regarding which endocapillary cells (mesangial or endothelial) participate in the proliferation. Ia (MHC class II antigen)-bearing mesangial cells (53), which might be resident macrophages, also could play a role in hypercellularity, but studies in humans have not been forthcoming.

Grishman and Churg (60) described proliferation of cells in the mesangium but did not commit themselves as to the nature of the cells. Many other investigators have mentioned the great difficulty in distinguishing between endothelial and mesangial cells in light microscopy of a hypercellular glomerulus.

Experimental studies also confirmed the idea that mononuclear phagocytes appear in the glomerular tuft in various forms of experimentally induced glomerulonephritis. Although most of these studies used models of Masugi nephritis and Habu snake venom, some used acute serum sickness models in the rabbit (48,63). Monocytes were found to be present in the latter model of acute glomerulonephritis by Hunsicker et al. (63) and by Holdsworth et al. (48), using electron microscopy and staining for nonspecific esterase. Thus, it appears that bone marrow–derived mononuclear cells play a significant part in the hypercellularity noted in the glomeruli of certain experimental diseases.

In human studies using staining for nonspecific esterase and electron microscopy, monocytes are identified in less than half the biopsies of acute glomerulonephritis examined, especially in the early stages of the disease (50,58). Specimens with

mesangial hypercellularity, but less exudative change, had fewer esterase-positive cells. It was suggested that early glomerular hypercellularity is owing to an influx of blood-borne cells, but at a later stage, it is caused mainly by proliferation of intrinsic glomerular cells (62,64). Magil et al. (62,64) verified the presence of glomerular intraluminal monocytes that correlated positively with the presence of deposits. They also described dissection of the glomerular endothelium from the capillary wall adjacent to deposits by the monocytes. Ferrario et al. (58) showed that the degree of proteinuria correlated well with the degree of glomerular mononuclear cell infiltration.

Chung and Kim (47) performed immunohistochemical studies with a monoclonal antibody to Ki-67 (a cell proliferation marker) on renal biopsies from 21 children with PSAGN. They found that the active phase of the disease was associated with more prominent glomerular Ki-67 expression compared with the convalescent phase of PSAGN. However, one has to note that even if in the active disease group, only 11 of 13 biopsies showed Ki-67–positive glomerular cells. Therefore, their results clearly indicate that although some degree of proliferation of endogenous glomerular cells takes place, the bulk of the hypercellularity is secondary to infiltrating inflammatory cells (47). Unfortunately, the study does not clarify the exact cell populations that undergo proliferation in these biopsies with PSAGN.

Inflammatory cells in acute diffuse proliferative glomerulonephritis have been studied by immunophenotyping, but only a few studies concentrated on PSAGN. Hooke et al. (56) found significantly increased numbers of glomerular monocytes and granulocytes, but no significant increase in the number of glomerular T cells or B cells in cases of acute postinfectious glomerulonephritis when compared with normal glomeruli. There was a rise in the number of interstitial T lymphocytes compared with the normal interstitial cell population, but the OKT4/OKT8 ratio was the same as in normal cell populations (56).

Parra et al. (51) studied the cell populations in glomeruli of patients with PSAGN using monoclonal antibodies and indirect immunofluorescence. They found infiltration of the glomeruli by monocytes, granulocytes, and lymphoid cells. T cells were noted adjacent to the Bowman capsule. $CD4^+$ (helper/inducer) lymphocytes were found in the glomeruli early in the course of the disease, whereas $CD8^+$ (cytotoxic/suppressor) cells were found later. Yoshizawa et al. (61) evaluated the role of the cell-mediated immune response in the kidneys of 22 patients with PSAGN. They found a substantial increase in the total number of granulocytes and monocytes/macrophages with only a slight rise in T cells. The number of cells correlated well with time after clinical onset. A positive linear correlation was confirmed between helper/inducer T cells and monocytes/macrophages. As with the study of Parra et al. (51), helper T cells tended to increase to a higher proportion early on, although suppressor T cells remained constant throughout the course of the disease. Although there were fewer total leukocytes than in patients with clinically overt disease, in asymptomatic patients with PSAGN, the proportions of infiltrating cells were similar (61).

Polymorphonuclear leukocytes often are numerous, although large numbers of these cells do not indicate a poor outcome. The leukotactic properties of complement have been verified. Lewy et al. (98) documented a case with a predominantly polymorphonuclear leukocytic reaction in which there were large numbers of glomerular subepithelial humps. These authors commented that in other cases, the greatest numbers of polymorphonuclear leukocytes were found when there were large numbers of humps.

Other Mesangial Changes Several probes have found increases in some naturally occurring substances in the glomeruli in postinfectious glomerulonephritis. Actomyosin has been shown to be mildly elevated in the mesangial regions (49), but the significance of this finding is unclear. Likewise, fibronectin has been demonstrated in the mesangial areas (122,123). This protein is present in the normal mesangium and is significantly elevated in a variety of conditions associated with mesangial increase. Mosquera and Rodriguez-Iturbe (124) found glomerular-binding sites for fluoresceinated peanut agglutination lectin in renal biopsies showing evidence of PSAGN. Peanut agglutination lectin has specificity for galactosyl radicals that are exposed after sialic acid removal, as one would see with neuraminidase. These findings suggested to the authors that sialic acid–depleting material (probably neuraminidase) was present in glomeruli early in the course of the glomerulonephritic process.

Several immunopathologic studies have been performed on renal biopsy material taken from patients with PSAGN. Parra et al. (125) confirmed enhanced expression of intraglomerular ICAM-1 (intercellular adhesion molecule 1) in early-stage biopsies; this expression decreased with time. The numbers of cells expressing lymphocyte function–associated antigen 1 (LFA-1) in glomeruli were also elevated in early biopsies. Levels of VCAM-1 (vascular cell adhesion molecule 1) were not higher. This study suggested that ICAM-1 (and possibly other adhesion molecules) is important in the recruitment/influx/localization of leukocytes in acute postinfectious glomerulonephritis. The study by Lhotta et al. (126) of ICAM-1 expression in various proliferative glomerulonephritides demonstrated that the changes in staining intensity were observed mainly on the glomerular endothelial cells with less mesangial staining. However, it should be noted that induction of E-selectin (ELAM-1) is not invariable in acute glomerulonephritis (127).

Subclinical and Resolving Glomerulonephritis Renal biopsies in patients with minimal urinary changes have been performed (usually in prospective studies) and show differing results. Some find no substantial abnormalities. Increased cellularity of the glomeruli also has been noted, as have changes indistinguishable from characteristic acute diffuse proliferative poststreptococcal glomerulonephritis (105,128,129). In renal biopsies taken several weeks after the clinical onset of disease, there is diffuse hypercellularity in mesangial regions of the glomeruli; the glomerular capillaries are patent, and the capillary walls appear thin and delicate (130) (Fig. 10.10). Some degree of resolution of the hypercellular process takes place, and the number of polymorphonuclear leukocytes is diminished. Mesangial hypercellularity appears to persist for many months in patients who eventually experience complete resolution of the glomerular lesion (131).

An old term for this morphologic picture is *chronic latent glomerulonephritis*. However, caution needs to be exercised for two reasons. First, an unusually thick paraffin section may give the false appearance of diffuse mesangial hypercellularity.

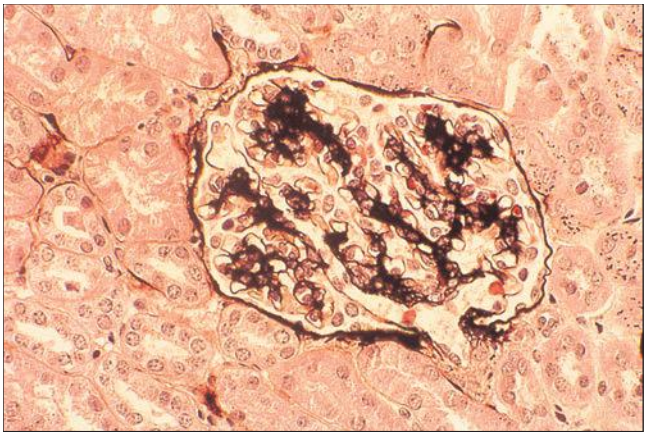


FIGURE 10.10 Resolving PSAGN shows mesangial expansion. Increased mesangial cellularity and mesangial matrix increase may persist for years. (Jones methenamine silver, ×200.)

Second, many cases termed *chronic latent glomerulonephritis* may not be resolving/resolved PSAGN, in our opinion, but rather represent a nonspecific histologic pattern associated with various renal injuries unrelated to previous infections (132). In one long-term follow-up study (more than 5 years) of 26 patients suffering from PSAGN, Buzio et al. (133) found diffuse mesangial hypercellularity in those patients with persisting urinary albumin or proteinuria.

It has been proposed that patients with well-documented PSAGN who show a mesangial proliferative picture on subsequent biopsy have a worse renal prognosis than those with typical resolving streptococcal glomerulonephritis. Patients with isolated mesangial C3 deposits in association with mesangial proliferative glomerulonephritis may actually have poststreptococcal glomerulonephritis, but there is little proof in most patients. Multiple entities may show this pattern, since the kidney responds in a limited fashion to many different injurious stimuli. The recently characterized entity, C3 glomerulopathy, should be considered in proliferative glomerulonephritis with isolated C3 deposits, particularly in the absence of an obvious preceding infection (134). Also, patients with underlying abnormalities of the alternative complement pathway activation may have an atypical course of postinfectious glomerulonephritis (135). Complete morphologic resolution occurs following PSAGN, but follow-up biopsies in such patients, obviously, are not performed. In fact, "incidental healed" postinfectious glomerulonephritis may be more common than anticipated. Haas (136), in a study from the Johns Hopkins Hospital, reviewed 1112 consecutive renal biopsy specimens and found 57 biopsies in which ultrastructural findings indicated resolving/healed PSAGN. According to Haas, resolving or largely healed postinfectious glomerulonephritis was present in 10.5% of renal biopsy specimens, excluding biopsies with a primary diagnosis of immune complex glomerulonephritis (136). The study was based on ultrastructural findings (subepithelial deposits in glomerular mesangial notch regions); therefore, this incidence may be somewhat overestimated because subepithelial deposits in the mesangial notch region are not specific for resolving postinfectious glomerulonephritis because they can be seen in other glomerular diseases, for example, in C3 glomerulopathy (including dense deposit disease and C3 glomerulonephritis). Interestingly, in Haas' study, 50% of the biopsies showing some evidence of incidental healing postinfectious glomerulonephritis had evidence of mesangial hypercellularity (136).

Tubules

The tubular changes are not as pronounced as those involving the glomeruli. When proteinuria is present, there may be hyalin droplets (protein reabsorption droplets, phagolysosomes) or vacuoles (dissolved lipid droplets) in the proximal convoluted tubular epithelium. Erythrocytes may be seen in the lumen of the tubules, and they are sometimes mixed with eosinophilic cast-like material. Polymorphonuclear leukocytes also can be present in the lumens, especially in the first portions of the proximal tubules. This feature is most commonly seen in patients with severe exudation or infiltration of polymorphonuclear leukocytes in the glomeruli. In a few patients, polymorphonuclear leukocytes can be seen between the tubular basement membrane (TBM) and the overlying tubular epithelial cells (Fig. 10.11). In patients who develop severe renal insufficiency, classic changes of acute tubular necrosis (ATN) are usually evident. With serial renal biopsies, these changes resolved. There was no apparent relationship between the morphologic tubular changes and Tm_{PAH}. In the most florid cases of acute glomerulonephritis with extensive crescent formation, there may be progressive tubular injury with tubular atrophy and loss, as well as tubulitis characterized by inflammatory cells between the TBMs and the tubular epithelium or within the tubular epithelium.

Interstitium

The degree of interstitial involvement is variable. The interstitial areas may show edema with separation of the tubules from one another. Scattered foci of inflammatory cells, made up of mixtures of polymorphonuclear leukocytes, monocytes, and lymphocytes, are sometimes present (Fig. 10.11). There may occasionally be severe interstitial mononuclear cell infiltration

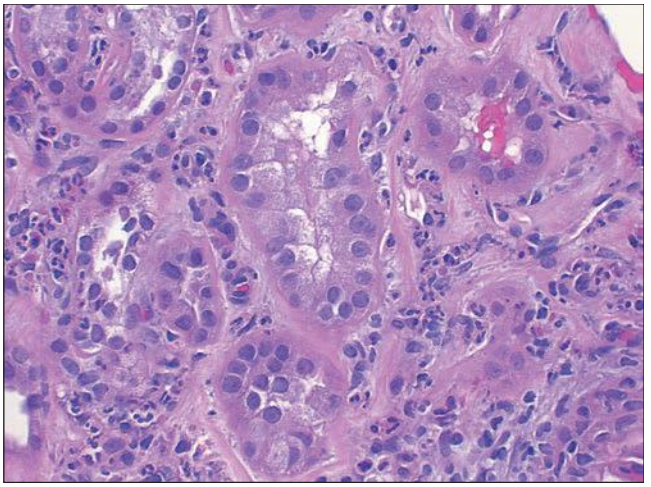


FIGURE 10.11 Unusually pronounced neutrophilic infiltration in the interstitium in this biopsy from a patient with PSAGN. Note that some neutrophils infiltrate the tubular epithelium. (H&E, ×600.)

and scattered regions of interstitial fibrosis. Usually, however, the interstitial changes are not remarkable or severe. As noted earlier, interstitial changes may be found in relation to tubular changes (137). Bohle et al. (138), using morphometric methods on tissue sections, showed that the level of serum creatinine correlated with the increase in interstitial volume. They explained this finding on the basis of a reduction of renal blood flow and, hence, the GFR, brought about by compression of the postglomerular vasculature.

Blood Vessels

The arteries and arterioles generally do not show changes. In older patients, preexisting vascular abnormalities, such as arterial and arteriolar sclerosis, may be seen, and, according to Gallo et al. (139), these may be accentuated and lead to greater renal parenchymal injury. Arteritis has been described (140), but in such cases, systemic necrotizing vasculitis must be excluded. There are other accounts of arteritis (141,142) as well, but they are rare. Fibrinoid necrosis of the arterioles may be associated with severe hypertension. As noted earlier, in rare instances, vascular changes of thrombotic microangiopathy (TMA) may be seen (143,144).

Immunofluorescence Findings

Immunofluorescence studies have been reported by many investigators (59,96,131,145–152). Classically, in biopsies taken early in the clinical course (first 2 or 3 weeks) of the illness, small, granular deposits are noted along the glomerular capillary walls following immunofluorescence studies with anti-IgG and anti-C3 fluoresceinated antisera (Figs. 10.12 and 10.13). The pattern is granular ("lumpy-bumpy") and usually more coarse than in patients with membranous glomerulonephritis. Large, coarsely granular immune complex deposits are usually easy to visualize using immunoperoxidase methodology as well on paraffin sections (Fig. 10.14). These deposits may assume a somewhat linear or band-like (garland) pattern in some areas, owing to the confluence of subepithelial deposits. The granular deposits correspond to the glomerular subepithelial deposits evident on electron microscopy, although there has been controversy over this feature in the past (153).

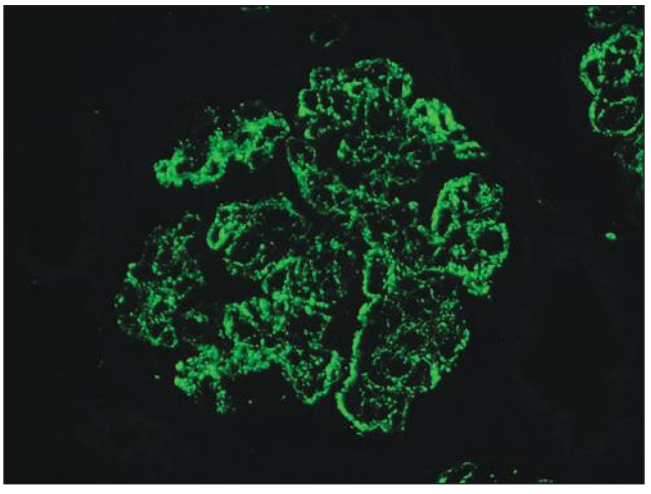


FIGURE 10.13 "Lumpy bumpy" coarsely granular C3 deposits along the glomerular capillary loops in PSAGN. (×400).

Sorger et al. (147–149) have described different immunofluorescence microscopy patterns called the garland pattern (Fig. 10.15), the starry sky pattern (Fig. 10.16), and the mesangial pattern (Figs. 10.17 and 10.18). The *garland pattern* has a discrete, more densely packed and sometimes confluent heavy disposition of IgG and C3, corresponding to numerous humps noted on the subepithelial side of the glomerular capillary wall (147,149). This arrangement is most often seen in patients with acute glomerulonephritis who have severe proteinuria (often with the nephrotic syndrome) (see Fig. 10.15). Other glomerular deposits are rare. The *starry sky pattern* has a more irregular, finely granular pattern, with the deposits (IgG, IgM, C3, IgA) being smaller and often situated on the GBM overlying the mesangial regions. This arrangement was most commonly seen in early cases (see Fig. 10.16). Only a few large, typical humps were noted in these cases. This picture may turn into the *mesangial pattern*, characterized by a granular deposition of IgG and C3 (usually with predominance of C3). It seems to be most closely related to a resolving pattern (see

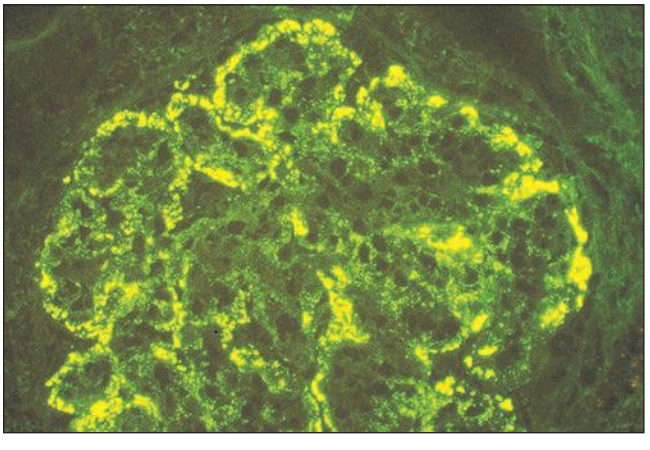


FIGURE 10.12 Immunofluorescence microscopy for IgG in a patient with PSAGN shows a coarsely granular pattern along the capillary walls and a less prominent granular mesangial pattern. (×400.)

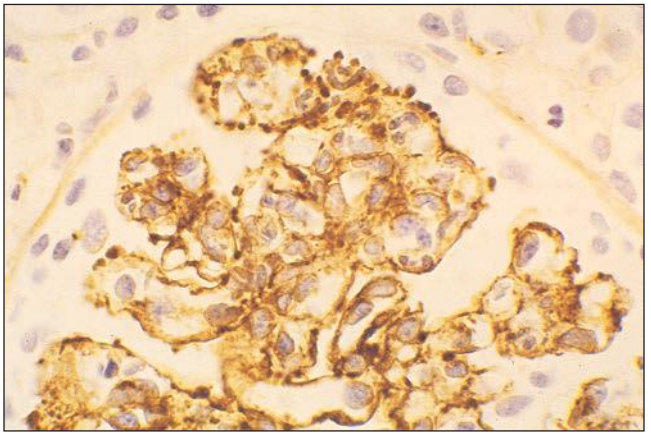
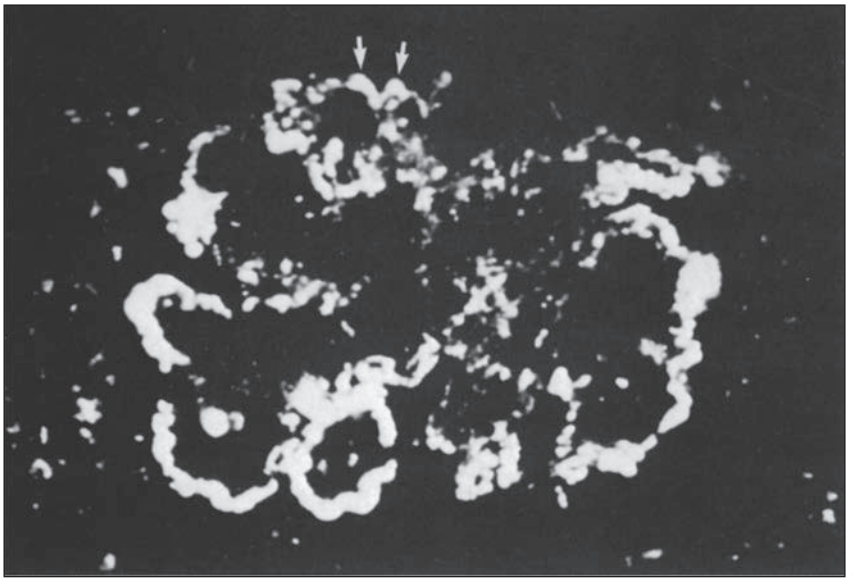
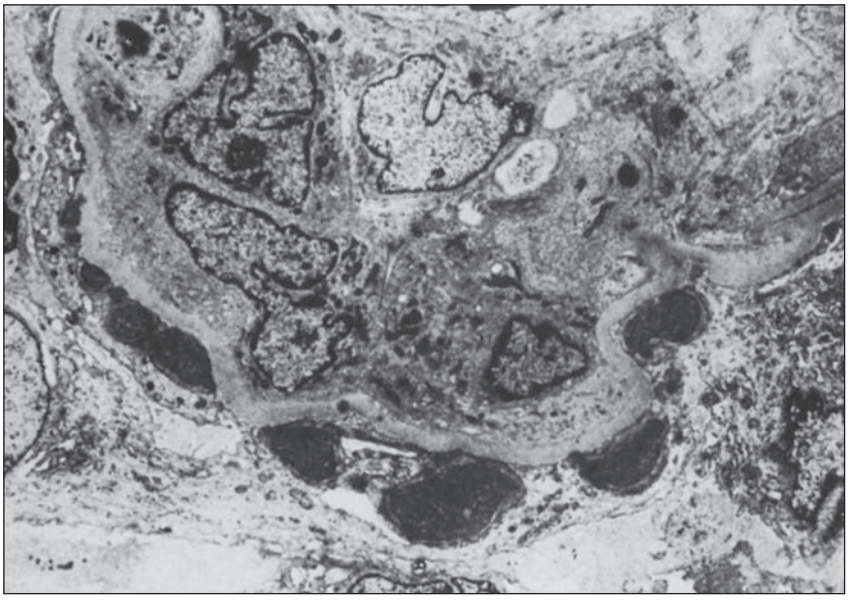


FIGURE 10.14 Immunoperoxidase method on paraffin section with an antibody to C3 highlights the coarsely granular large subepithelial deposits in this case of PSAGN. (×600.) (Courtesy of Dr. J. Charles Jennette.)





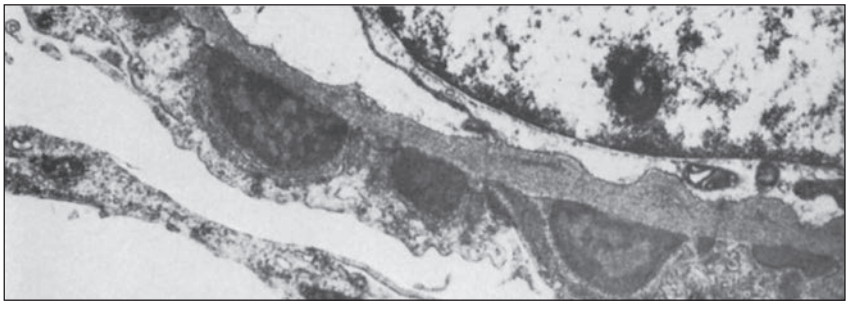
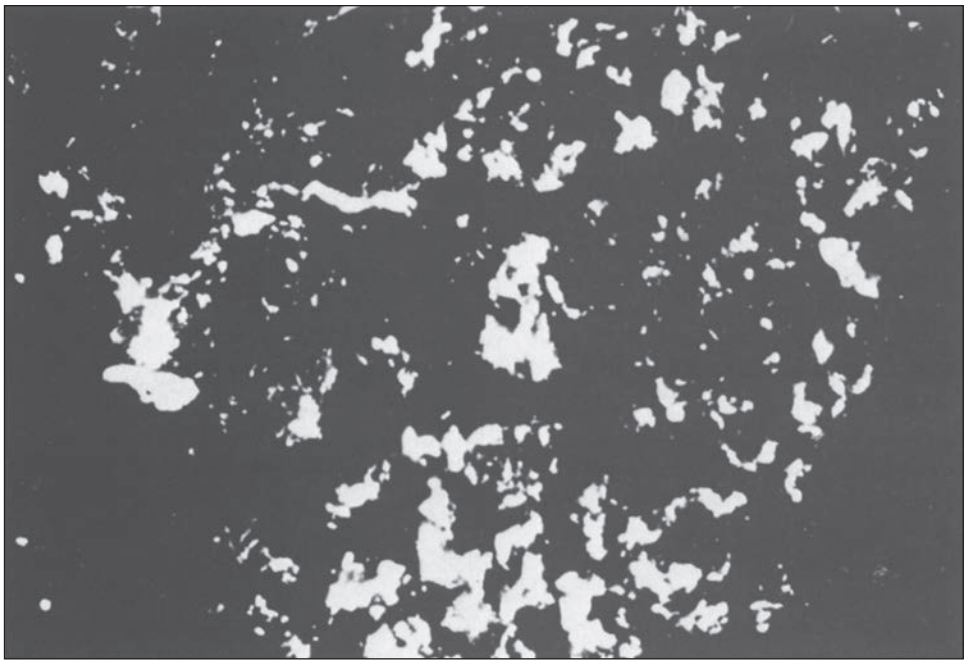


FIGURE 10.15 **A:** Immunofluorescence shows a garland pattern. The garland-like outline of the glomerular loops is due to large subepithelial deposits on the outer side of the GBM (*arrows*). The mesangial regions appear to be largely empty. (IgG, ×450.) **A,B:** Accompanying electron micrographs show part of a glomerulus from a patient with a garland pattern. In **B,** there are hypercellularity and numerous subepithelial deposits of varying density. (×5700.) In **C,** taken at a higher magnification, there are variegated deposits of different sizes. (×9000.) From a 37-year-old man with a 2-week history of poststreptococcal glomerulonephritis. (From Sorger K. *Postinfectious Glomerulonephritis*. Stuttgart, Germany: Gustav Fischer Verlag, 1986.)

Fig. 10.17). The deposits are generally noted in the mesangial matrix of the glomerulus and are accompanied by mesangial hypercellularity.

Edelstein and Bates (154) studied 42 adult patients with characteristic acute postinfectious glomerulonephritis and divided the biopsies into these three subtypes. There was no significant difference among the three subgroups of patients with regard to age, blood pressure, serum creatinine, ASO titers, or decreased serum C3 levels at presentation. Patients with the garland pattern had significantly more proteinuria, whereas the renal biopsies with the mesangial pattern had a lesser degree of glomerular hypercellularity and leukocytes.



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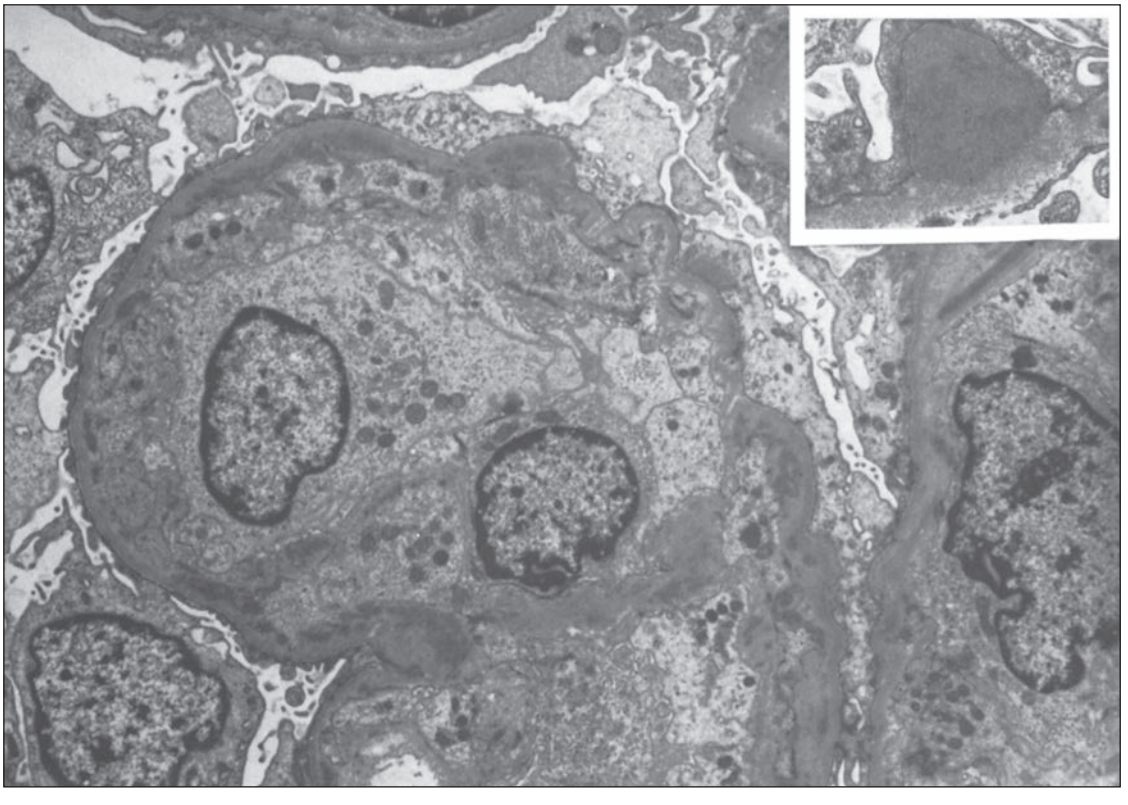

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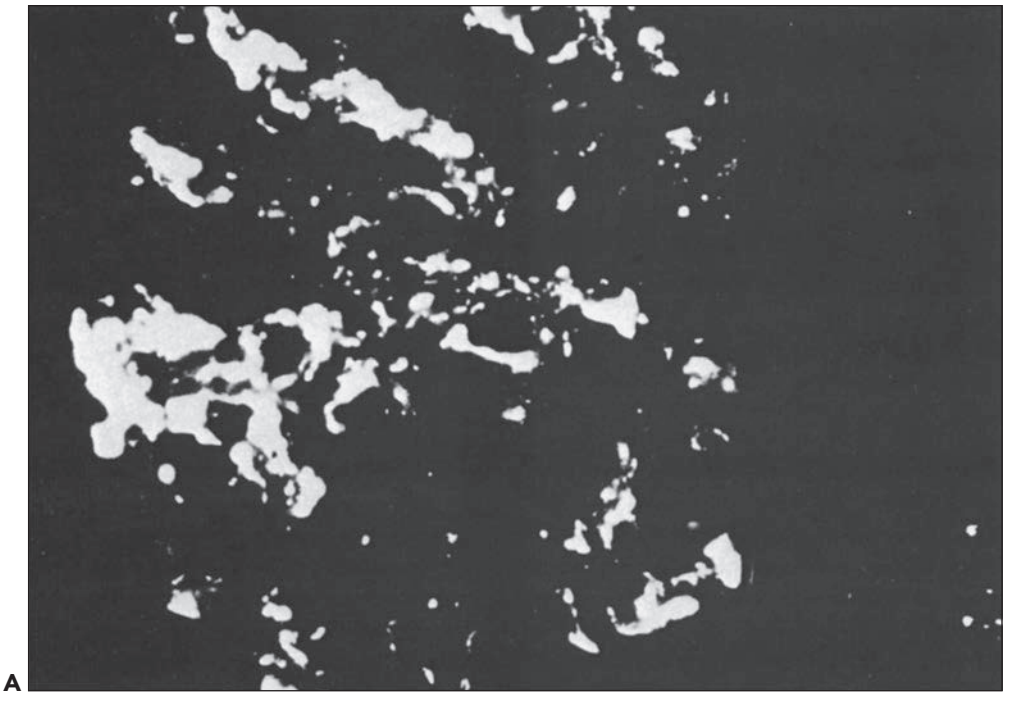
FIGURE 10.16 **A:** Immunofluorescence shows a starry sky pattern. There are diffuse and irregularly distributed fine and coarse granular deposits in the glomerular capillary walls and in the glomerular mesangial regions. (C3, ×704.) **B:** The accompanying electron micrograph shows a segment of a glomerular capillary loop from a patient with a starry sky pattern. The lumen of the glomerular capillary is totally occupied by a monocyte and by endothelial cells with prominent nuclei and swollen cell bodies. Numerous subendothelial deposits are present. (×5280.) **Inset:** A pointed, arch-like glomerular subepithelial deposit with sparse areas of higher electron density. (×17,600.) From a 56-year-old man with a 3-week history of poststreptococcal glomerulonephritis. (From Sorger K. *Postinfectious Glomerulonephritis*. Stuttgart, Germany: Gustav Fischer Verlag, 1986.)



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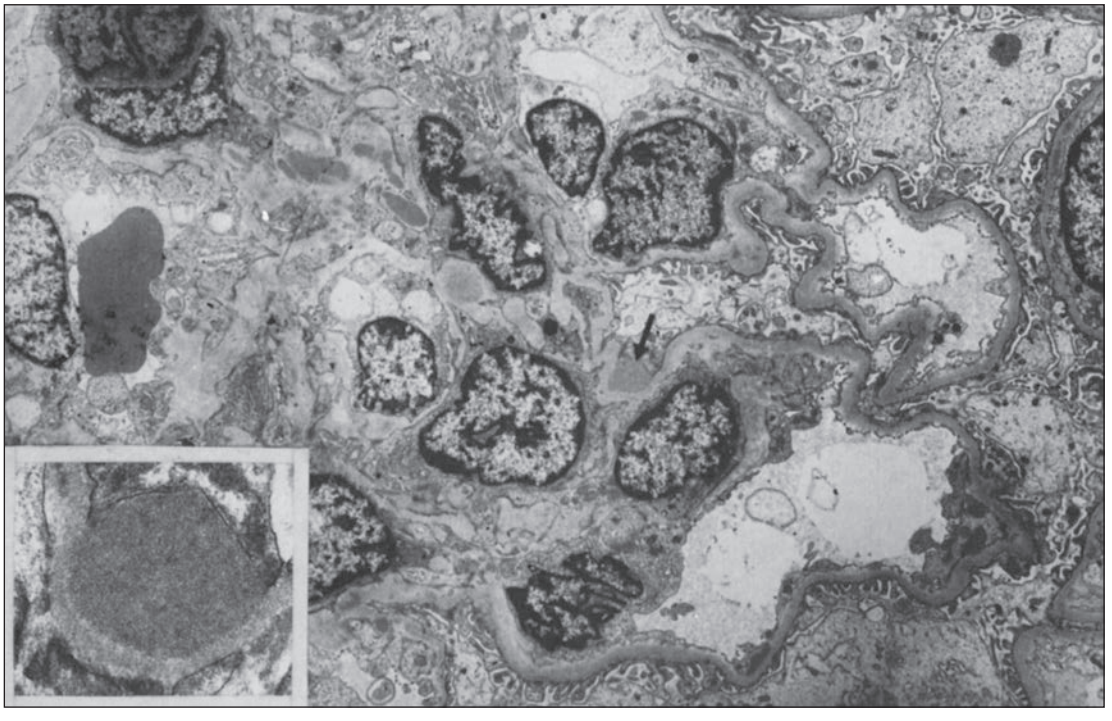


B

FIGURE 10.17 **A:** Immunofluorescence shows a mesangial pattern. Granular deposits are found in the mesangial regions, although the glomerular capillary wall remains largely negative. (C3, ×704.) **B:** The accompanying electron micrograph shows the corresponding ultrastructural appearance. A portion of the glomerulus shows marked proliferation of mesangial cells but free and open glomerular capillary lumens. Mesangial deposits are located in the mesangial matrix, and individual subepithelial deposits are present in the region of the mesangial waist (*arrow*). Less frequently, glomerular subendothelial deposits are situated along the loop. (×5280.) **Inset:** A glomerular subepithelial deposit with an almost homogeneous, comparatively pale density. (×17,600.) From an 18-year-old boy with a 5-week history of illness. (From Sorger K. *Postinfectious Glomerulonephritis*. Stuttgart, Germany: Gustav Fischer Verlag, 1986.)

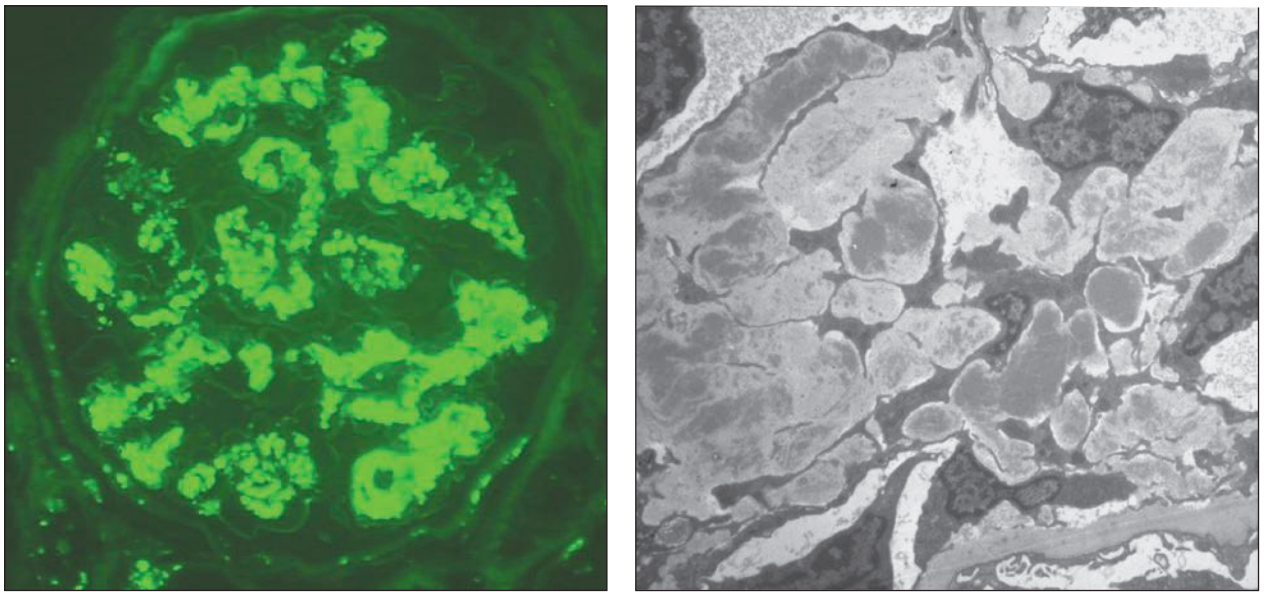


FIGURE 10.18 **A:** Coarsely granular predominantly mesangial C3 deposits in PSAGN (×400). **B:** Accompanying electron micrograph from the same patient showing mesangial electron-dense immune-type deposits. (Uranyl acetate and lead citrate, ×3000). Few subepithelial humps were also seen. The patient was a 51-year-old diabetic male with low C3, normal C4, very high antistreptolysin-O titer after a sore throat. The biopsy showed diffuse endocapillary proliferative glomerulonephritis with polymorphonuclear leukocytes in the glomeruli as well as in the interstitium. The biopsy findings suggested a very active disease. The biopsy was performed 2 months after the episode of streptococcal infection. The clinical history is supportive of PSAGN.

The starry sky pattern was noted in four of five patients with a crescentic pattern and six of seven patients with a chronic course (154). There is no evidence so far that different etiologic factors are responsible for these three subtypes (148). The individual immune response of the host and the stage of the disease are likely to play a role in their genesis. A diffuse granular pattern for IgG and, usually, C3 is also found in patients with subclinical glomerulonephritis (146,150,151) and in those with minimal urinary changes.

There is usually more intense and more constant staining with anti-C3 than with anti-IgG (145,146,150,151). In fact, it is common to see granular glomerular C3 without any demonstrable IgG. Some authors have noted the combination of granular and patchy, interrupted linear staining along the glomerular capillary wall and in the mesangial regions (59,88). At times, there seems to be an exclusively patchy, interrupted linear pattern for C3 along GBMs close to the mesangium as well as in the mesangium, with no staining for IgG (154). This interrupted linear pattern has been found most commonly either in patients in whom the initial renal biopsy was performed at a later stage than usual or in subsequent biopsies (59). C3 without the presence of IgG has been recorded in the mesangial areas with no capillary wall deposits (149). This pattern also tends to be seen in patients who undergo biopsy later than usual (i.e., several weeks after the clinical onset of disease).

Fish et al. (59) have advanced various explanations as to why C3 is present in the absence of IgG. They suggested that IgG may have been covered up by C3, thus preventing its detection. Another explanation could be that C3 reaches detectable levels for the immunofluorescence technique, while IgG remains below the threshold level of detection. It was thought that the interrupted linear deposits of C3 in the absence of IgG could be the result of a direct toxic effect of the organism (i.e., *Streptococcus*) on the glomerulus and that only a certain percentage of patients (especially those destined to experience severe acute nephritis) proceed to nodular deposits. As we will discuss briefly later, another explanation for the absence of IgG is that PSAGN may represent a transient form of C3 glomerulonephritis induced by streptococcal infection/antigens. In C3 glomerulonephritis, the glomerular deposits do not truly represent immunoglobulin-containing immune complexes.

IgM is frequently present and was recorded in more than 50% of cases in one series (131). Other authors (146) have not found IgM. IgA is usually absent (59,145,146), but it has been noted from time to time (131,150,151). If IgA immunofluorescence is strong in postinfectious glomerulonephritis, the possibility of an underlying staphylococcal infection has to be considered irrespective of presence or absence of diabetes mellitus (section on Glomerulonephritis associated with staphylococcal infections). IgE has seldom been sought; in one series of 10 patients, it was present in 5 biopsies (151). Fibrin/fibrinogen-related antigen also can be detected in the mesangial regions (as well as in the Bowman space in the crescentic form) (59,131,146).

Westberg et al. (155) noted properdin in the glomeruli in eight cases of postinfectious glomerulonephritis. In three of these patients, the pattern was granular along the glomerular capillary walls, whereas in five, it was noted in the mesangium together with C3. Various other authors (146,150) have also found properdin in several biopsies. Classic pathway components of complement, such as C1q and C4, are generally lacking (146,150,151). These various observations support the role of the alternative pathway of complement activation in postinfectious glomerulonephritis (151).

Parra et al. (51) studied the membrane attack complex in glomeruli of patients with PSAGN using monoclonal antibodies and indirect immunofluorescence. Membrane attack complex was noted along the GBM early and within the mesangial regions later in the course of the disease (a distribution similar to the deposition of C3 and C5). Rarely, immunoglobulins and complement components may be detected in renal arterioles, especially in those rare patients with necrotizing arteritis. Immunohistochemical studies by Kamitsuji et al. (156) localized intraglomerular deposits of fibrin and cross-linked fibrin in the proliferative glomerulonephritides.

As noted earlier, attempts to identify and localize the streptococcal antigen have usually failed. However, studies by Seegal et al. (157) demonstrated streptococcal antigen in over half the cases studied. Andres et al. (158), using ferritin-conjugated antibodies to type 12 streptococcal products, confirmed the presence of labeled antibody in the GBM, mesangium, and arterioles. No staining was noted in the glomerular subepithelial deposits. Some studies identify the streptococcal pyrogenic exotoxin B (SPEB) and nephritis-associated plasmin receptor (NAPlr) in the glomeruli of biopsies with PSAGN (159–161). The discrepancy between the results of various studies suggests that either the wrong antibody or the wrong antigen is being studied or that the antigen is being lost or masked in the glomeruli in these studies or that streptococcal antigens are not present in the glomerular deposits at all.

Deposits of immunoglobulins and, especially, complement may be detected in the glomeruli for months to years after apparent clinical resolution (136). The intensity of the immunofluorescence staining usually correlates with the severity of the glomerular lesion, although severe diffuse glomerulonephritis may be accompanied by unimpressive or negligible deposits.

Electron Microscopic Findings

There are many reports of the ultrastructural findings in acute glomerulonephritis (59,136,149,162–164). Many of the findings merely confirm what has long been noted at the light microscopic level, that is, increased numbers of endocapillary and infiltrative inflammatory cells in the glomerular tuft. There is swelling of both endothelial and mesangial glomerular cells, with closure of the capillary lumens by the increased numbers of cells, or swelling of the native glomerular cells. The GBMs generally appear normal in contour, thickness, and texture, although patchy thickening may occasionally be noted. There may be widening of the lamina rara interna by subendothelial electron-lucent "fluff" or fibrillar/finely granular amorphous material. The outer layer of the GBM may show "scalloping" or irregularity of the lamina rara externa and lamina densa. The GBM may contain lucent areas that may represent resolving deposits that are described and discussed later. Often, the glomerular endothelium is focally disrupted and denuded, with polymorphonuclear leukocytes directly adjacent to the denuded GBMs.

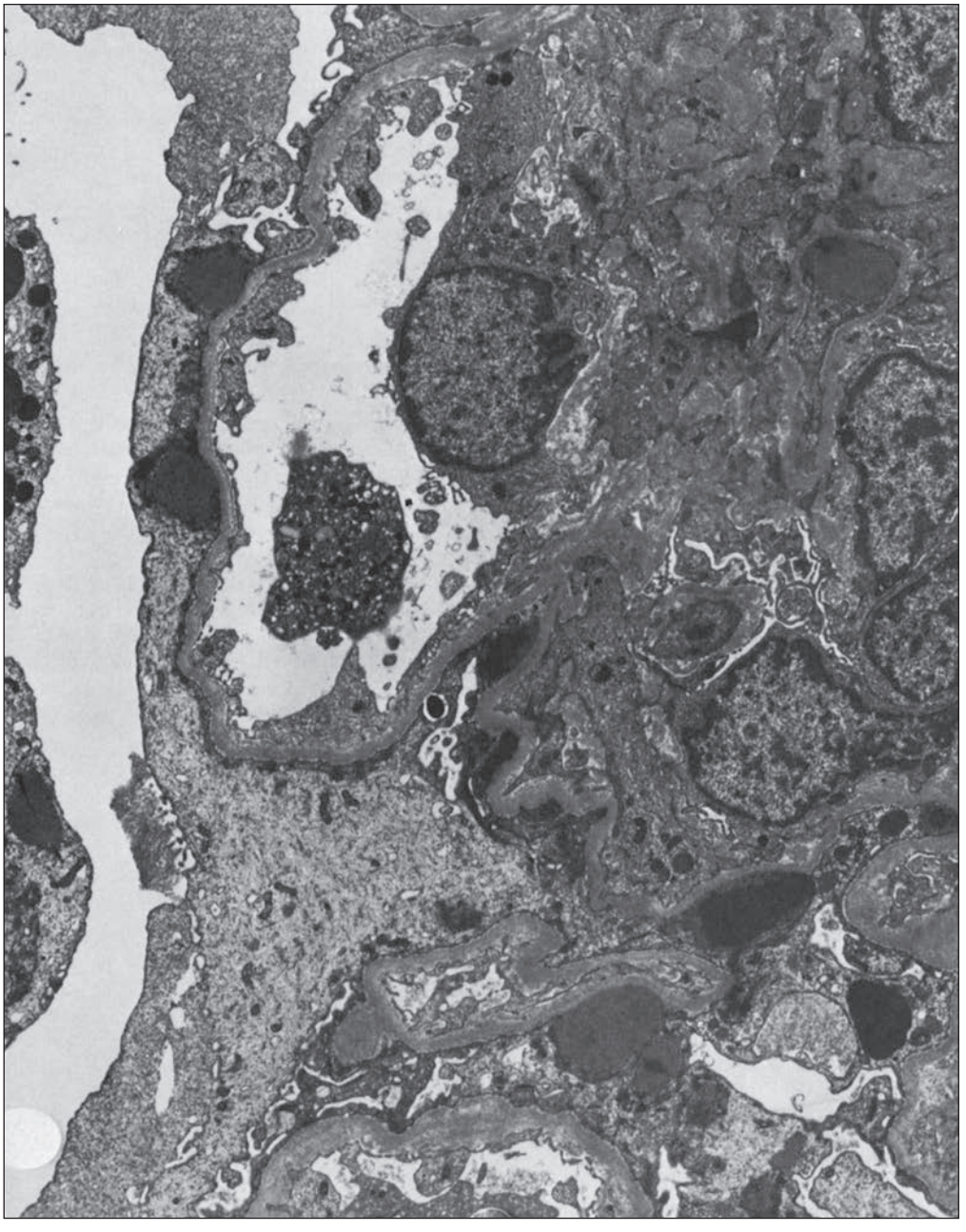
The most consistent classic diagnostic change is the presence of glomerular subepithelial electron-dense deposits, often referred to as "humps" (Figs. 10.19 and 10.20). A "hump" is a term used in renal pathology to describe subepithelial electron-dense immune-type deposits that bulge outward toward the Bowman capsule beyond the boundary of the glomerular basement membrane. They can be large or small in size. Typically, they are more unevenly distributed and more heterogeneous in size than the subepithelial deposits of membranous glomerulopathy. They are especially abundant in the first few weeks of acute postinfectious glomerulonephritis, and they decline in number afterward. They are usually less than 1 μm wide and long, but they sometimes are up to 3 μm wide and 6 μm long. In the study of Lewy et al. (98), two patients had quite elongated cigar-shaped glomerular subepithelial humps; these patients also had the nephrotic syndrome. The subepithelial humps are sometimes separated from the lamina densa by a zone of translucence that is continuous with the lamina rara externa; on other occasions, they merge with the underlying lamina densa. The deposits often bulge or project toward the cytoplasm of the overlying podocyte that often shows effacement of foot processes just above the deposit. There is frequently condensation of the microfilaments (especially actin) at the base of the effaced podocyte adjacent to the hump. The electron density of the deposits is variable, and the granularity may range from fine to coarse (165) (Figs. 10.21 and 10.22). Occasionally, the subepithelial deposits are markedly variegated with an irregular admixture of dense and less dense zones. Although there is no direct correlation between the fine ultrastructural appearance of the deposit and the clinical or nonultrastructural morphologic findings, Tornroth (164) has suggested that electron-lucent regions in the deposit may represent regions of resolution.

The deposits are usually plentiful and discrete and are most commonly found on that part of the GBM overlying the mesangial regions (i.e., the paramesangial GBM). West and McAdams (166) described a population of pediatric patients with PSAGN who had prominent hypoalbuminemia and edema with no or only very few subepithelial deposits along the glomerular basement membrane covering the mesangium. At times, the subepithelial deposits may be confluent along short stretches of the basement membranes. Similar discrete electron-dense immune-type deposits may be seen in the lamina densa and the subendothelial regions (59,66,149,163,164) (Fig. 10.23). Although the glomerular subepithelial hump is the most characteristic lesion by electron microscopy, similar subepithelial deposits are seen in various other glomerular disorders, such as membranous glomerulonephritis, MPGN, systemic lupus erythematosus, IgA vasculitis (Henoch-Schönlein purpura), and especially C3 glomerulopathy (including dense deposit disease and C3 glomerulonephritis). The subepithelial humps of C3 glomerulopathy have the greatest resemblance to the humps of PSAGN.

Discrete, electron-dense, immune-type deposits collect in the mesangial regions in classic postinfectious glomerulonephritis (149,167) (see Fig. 10.18B). The mesangial regions contain large numbers of cells whose identity is often elusive. In addition to native mesangial cells, there appear to be varying quantities of infiltrating inflammatory cells. Polymorphonuclear leukocytes are the easiest cells to identify in the glomerular mesangial regions, and they may be extensive in the exudative form of glomerulonephritis. There may be a mild increase in the amount of mesangial matrix. The Bowman space may contain debris, fibrin, large epithelial cells, erythrocytes, and polymorphonuclear leukocytes, particularly if crescents are present.

During the recovery phase (based on observations of patients undergoing serial biopsy), the glomerular subepithelial humps usually disappear within 6 weeks of the clinical

A



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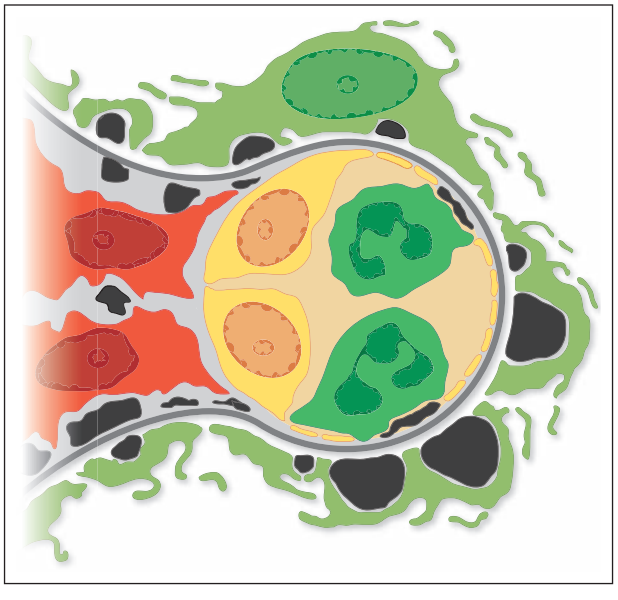


FIGURE 10.19 Electron micrograph and drawing showing the ultrastructural features of PSAGN. A: This electron micrograph shows a number of discrete electron-dense osmiophilic deposits in the subepithelial portions of the glomerular capillary walls. Some of the glomerular capillaries are narrowed or compressed, but one is patent. (Uranyl acetate and lead citrate, ×6930.) (Courtesy of Drs. William Murphy and Lillian Gaber.) **B:** Drawing depicting a single glomerular capillary with features of PSAGN including variably sized subepithelial, small subendothelial, and multiple mesangial electron-dense deposits (*black*), mesangial hypercellularity (*red*), endothelial hypercellularity (*yellow*), capillary margination of neutrophils (*dark green*), and effacement of podocyte foot processes (*light green*). Compare this drawing with features in the electron micrographs in Figures 10.15 to 10.23.

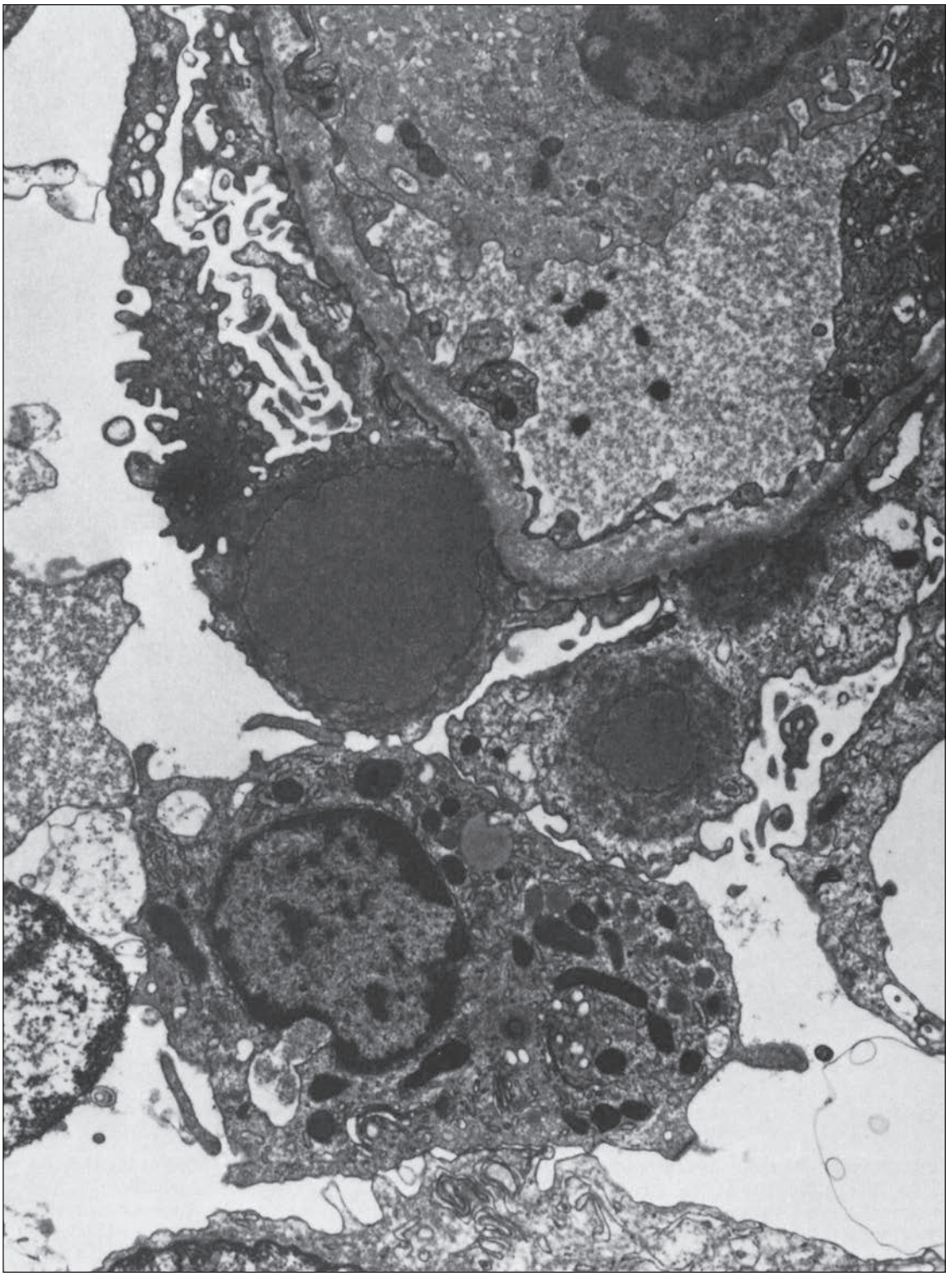


FIGURE 10.20 Glomerular capillary wall from a patient with PSAGN. There is a large, discrete, electron-dense (osmiophilic) immune-type deposit in the glomerular subepithelial region of the capillary wall. This hump, or deposit, is large and abuts on the glomerular capillary wall. There is effacement or fusion of the glomerular visceral epithelial cell over the deposit. (Uranyl acetate and lead citrate, ×10,125.) (Courtesy of Drs. Tito Cavallo and Srinivasan Rajaraman.)

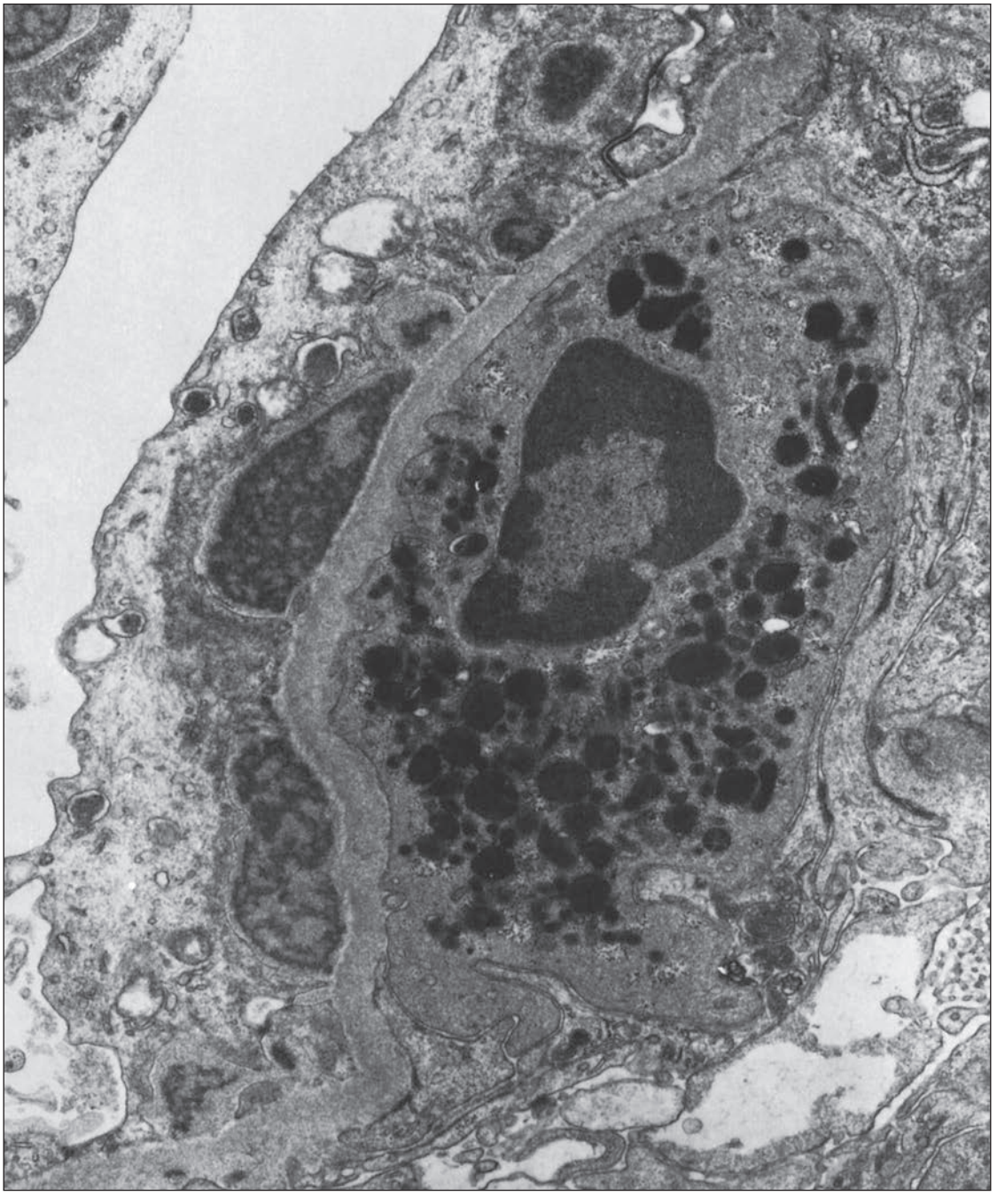
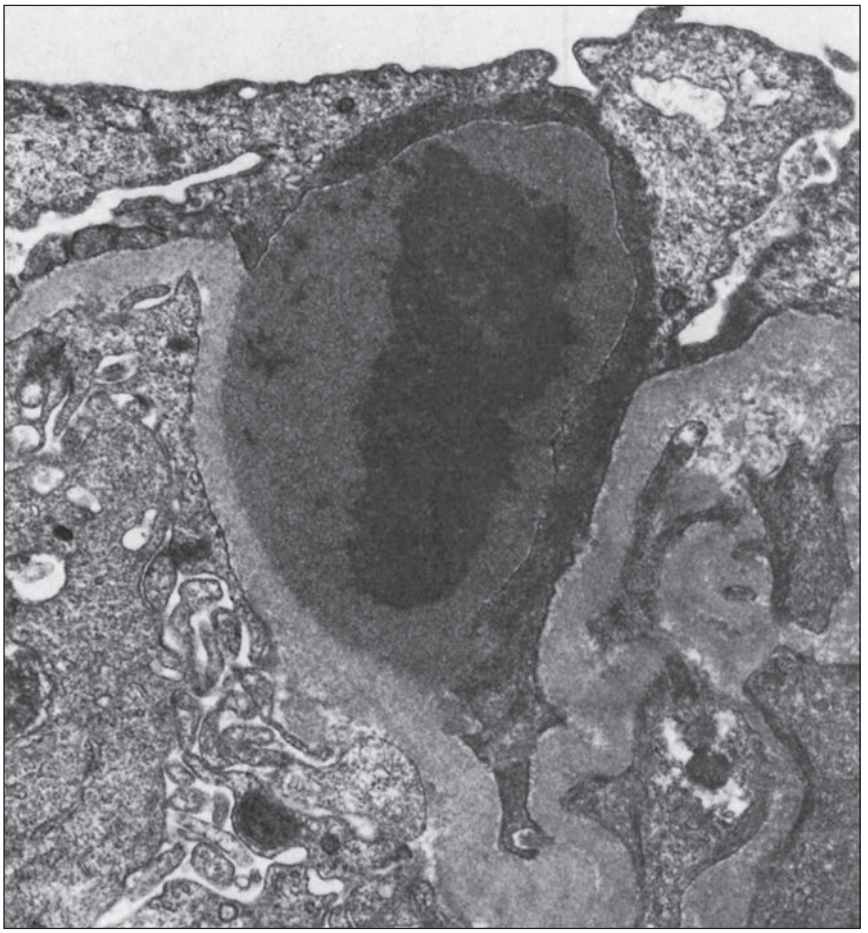


FIGURE 10.21 Electron micrograph of a segment of the glomerular capillary wall shows large, discrete, subepithelial electron-dense deposits. Note the heterogeneous or variegated appearance of these humps (i.e., varying degrees of osmiophilia or electron density). There is loss of the glomerular endothelium, and a polymorphonuclear leukocyte abuts the naked, or denuded, GBM. Polymorphonuclear leukocytes are often found near these glomerular subepithelial deposits. (Uranyl acetate and lead citrate, ×14,400.)

onset of disease (162). Sometimes, they persist for longer periods of time (163), but the clinical course in such cases is not clear. The fate of the glomerular subepithelial deposits has been studied by Tornroth (164), who has shown that the electron density (osmiophilia) of the deposits diminishes with time, so that electron-lucent regions are formed in the subepithelial zone that eventually disappear. The deposits may disappear by dissolution and passage into the blood or urinary ultrafiltrate or by pinocytotic removal by podocytes. Glomerular intramembranous electron-lucent regions have been seen in later biopsies (after 1 month) and, in some cases, these regions protruded toward the epithelium and were covered on that side by a thick layer of basement membrane–like material.



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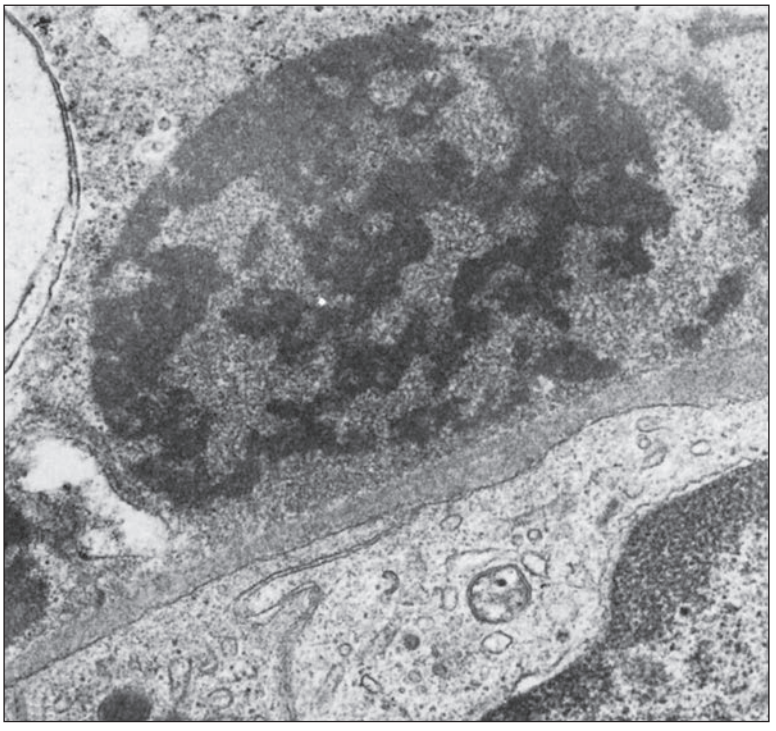


B

FIGURE 10.22 **A:** Electron micrograph of a segment of the glomerular capillary wall from a patient with typical PSAGN. Note that the electron density (i.e., osmiophilia) of the glomerular subepithelial deposit is not homogeneous. **B:** A similar variegated appearance of the deposit. These regions of greater electron lucency suggest to some investigators that the deposit is being "washed out" or is in the process of dissolution. (Uranyl acetate and lead citrate, **A,** ×20,100; **B,** ×23,450.) (Courtesy of Drs. William Murphy and Lillian Gaber **[A]** and Drs. Conrad L. Pirani and Vivette D'Agati **[B]**.)

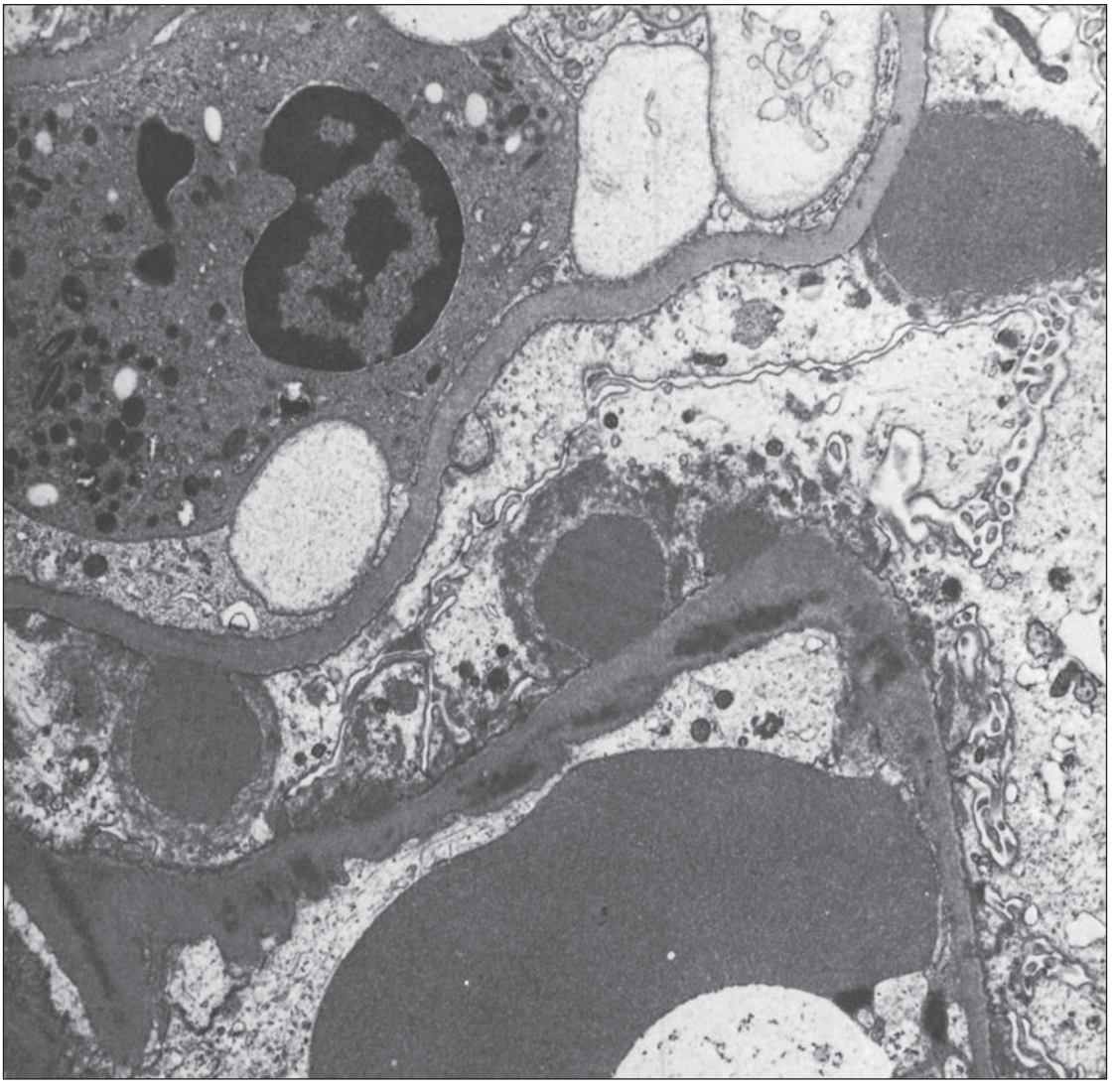


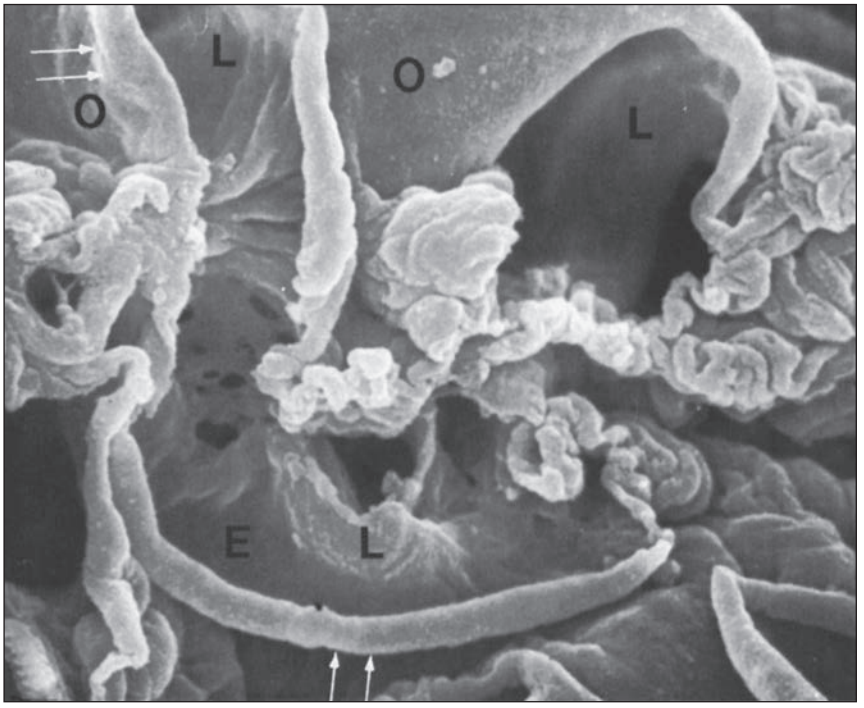
FIGURE 10.23 Electron micrograph of a segment of glomerular capillary wall from a patient with PSAGN. Glomerular subendothelial deposits can sometimes be found in these patients, although the predominant deposit is usually the typical subepithelial deposit. (Uranyl acetate and lead citrate, ×6090.) (Courtesy of Drs. Conrad L. Pirani and Vivette D'Agati.)

Other deposits were found deeper in the lamina densa, giving it a somewhat mottled appearance (164). Kobayashi et al. (163) showed that the deposits became buried in the GBM and also acquired a fine granularity with an electron density less than that of the original humps. Glomerular subendothelial deposits that were present early disappeared with time (163,164). The GBM became irregular in thickness and contour. Increased cellularity may persist in the mesangial regions for many months, even in those patients in whom the clinical picture and urinary sediment have returned to normal. In patients who have chronic proteinuria, an increase in mesangial matrix is often found. It appears that there are more subepithelial humps in those patients with a severe, protracted clinical picture than in those with immediate clinical recovery (163). Size of the deposits does not seem to correlate with clinical course or outcome (168).

Haas (136) emphasized the significance of scattered intramembranous and subepithelial remnant deposits following possible history of PSAGN. Using careful ultrastructural studies, Haas identified 57 renal biopsies with such deposits out of 543 biopsies that did not have a primary diagnosis of immune complex glomerulonephritis. Haas emphasizes the diagnostic significance of subepithelial deposits in the mesangial notch region. The mesangial notch region represents a fold of the glomerular basement membrane overlying the mesangium. Interestingly, 40% of the biopsies that, according to Haas, revealed incidental healed postinfectious glomerulonephritis also showed evidence of diabetic nephropathy (136). The author recognizes that the shortcoming of the study is that the diagnosis of incidental healed postinfectious glomerulonephritis was entirely based on morphologic (ultrastructural) findings. Authors of this chapter agree that scattered intramembranous deposits of variable electron density and deposits in the mesangial notch region occur in biopsy specimens, but these deposits are not specific for postinfectious glomerulonephritis.

Ultrastructural studies in prospective series of patients with minimal urinary findings have shown either a lack of electron-dense deposits (169) or glomerular subepithelial or subendothelial deposits. In one case, the deposits were confined to the glomerular subendothelial zone. In another series, the ultrastructural findings in patients with subclinical glomerulonephritis were studied (103). The only biopsies in which glomerular subepithelial deposits were documented were from cases overt acute glomerulonephritis by light microscopy.

Focal disruptions or gaps of the GBM have been identified (170–172) and, rarely, mononuclear cells and erythrocytes can be seen migrating through these gaps (171). Usually, however, the gaps are covered by glomerular endocapillary cells and podocytes. Bonsib (170) conducted interesting scanning electron microscopic studies following the selective removal of glomerular visceral epithelial cells by a sequence of lytic and solubilization procedures. The changes seen in acute postinfectious glomerulonephritis are illustrated in Figure 10.24. There are several distinct crater-like GBM formations (Fig. 10.24B)



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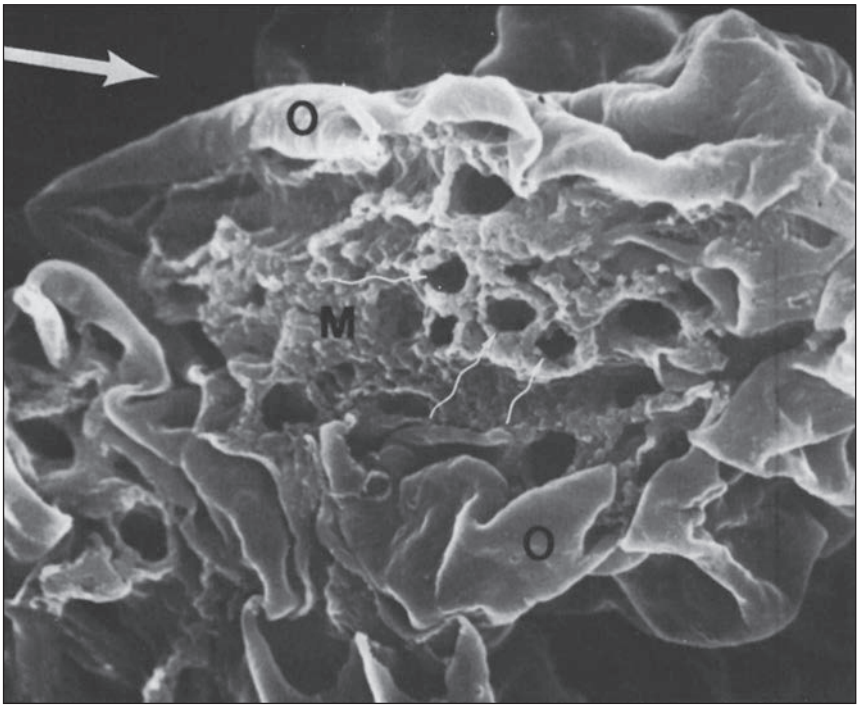
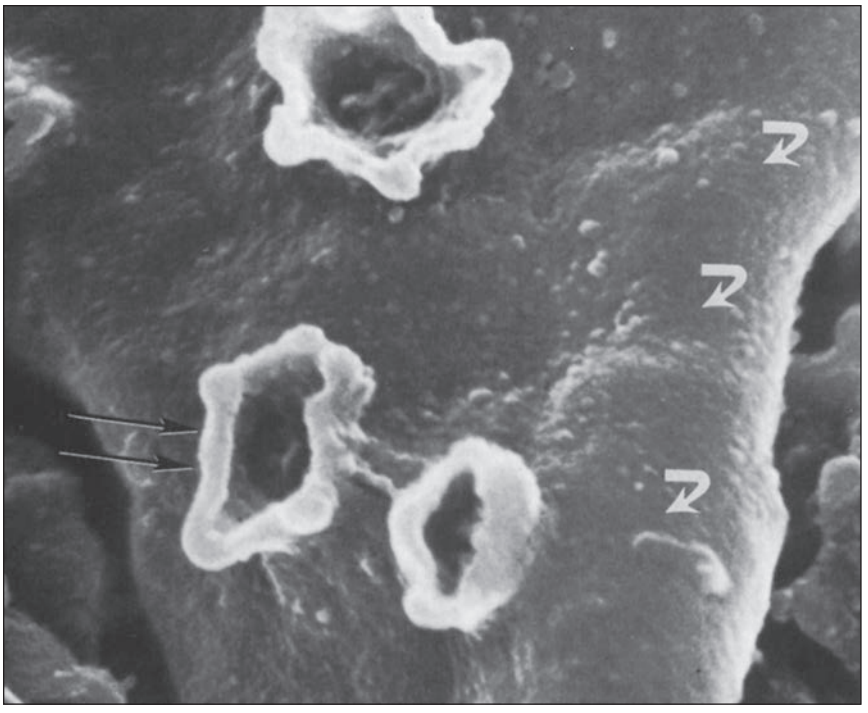


B

FIGURE 10.24 Scanning electron micrographs using the technique of Bonsib (170), in which the cellular elements have been removed by enzymatic digestion, leaving behind only the basement membrane, mesangial matrix, and other basement membrane–like substances. **A:** A segment of a normal glomerulus for purposes of orientation shows the open capillary lumen (L) and endothelial (E) aspect of the GBM (*thin arrows*). The subepithelial outer (O) surface of the GBM is also identified. **B:** A segment of a glomerulus from a patient with acute proliferation, as manifested by alterations in the mesangial matrix (M); holes (*wavy white arrows*) represent the former site of either proliferating cells or deposits. Orientation is provided by the outer (O) aspect of the GBM and urinary space (*thick white arrow*). **C:** A segment of a glomerulus from a patient with later changes seen in PSAGN, showing the subepithelial aspect of the GBM (*curved white arrows*) with reaction (*dark arrows*) to the site of deposit. (**A,** ×6375; **B,** ×2550; **C,** ×13,125.) (Courtesy of Dr. Steven M. Bonsib.)



C

FIGURE 10.24 (*Continued*)

that are empty, reflecting the solubilization of the subepithelial immune complexes. The craters are uniform in size and shape. Every glomerulus studied contained at least several craters that were located at various sites within the glomerular tuft. The case from which Figure 10.24C was prepared was unique because of the presence of subepithelial humps several years after the acute nephritic episode and because of the large size of GBM craters.

Etiology and Pathogenesis

The relationship between streptococcal infection and acute glomerulonephritis is well established and much has been learned about the mechanism of action by which the infection leads to the characteristic glomerular changes (173). It has been known for a long time that the blood and urine are sterile in patients with acute glomerulonephritis (11), and the kidney parenchyma is also sterile. The renal changes in acute glomerulonephritis were noted to be unlike those in patients with streptococcal septicemia, in which the major changes are interstitial nephritis and abscess formation. However, some studies have shown that streptococcal septicemia can lead to proliferative glomerulonephritis, a finding that is especially common in patients with acute bacterial endocarditis. Although streptococcal toxins could play a role in acute glomerulonephritis, it is unlikely, because the renal injury would be expected to occur at the height of the infection (whereas it takes place during the subsidence of the infection). Moreover, acute proliferative glomerulonephritis is not the type of morphologic change usually noted in patients with various circulating toxins; additionally, it would be anticipated that the renal changes would be proportional to the severity of the infection, which is not the case.

Immune-Mediated Disease and Experimental Studies—Historical Perspective

It is now widely accepted that acute poststreptococcal and other forms of postinfectious or infection-associated glomerulonephritis stem from an immunologic phenomenon. There is much to support an immune complex mechanism of action. Schick (9) noted the latent interval between clinical signs of infection and the onset of acute glomerulonephritis and likened it to the course of events in acute serum sickness and other allergic states. The latent interval after infection has been well documented a long time ago and usually ranges between 7 and 21 days (average, approximately 10 to 11 days).

Much of the support for immune complex pathogenesis comes from the analogy to acute "one-shot" serum sickness in the rabbit. When human acute postinfectious glomerulonephritis is compared with acute serum sickness, there are obvious similarities. Von Pirquet (174), in 1911, thought that the similarities between postinfectious glomerulonephritis and acute serum sickness syndrome supported his concept of allergy. Longcope (175) showed that parenteral administration of foreign protein in experimental animal models could induce glomerulonephritis. There is a latent interval between the injection of foreign protein and development of acute glomerulonephritis that is quite similar to the latent interval between streptococcal infection and the clinical onset of human renal disease. By immunofluorescence microscopy techniques, it is possible to demonstrate antigen, antibody, and complement in the glomeruli. This finding correlates with the formation of a variety of circulating immune complexes.

Ultrastructural studies in both human beings and experimental animal models also show similar glomerular subepithelial electron-dense "immune-type" deposits (176–179). Low levels of serum complement are found in both instances. As in the human counterpart, experimental acute serum sickness is a self-limited disease that generally resolves over a period of weeks.

Unfortunately, there is no perfect animal model for PSAGN. Many attempts have been made to induce an animal model of PSAGN by the injection of intact streptococci (180–183), crude culture supernatants (94), or specific components of the streptococci (47–66,85–116,118,122–127,130–186).

Although some of these experimental manipulations produced histologic lesions somewhat similar to the disease pattern in man, most called for the periodic administration of the putative factors thought to be involved; this, of course, does not precisely mimic the gradual release of streptococcal products that probably occurs at the site of infection in the clinical condition in humans (85). Also, many of the experimental studies were performed at a time when electron and immunofluorescence microscopy and other biochemical determinations were not available, making it difficult to carry out an adequate comparison (85).

Holm (85) and Nordstrand et al. (187) developed animal models in rabbits and mice that permitted the establishment of a focal infection using subcutaneous tissue cages and continuous monitoring of the infection and the release of streptococcal factors. According to the authors, these models simulate PSAGN clinically, histologically, and immunologically; however, not all investigators agree that this is a solid model of the human disease. Yoshizawa et al. (188) developed a rabbit model with the infusion of a peculiar streptococcal antigen called *preabsorbing antigen* (PA-Ag). After infusing 18 mg of this antigen into rabbits for 8 days, the animals developed proliferative immune complex glomerulonephritis with glomerular deposition of C3 without deposition of immunoglobulins. Electron microscopy revealed hump-like subepithelial deposits. Burova et al. (189) induced proliferative glomerulonephritis in the rabbit following repeat infusions of GAS strains bearing IgG-binding M family proteins. The animals had glomerular IgG and C3 deposition. Infusion of mutant bacterial strains, lacking the IgG-binding proteins, did not result in glomerulonephritis. The authors postulate that streptococcal IgG-binding proteins have an important role in triggering PSAGN in their model (189).

Search for the Antigen

The identity of the nephritogenic fractions of the bacteria is the subject of controversy. Rodriguez-Iturbe (20) has suggested two major possibilities: that the nephritogenic antigen is a specific component of some streptococci or that the streptococcal infection itself triggers an autoantigenic reactivity in the host. However, as noted later, it has been very difficult to establish the presence of streptococcal antigen either within the presumed immune complexes in the glomeruli or in the circulating immune complexes. The potential nephritogenic streptococcal antigens that have been proposed to play a causative role are summarized in Table 10.3.

Treser et al. (194) described how IgG fractions from the serum of patients with acute postinfectious glomerulonephritis caused staining of the glomerular capillaries and mesangium of patients with early-stage acute glomerulonephritis. This staining was abolished if the serum fraction had been previously absorbed with frozen and thawed nephritogenic β-hemolytic streptococcal organisms. The plasma membrane appeared to be the fraction responsible. This staining activity was not abolished by absorption with other bacteria, and the antisera against streptococcal plasma membranes had staining properties similar to those of the sera of the patients with acute postinfectious glomerulonephritis. The conclusion drawn was that the streptococcal plasma membrane constituents were present in the glomeruli of patients with PSAGN (195). These same workers (195) were able to show antigenic sites in the mesangial matrix and on the glomerular subendothelial region using immunoferritin ultrastructural techniques (195). There is some evidence that antibodies to streptococcal cell membrane antigens may cross-react with antigens in the glomerular basement membrane (221). Studies by Lange et al. (196) and others (158,222,223) have suggested that free antigen may be found in situ in the glomeruli and is available for the deposition of circulating antibodies. Cationic antigens, which are able to penetrate the fixed glomerular polyanionic charge barrier of the capillary wall, could be candidates for triggering an in situ immune complex reaction (119,224,225).

TABLE 10.3 Potentially nephritogenic streptococcal antigens

Antigen	References
Streptococcal M protein and its fractions	(190–193)
Endostreptosin	(194–201)
Streptokinase	(202–204)
Nephritis strain–associated protein or streptococcal pyrogenic exotoxin exotoxin B or Nephritis plasmin binding protein	(85,186,205–212)
Nephritis-associated plasmin receptor or streptococcal glyceraldehyde 3-phosphate dehydrogenase	(161,213–217)
Preabsorbing antigen	(188,218–220)

Streptococcal M protein is a strong candidate for the relevant antigenic bacterial fraction (190). M protein fractions can complex with fibrinogen and localize in glomeruli (226), and glomerulonephritis can be induced with injection of M protein-M protein/fibrinogen complexes. M protein may be antigenically cross-reactive with the GBM (191). However, Treser et al. (227) have suggested that the nephritogenic fraction is different from the M protein. Serum from patients convalescing from poststreptococcal glomerulonephritis, when labeled, could identify free antigenic sites in renal biopsy specimens showing poststreptococcal glomerulonephritis; the fact that this serum had these antibodies independent of the M type of the original infection suggested that a non–M antigen was present in the glomerulus. In contrast, Mori et al. (192) found that IgG titers against the C region of the M protein of group A streptococci are elevated in patients with PSAGN compared with patients with uncomplicated streptococcal pharyngitis, chronic glomerulonephritis, and healthy controls. IgG titers against the A and B regions of streptococcal M protein were not different between these groups.

Several streptococcal fractions have been studied in search of the trigger for glomerulonephritis. One streptococcal fraction, endostreptosin, has been extensively studied (194–201). This antigen is demonstrable in the glomerulus only during the initial phase of acute glomerulonephritis and reacts with antibodies present in the convalescent sera of patients with acute glomerulonephritis. In the late phases of the disease, the antigen can no longer be detected, presumably because all the previously noted antigenic sites have been covered by the specific antibody.

Endostreptosin's molecular weight is between 40 and 50 kDa (186) and is most likely derived from the streptococcal cytoplasm. Seligson et al. (200) have suggested that acute

elevations of endostreptosin titers are generally diagnostic of PSAGN. Although low titers of antibody have been found in as many as 70% of normal individuals, significantly higher titers of antibodies are found in patients with poststreptococcal glomerulonephritis (200). Most patients with acute rheumatic fever do not have these high levels of antibody titer. Thus, Lange et al. (198) believe that elevated levels of antibody to endostreptosin are diagnostic of postinfectious glomerulonephritis and correlate well with the course of the pathologic disease process. Experimental studies by Cronin and Lange (197), using Wistar Furth rats, showed deposition of endostreptosin along the GBMs 1 day after injection of immunoaffinity-isolated endostreptosin. Rats killed on days 8 to 12 showed increasing deposition of IgG and C3 with diminished staining for endostreptosin. No antiendostreptosin antibodies were detected in the sera in the first 3 days, whereas rats from day 4 onward had low levels of these antibodies. According to these authors, endostreptosin does not appear to be immunologically related to streptococcal exoenzymes or the streptococcal cell wall (197). Endostreptosin is similar to the preabsorbing antigen described by Yoshizawa et al. (188,201,218) and Holm et al. (228).

Yoshizawa et al. (218) isolated a 43-kDa protein from nephritogenic streptococci ("preabsorbing antigen") and noted identical precipitation lines by immunodiffusion between rabbit antisera against preabsorbing antigen and the sera of patients with PSAGN. Antibodies to preabsorbing antigen were found in 30 of 31 patients with acute glomerulonephritis but only very rarely in control groups. The preabsorbing antigen is present in the glomeruli in the early phases of human PSAGN and appears to activate C3 by the alternate pathway (factor B). These authors developed a rabbit glomerulonephritis model by administering preabsorbing antigen for 8 days (188). Light microscopy revealed proliferative glomerulonephritis; immunofluorescence showed glomerular capillary and mesangial C3 deposits; and electron microscopy revealed occasional subepithelial hump-like deposits. Interestingly, IgG and preabsorbing antigen were not detected in the glomerular deposits (188).

Villarreal et al. (206) identified an extracellular protein unique to nephritogenic strains from cultures of type 12 organisms. This fraction (called *nephritis strain–associated protein, NSAP*) was noted in 56% of renal biopsies with signs of poststreptococcal glomerulonephritis; it was not found in biopsies from patients with other forms of nonstreptococcal glomerulonephritis or rheumatic fever. The vast majority of patients with glomerulonephritis had serum antibodies to the fraction (205). Holm et al. (85,207) suggested that the ability of NSAP to convert plasminogen to plasmin (possibly in situ) might be related to many of the pathologic events taking place in PSAGN. The plasmin formed by the interaction between NSAP and plasminogen splits the C3 molecule and activates the alternative pathway of complement activation, thereby initiating the inflammatory glomerular response. Interaction with plasmin or plasminogen can cause glomerular damage by degrading the GBM through the activation of latent metalloproteinases or collagenases. The circulating or in situ immune complexes can then move across the altered GBM and accumulate as subepithelial "humps." NSAP (also called streptococcal pyrogenic protease exotoxin B [SPEB] or nephritis plasmin-binding protein [NPBP]) can directly cause tissue destruction by cleaving extracellular matrix proteins including fibronectin and vitronectin and might aggravate inflammation via superantigenic effects on the immune system, similar to staphylococcal enterotoxins A and C. SPEB can directly bind to class II MHC molecules on antigen-presenting cells and specific Vβ chain of T-cell receptors causing proliferation and massive activation of T cells, liberating copious amounts of Th1 cytokines. Antibodies to streptococcal glyceraldehyde 3-phosphate dehydrogenase (GADPH) and SPEB (NSAP) have been found specifically in patients with poststreptococcal glomerulonephritis and persist for 10 years and 1 year, respectively, after acute attack, thought to give long-lasting immunity (208). The genes for both these proteins are highly conserved among isolates of group A streptococci. Studies using double immunofluorescence staining methods for NSAP and collagen type IV demonstrate that NSAP localizes to the inner side of the glomerular capillary walls (209,210,229).

NSAP has a subunit of 46 kDa. The molecule has been isolated and purified (186); it has antigenic, biochemical, and structural similarities to streptokinase from group C streptococcal organisms, and it binds to plasmin and is a plasminogen activator. This protein is not related to group A streptokinase (230) or to a recently described streptococcal dehydrogenase protein according to these authors (213,230). Amino acid sequence analysis and immunologic reactivity studies suggest that this protein is the SPEB precursor (previously termed *zymogen streptococcal proteinase precursor*) (213).

Vogt et al. (214,231) isolated and identified a number of different cationic proteins from nephritogenic streptococci. Cationic moieties are known to have affinity for the GBM. Publications from the group at the Rockefeller University indicate that the cationic protein described by Vogt et al. (214,231) is structurally identical to SPEB (159). This group and other investigators suggest an important role of SPEB in PSAGN (159,232). Cu et al. (159) found that SPEB antibodies were present in the sera of patients with PSAGN significantly higher than in patients with acute renal failure, scarlet fever, and normal sera. Following injection of SPEB into male Sprague-Dawley rats, Romero et al. (232) found that inflammatory cells are accumulated in the glomeruli and in the interstitium. The same authors also found elevated levels of apoptosis in human SPEB-treated leukocytes (233). Savill (234) also proposes a role of apoptosis in the pathogenesis of PSAGN.

Glurich et al. (235) found that a number of surface proteins from nephritogenic streptococcal strains (M type 12) bind to the rabbit kidney in vitro and in vivo. Streptococcal components bound in vitro to several constituents of the glomerular capillary walls (heparan sulfate, laminin, and collagen IV), suggesting that bacterial proteins, when released by these bacteria during infection, become planted antigens that contribute to the pathogenesis of acute glomerulonephritis.

Some promising studies have suggested that streptokinase is the most important bacterial product leading to PSAGN (202–204). Holm et al. (202), in a steel net tissue cage model of "slow release" in a rabbit model of acute glomerulonephritis, showed loss of nephritogenic potential by deletion of a streptokinase gene (in a nephritogenic type 49 strain) in a molecular construct prepared by electrotransformation.

Nordstrand et al. (203,204) demonstrated an important role for streptokinase in the pathogenesis of PSAGN in their mouse model. Nephritogenic group A streptococci could cause glomerulonephritis only if they contained the nephritis-associated

streptokinase gene (SKA1). Strains with deleted SKA1 gene did not cause glomerulonephritis in their mouse model (203,204). Studies conducted by Mezzano et al. (236) and others (237,238) have failed to make a strong connection between streptokinase and PSAGN. Mezzano et al. (236) did not find any unique reactivity to group A streptokinase in the sera of patients with PSAGN, and they also failed to establish the presence of streptokinase in renal biopsies early in the course of disease in 10 patients with PSAGN. Okada et al. (238) studied the major variable region of streptokinase genes of *S. pyogenes* strains isolated from patients with and without PSAGN. The major variable region of the streptokinase gene did not show any apparent relationship to poststreptococcal glomerulonephritis, suggesting that unique classes of streptococcal streptokinase do not play a role in the pathogenesis of PSAGN (238).

Considerable attention has been given to NAPlr in PSAGN (213,214,217). NAPlr is proved to be homologous to streptococcal glyceraldehyde-3-phosphate dehydrogenase (GAPDH). Yoshizawa et al. (161) found that 92% of patients with early PSAGN had anti-NAPlr in their serum and 80% of the renal biopsies of early cases showed deposits of NAPlr. In a subsequent study, authors showed that distribution of glomerular plasmin-like activity and glomerular NAPlr is identical and postulated that NAPlr traps and maintains plasmin in the active form in the glomeruli, which, in turn, induces glomerular damage (215). Those authors propose that following infection with a nephritogenic strain of group A streptococci, NAPlr will be released into the circulation, which will bind to the glomerular mesangium and the glomerular basement membrane. This bound NAPlr traps plasmin and maintains its activity, which in turn may degrade the glomerular basement membranes by itself or through activation of matrix metalloproteinases (216). Plasmin activity may also attract neutrophils and macrophages to the site of inflammation. The circulating immune complexes, therefore, can easily pass the damaged glomerular basement membrane and accumulate along the subepithelial surface as large subepithelial deposits (215). Although these studies and the hypothesis are very attractive, Rodriguez-Iturbe points out that Yoshizawa et al. studied patients with upper respiratory infection; therefore, the results may not be applicable to PSAGN following skin infections (239). Transient immunostaining for NAP1r antigen has been demonstrated in the glomeruli during the early stages of PSAGN, and the staining diminishes within several months. This antigen is reported to be localized in mesangial cells, endothelial cells, and neutrophils, similar to the localization of SpeB antigen (215,239). However, glomerular NAP1r deposition has also been found in other glomerular diseases including IgA vasculitis (Henoch-Schönlein purpura), lupus glomerulonephritis, and dense deposit disease (240,241). Therefore, the specificity of this nephritogenic antigen for PSAGN is somewhat questionable.

In summary, the search for antigens responsible for the development of PSAGN continues. In fact, there is still no proof that immune complexes containing streptococcal antigens are causing PSAGN. A large number of streptococcal proteins have been hypothesized to be important in the causation of PSAGN, through their binding to plasmin, release of matrix metalloproteinases, destruction of glomerular capillary basement membranes, and recruitment of inflammatory cells. Lack of specificity of these proteins to PSAGN alone is what plagues the findings. Another important obstacle is the fact that not only *Streptococcus* but a large number of other infectious agents can cause immune-mediated glomerulonephritis, suggesting that not one but a large spectrum of bacterial proteins may be capable of binding to glomerular matrix and basement membranes and causing tissue injury, complement activation and recruitment of inflammatory cells to the site.

Circulating Immune Complexes and Cryoglobulins

Ninety percent of patients with PSAGN have elevated serum levels of IgG and IgM. Various techniques have been used to detect circulating immune complexes (201,242–246). Circulating immune complexes (as measured by C1q-binding activity) are found in the serum of two thirds of patients in the 1st week of the disease. After 4 weeks, they are evident in approximately 20% of patients (246,247). It has been suggested that circulating immune complexes correlate with the severity of renal disease and with the detection of renal immune deposits (224). Rodriguez-Iturbe et al. (83,239) and others (245), however, did not find a correlation between this assay and the intensity of the clinical manifestations. Lin (244) found that patients with poststreptococcal glomerulonephritis had significantly elevated levels of circulating immune complexes during the acute phases; 6 months later, the levels were only slightly elevated, and by 9 months after the initial attack, no circulating immune complexes were detectable. In patients who had persistent hematuria and proteinuria, however, immune complexes continued to be detected during this time.

Cryoglobulins (usually type III) are frequently found in patients with PSAGN (131,145,248). In fact, Rodriguez-Iturbe (20) noted cryoglobulins in two thirds of patients in the first 2 weeks of the disease. Most of these studies have found that the cryoglobulins contain combinations of IgG, C3, and/or IgM. IgA is less commonly found in precipitates. Streptococcal antigens are not generally evident in the cryoprecipitates (248). McIntosh et al. (248) suggested that the detection of serum cryoglobulins is a better indicator of clinical and morphologic renal disease than measurement of serum complement.

Serum from patients with PSAGN contains components of mesangial matrix and GBMs (194–196,221,223), and nephritogenic antigens have been observed in circulating immune complexes in patients with PSAGN (but not in patients with acute rheumatic fever) (219,248). Yoshimoto et al. (249) noted high levels of antibodies to streptococcal cell membrane antigens. Kefalides et al. (223) recorded that the sera from patients with postinfectious glomerulonephritis contained antibodies against major macromolecular components of the GBM (i.e., type IV collagen, laminin). Because circulating immune complexes of various types have been observed in patients with streptococcal infections alone (without glomerulonephritis), it is possible that these complexes represent a systemic inflammatory response rather than being the cause of glomerular damage (201).

Complement and Complement Receptors

The fact that PSAGN is associated with low levels of serum complement has been proven by many investigators (98,106,199,250–252). Serum complement levels are almost always low in the acute stages of PSAGN. Rodriguez-Iturbe (20) noted depressed levels in 93% of patients. Lange et al. (196) suggest that in the acute stage of a clinical disease thought

to be PSAGN, the absence of a low complement level indicates that the patient does not have PSAGN. It is worth noting that patients with postinfectious glomerulonephritis, not related to streptococcal infection, may have normal serum complement levels more commonly than patients with PSAGN (2). Serum complement levels rise to normal levels after several weeks and almost always return to normal within 6 weeks. In more than half the patients of Fischel and Gajdusek (251), normal serum complement levels had been attained within 3 weeks of the acute clinical onset of disease. All 32 patients studied by Cameron et al. (250) had regained normal serum complement levels within 4 months and all but 2 within 2 months.

It has been suggested that the persistence of low serum complement levels is associated with a poor prognosis (252); however, in such patients, renal biopsy must be performed to exclude other glomerular diseases, such as MPGN or C3 glomerulopathy. Most authors have not found a correlation between the level of serum complement and the degree of proteinuria (251), indicating that complement was not diminished because of loss of complement in the urine. As noted earlier, the low serum complement level is evidence in favor of an antigen-antibody reaction. Because the serum complement level rises soon after the acute phase of the disease, it is generally not thought that there is a generalized disorder in the synthesis of complement (251). One study (253), however, did show that children with postinfectious glomerulonephritis had depressed synthesis of C3 relative to normal subjects. Serum complement levels are low even in patients with subclinical glomerulonephritis (103,106).

The serum complement studies have measured either total hemolytic complement or components of the complement cascade, such as C3. Many studies have shown that although serum levels of C3 are depressed, the classical pathway components of the complement cascade, such as C1q, C2, or C4, have been normal or only slightly depressed (52,65,250). These studies suggest that the alternative pathway of complement activation is operating, a suggestion strengthened by immunofluorescence studies that show the deposition of properdin in the glomeruli (131,155). Other studies that reveal C3 deposition, but no apparent IgG (59,145,150,151,254), also suggest that the alternative pathway often operates in acute postinfectious glomerulonephritis. Matsell et al. (255) have found terminal complement pathway activation and the local generation of terminal complement complexes in patients with PSAGN. All patients had elevated plasma C5b-9 concentrations at the onset of clinical nephritis; there was an inverse linear relationship with time after onset of clinical disease. Renal biopsies of five patients established colocalization of C5b-9, S-protein, and C3 deposition along the glomerular capillary walls and mesangial areas (255).

Other studies, by Tanuma et al. (256), suggest the possibility of accelerated decay of the cell-bound C4b2a complex by serum of patients with both PSAGN and MPGN. This accelerated decay of C42 convertase might interfere with the clearing and processing mechanism(s) of circulating immune complexes. C3 nephritic factor (C3NeF) autoantibody activity (which stabilizes the alternative pathway convertase complex) has been detected in the serum of children with PSAGN. This finding was associated in the acute phase with decreased plasma levels of C3. C3NeF activity declined within weeks as the plasma levels of C3 progressively returned to normal. C3NeF activity was undetectable within 1 to 4 months following normalization of the plasma C3 levels (257).

Neuraminidase (sialidase) has been implicated in the pathogenesis of PSAGN. Neuraminidase-treated leukocytes preferentially accumulate in the kidneys with PSAGN and a large number of the infiltrating inflammatory cells represent desialized leukocytes (255). Interestingly, Fujita et al. (258) indicate that neuraminidase plays a potentially important role in the activation of the alternative complement pathway. Based on their in vitro data and on in vivo experience, they postulate that increased neuraminidase levels may be responsible for complement activation and subsequent low complement levels in PSAGN (258). Furthermore, they also found that free sialic acid might have an inhibitory effect on complement activation and may be implicated in the improvement of hypocomplementemia, if neuraminidase levels decrease (258). Somewhat related to neuraminidase-mediated complement activation is the third pathway of complement activation, the lectin pathway (259). Lectin pathway activation starts with molecules consisting of mannose-binding lectin (MBL) and two associated serine proteases (259). In many forms of infections, the lectin pathway of complement activation is a very important first line of host defense because of its immunoglobulin-independent opsonizing ability. Ohsawa et al. (219) postulated that the lectin pathway is also important in PSAGN and detected MBL in the glomeruli in kidney biopsies from patients with PSAGN. Mannose-binding lectin recognizes mannose and *N*-acetylglucosamine residues and, to a lesser degree, also galactosamine residues. Group A streptococci carry *N*-acetylglucosamine in the cell wall polysaccharides, which can be recognized by molecules containing MBL with subsequent complement activation. A study from Sweden (193) examined sera from 56 children and 17 adults with PSAGN and found no or minor concentrations of MBL in these patients, which does not support a role of the lectin pathway of complement activation in the pathogenesis of PSAGN.

The Relationship of Abnormal Alternate Pathway Complement Activation, C3 Glomerulopathy, and PSAGN

C3 glomerulopathy is a recently described entity associated with abnormalities in alternate pathway complement activation. C3 glomerulopathy includes dense deposit disease as well as a histopathologic spectrum of disease called C3 glomerulonephritis. C3 glomerulonephritis lacks the diagnostic intramembranous deposits of dense deposit disease but has extensive deposits of C3 with little or no accompanying IgG. The light microscopic features of C3 glomerulonephritis vary from focal or diffuse proliferative to MPGN. The disease is detailed in Chapter 9 of this book. Obviously, C3 glomerulonephritis and PSAGN have many similarities. In both diseases, the serum C3 levels are low, and both are associated with alternative complement pathway activation. IgG deposits are not seen in the glomeruli in C3 glomerulonephritis, but they are also frequently absent in PSAGN. Theoretically, PSAGN may represent a transient acute form of C3 glomerulopathy with direct alternative pathway complement activation induced by streptococcal infection without the need for mediation by immune complexes. As detailed above, streptococcal antigen can activate the alternate complement pathway, and it is

theoretically possible that in patients who have mild underlying complement regulatory deficiency, streptococcal infection could evoke an acute glomerulonephritis. There were several recent reports supporting this hypothesis (260–262). Vernon et al. report a 7-year-old female who clinically developed typical symptoms of PSAGN following streptococcal pharyngitis. However, she developed persistent hematuria, proteinuria, and persistently low C3 levels, and the kidney biopsy performed 1 year after presentation revealed proliferative glomerulonephritis with prominent glomerular capillary C3 deposits. Ultrastructural examination showed intramembranous subendothelial and occasional hump-like subepithelial deposits. The patient was found to be heterozygous for factor H–related protein V deficiency, which is responsible for one form of C3 glomerulopathy. Authors postulate that the streptococcal infection and the heterozygous complement factor H–related protein V deficiency were responsible for the glomerular disease (262). Sandhu et al. (260) described a similar clinical course in a 63-year-old male; however, in their patient, genetic workup was not performed. Sethi et al. from the Mayo clinic reported on 11 patients with atypical postinfectious glomerulonephritis. These patients had a clinical presentation suggestive of acute postinfectious glomerulonephritis; however, their symptoms proved persistent. They found a variety of defects in complement-regulating proteins and antibodies to the C3 convertase in their patients. They also suggest that after bacterial infections, a so-called postinfectious glomerulonephritis may turn into an overt C3 glomerulonephritis if patients have an underlying deficiency in regulation of the alternate pathway activation. These included the presence of C3 nephritic factor, factor H gene mutation, as well as complement factor H–related protein V mutation (261). These authors also indicate that, following bacterial infection and subsequent alternate pathway complement activation, a persistent glomerulonephritis consistent with C3 glomerulonephritis can develop if the patients have an abnormality in the proteins regulating alternate complement pathway activation. These are intriguing data that will need further in-depth investigation. It is theoretically possible that at least a subpopulation of patients with PSAGN has a mild genetic or acquired deficiency in one of the alternate pathway complement regulatory proteins that could trigger uncontrolled complement activation with subsequent glomerulonephritis. Apparently, most patients, particularly children, recover from the disease, but if the complement regulatory protein abnormality is more prominent, the glomerulonephritis may become persistent and progressive. This theory might explain why significant amounts of immunoglobulins are frequently absent from the glomerular deposits and why no reliable pathogenic antigen has been identified in spite of extensive research.

Other Pathogenic Mechanisms of Postinfectious Glomerular Inflammation

In addition to the classic concept that streptococcal organisms produce a protein fraction that is immunogenic and causes an antibody response, there is also a theory that the streptococcal organism may trigger an autoimmune disease by inducing antigenic modification of normal autologous proteins (143,263–266). Some authors proposed that acute postinfectious glomerulonephritis is in part or totally an autoimmune immune complex disease in which autologous IgG is modified by a number of streptococcal enzymes or products of the bacterial organism released during infection (e.g., neuraminidase). In this way, IgG becomes autoimmunogenic and stimulates the production of anti-IgG antibodies (205,263,264).

Marin, Mosquera, and Rodriguez-Iturbe (254,264) reported that nephritogenic streptococci are frequently neuraminidase producers. Others have described similar findings (267), although not all researchers agree (268). Circulating anti-immunoglobulins have been detected in half of patients (20), and glomerular fixed antiglobulins have been encountered in renal biopsy specimens from patients with poststreptococcal glomerulonephritis (202,248,263). IgG eluted from the kidney shows anti-IgG reactivity (259). Rheumatoid factor also has been noted in patients with PSAGN. Vilches and Williams (269) found persistent anti-DNA antibodies and DNA-anti-DNA complexes in two patients with poststreptococcal glomerulonephritis. Fillit et al. (270) noted that sera from patients with poststreptococcal glomerulonephritis contained antibodies to glomerular heparan sulfate proteoglycan. Kemeny et al. (220) demonstrated intact linear GBM staining with monoclonal antibodies to heparan sulfate proteoglycan in patients with acute poststreptococcal glomerulonephritis (as seen in normal kidneys) in contrast to most other forms of glomerulonephritis in which the staining was lost.

An experimental rabbit model of streptococcal infection–induced glomerulonephritis emphasizes the role of streptococcal IgG FC-binding proteins. These authors postulate that after streptococcal infection, human IgG will bind to the streptococcal FC receptors and will elicit an anti-IgG antibody response. This antibody response will then result in the glomerular deposition of IgG and complement-containing immune complexes (189). They were able to inhibit this glomerulonephritis with the administration of IgG FC but not with FAB fragments supporting the importance of FC-mediated pathogenesis in this form of experimental glomerulonephritis.

Certain molecules of virulent GAS contain structural elements that appear to be capable of evoking cross-reacting autoimmune reactions with certain host tissues (271,272). Heart reactive antibodies are produced in rabbits immunized with GAS, and these antibodies bind to certain cardiac components. These antibodies are different from those detected in patients with other nonstreptococcal, nonrheumatic cardiac disorders. The titer of antibodies to heart sarcolemmal sheath proteins is also higher in children with PSAGN (211). Antimyosin antibodies, found in patients with acute rheumatic fever, have also been discovered in patients with PSAGN. Antimyosin antibodies in acute rheumatic fever share a common determinant or idiotype with antibodies in poststreptococcal glomerulonephritis. Kraus and Beachey (220) have identified a renal autoimmune epitope in the M protein molecule of streptococci. The work of Kraus and Beachey (271) and others incriminates certain proteins (M protein) of streptococci in molecular mimicry between *Streptococcus* and host tissues. Thus, immune complex deposition in tissues expressing antigens cross-reactive with infectious agents could be important in the pathogenesis of PSAGN.

Cell-mediated mechanisms have traditionally not been considered an important factor in the initiation of acute glomerular injury. Increasingly, however, they have been studied and are now thought to play an ancillary role in the progression of acute glomerulonephritis to a chronic stage (273–276).

They also may be important in those patients with severe acute postinfectious glomerulonephritis who have few immune deposits. Zabriskie et al. (275,276) have suggested that proteins from nephritogenic streptococci may deposit in the glomerulus and release a glycopeptidase capable of altering the composition of the GBM and exposing new antigens. Progression might take place through antibodies on sensitized lymphocytes directed against the "new" GBM antigens. The same researchers demonstrated that lymphocytes from patients with nonresolving poststreptococcal glomerulonephritis showed significant inhibition of cell migration and increased DNA synthesis in the presence of GAS antigens; lymphocytes from patients with unrelated renal diseases showed lesser degrees of reactivity (275,276).

Altered lymphocyte transformation using streptococcal protoplast membrane antigens in 12 patients known to have had PSAGN with persistent renal disease has been noted by Bhat et al. (277). A depressed immune response was found in these patients compared with normal subjects. The authors concluded that the depressed cellular immune response could be responsible for the chronic renal disease by facilitating the persistence of a humoral immune mechanism. Reid et al. (275) also suggested that the percentage of T lymphocytes (especially T gamma, the T cells bearing Fc receptors for IgG) is reduced. Patients with a well-documented history of postinfectious glomerulonephritis and end-stage renal disease (ESRD) respond to altered basement membrane antigens, whereas patients with ESRD stemming from other renal conditions do not (278). None of these patients respond to native GBM antigens (278). Reactive oxygen species produced by glomerular macrophages have been shown to contribute to GBM injury in a rabbit model of diffuse proliferative glomerulonephritis (279), but macrophages also can contribute to the glomerular handling of circulating immune complexes (280).

Various authors have investigated interleukin (IL) production in patients with PSAGN (212,266,267,281,282). There was enhanced IL-1 and tumor necrosis factor–alpha secretion by peripheral blood monocytes from patients with PSAGN. This secretion was found in unstimulated and lipopolysaccharide-stimulated monocytes (281) and by monocytes stimulated with soluble immune complexes (212). IL-6 and IL-8 have been demonstrated in the urine of patients with various renal diseases (including PSAGN) (282,283). IL-8 and TGF-beta were localized to the glomeruli in biopsies from patients with PSAGN. Increased TGF-beta expression was also seen in the tubulointerstitium (267). Urinary IL-8 levels were higher in patients with glomerular leukocyte infiltration than in those patients without infiltration, and IL-8 was detected immunohistochemically in diseased glomeruli, suggesting its local production (283). Increased urinary levels of IL-8 and monocyte chemoattractant protein-1 were found in the acute phase of PSAGN (266).

Fibrin/Fibrinolysis

Various studies on coagulation have been performed in patients with acute glomerulonephritis (156,284). One study showed that during the acute phase, there was evidence of fibrin formation as judged by an increase in plasma high molecular weight fibrinogen complexes and the development of either hypofibrinogenemia or hyperfibrinogenemia, an elevation in fibrin degradation (split) products in the urine (284). With recovery, these abnormalities diminished. There is no correlation between the levels of serum C3 and serum fibrinogen degradation products (285). Platelets may play a role in various forms of glomerulonephritis (286), and glomerular platelet antigens have been noted in a variety of human glomerular diseases (287). Ultrastructural evidence of platelets in PSAGN in humans is unusual; however, platelets are thought to be evanescent at sites of acute injury and may be missed by electron microscopic studies, especially if the biopsy is done late in the course of the disease. Investigators have found evidence of the participation of platelets in PSAGN (288); diminished platelet survival time in these patients is considered an index of platelet activation. Also, Mezzano et al. (289) found platelet-activating factor in the plasma of 49 of 50 patients with PSAGN.

As listed previously, TMA, including hemolytic uremic syndrome, complicating acute postinfectious glomerulonephritis has been reported (143,144,290,291). Interestingly, the TMA in patients with concomitant PSAGN is generally benign, and most patients recover from both TMA and PSAGN. It is possible that the TMA in these patients is secondary to endothelial injury that is caused by circulating antibodies that cross-react with endothelial cells and subsequent complement activation. A popular theory is that removal of sialic acid from the cell membranes of endothelial cells, red blood cells, platelets, and inflammatory cells by streptococcal neuraminidase will result in the exposure of the Thomsen-Friedenreich antigen. The exposed Thomsen-Friedenreich antigen will react with an anti-T IgM antibody, present in the plasma, which in turn will cause endothelial injury and subsequent activation of the coagulation cascade. If this is true, it is puzzling why so few patients with PSAGN develop TMA.

Genetic Predisposition

PSAGN occurs in siblings of patients with this disease (292). Dodge et al. (102,292) reported that 20% of index patients had siblings with subclinical or clinical acute glomerulonephritis. Rodriguez-Iturbe et al. (21) noted an attack rate for siblings in affected families in nonepidemic conditions of 38.5%. This rate is even higher than the attack rate in epidemic conditions; thus, a familial susceptibility to the disease was presumed (21,104). Lange et al. (199) also found a high rate of asymptomatic glomerulonephritis (detected by urinalysis, hypocomplementemia, or elevated antibody titers to streptococcal antigens) in the family members of patients with symptomatic poststreptococcal glomerulonephritis (22%). It is conceivable, of course, that these findings could be explained on the basis of shared environments and shared infections. Layrisse et al. (217) suggested that HLA-DRw4 is more common in patients with PSAGN, but at present, no firm conclusions can be reached about the association between certain HLA antigens and the development of PSAGN. As indicated previously, patients who have mild genetic form of alternate complement pathway regulatory protein deficiency may be predisposed for the development of PSAGN, including atypical protracted forms of the disease (260,261).

Differential Diagnosis

Acute Postinfectious Glomerulonephritis of Nonstreptococcal Origin

The morphology of the various nonstreptococcal postinfectious or infection–related glomerulonephritides vary somewhat, according to the underlying pathogen. Glomerular subepithelial

humps are usually less prominent, and one can find more intramembranous or subendothelial and mesangial deposits, such as in staphylococcal infection–related glomerulonephritis or in shunt nephritis. In staphylococcal infection–associated glomerulonephritis, the glomerular deposits, in addition to C3, frequently also contain IgA. Glomerular IgA deposits do not occur in PSAGN. However, in many biopsies, based on morphologic examination alone, it is impossible to determine whether the etiologic agent is GAS or a nonstreptococcal pathogen. Only detailed clinical history and identification of the exact pathogen enables the definitive diagnosis. These entities will be discussed in more detail later in this chapter.

C3 Glomerulopathy

C3 glomerulopathy (particularly the hypercellular C3 glomerulonephritis) can be very difficult to differentiate from PSAGN based on morphologic findings alone. C3 glomerulopathy, as discussed in Chapter 9, is associated with congenital or acquired dysregulation of the alternate pathway complement activation with glomerular C3 deposits in the absence of immunoglobulin deposits (134). C3 glomerulopathy encompasses C3 glomerulonephritis in which proliferative renal lesions are seen with C3 deposits but with little or no immunoglobulin deposits, dense deposit disease, familial MPGN type III and familial complement factor H–related protein 5 abnormality nephropathy (134). Differentiating PSAGN from C3 glomerulopathy, particularly C3 glomerulonephritis, can be difficult, because C3 glomerulonephritis, just like PSAGN, may show glomerular endocapillary and mesangial hypercellularity (sometimes including numerous neutrophils) and C3 containing mesangial and glomerular capillary deposits, including occasional subepithelial humps (261). If the biopsy in PSAGN is performed in the resolving phase, the glomerular hypercellularity is mostly seen in the mesangium and the C3 deposits may also be mainly mesangial. Serum C3 levels are usually low both in PSAGN and in C3 glomerulopathy/glomerulonephritis. There are two major differences between PSAGN and C3 glomerulonephritis; PSAGN is preceded by streptococcal infection and almost always is a self-limiting benign disease with recovery without intervention. In contrast, C3 glomerulopathy is usually not preceded by an infection and the disease is associated with persistent proteinuria/hematuria, persistently low serum C3 levels and usually slow disease progression. Differentiating dense deposit disease from PSAGN pathologically is relatively straightforward because of the characteristic intramembranous dense deposits, seen by electron microscopy. The other familial forms of C3 glomerulopathy can potentially cause a differential diagnostic problem, but the family history of renal disease and the persistent clinical symptoms should provide a clue. As indicated above, the differential diagnosis can be particularly complex if an infection such as a streptococcal infection evokes the alternate pathway complement regulatory abnormality, which can happen in patients who have otherwise subclinical mild form of dysregulation of the alternate complement pathway activation (260,261). The classification and definition of C3 glomerulopathy/glomerulonephritis are discussed in more detail in Chapter 9.

Membranoproliferative Glomerulonephritis

The differentiation of MPGN (MPGN type I with C3 and IgG deposits) from PSAGN is not a challenge for an experienced renal pathologist, if the case is typical. Unfortunately, "typical" cases are becoming more and more an atypical occurrence in our renal biopsy material. Therefore, this differential diagnosis may cause a dilemma. In early stages of active MPGN type I, the glomerular hypercellularity can be quite striking and endocapillary polymorphonuclear leukocytes may be prominent. Immunofluorescence reveals granular glomerular C3 deposition with IgG, which can be seen in both MPGN and PSAGN, and occasionally, it is difficult to decide whether the immunofluorescence findings represent a garland pattern in PSAGN or subendothelial deposits in MPGN. Ultrastructurally, MPGN is characterized by subendothelial deposits, but the presence of subepithelial humps in MPGN is not unusual, and occasionally, quite a few humps can be identified. In PSAGN, usually subepithelial humps predominate, but in many cases, subendothelial deposits are also seen. Mesangial deposits are present in both MPGN and PSAGN. Based on the above, it is evident that there are morphologic overlaps between PSAGN and MPGN type I. The clinical presentation can also be quite similar because both diseases frequently present with nephritic syndrome and variable degrees of proteinuria and hypocomplementemia. Proteinuria occasionally can be quite prominent in PSAGN. Serum complement levels (in particular, C3 levels) are low in both diseases. C3NeF is not always present in MPGN and may occasionally be seen in PSAGN. We have encountered a few renal biopsies in which we were unable to decide whether the biopsy represented an early active stage of MPGN type I or PSAGN. In such cases, only careful follow-up will establish the diagnosis because the great majority of PSAGN cases will gradually improve and resolve, whereas MPGN type I, if untreated, usually progresses.

Cryoglobulinemic Glomerulonephritis

In a typical case, the differential diagnosis is obvious because of the intracapillary hyalin thrombi, which represent cryoglobulin precipitates in the glomerular capillaries. However, particularly in a small biopsy specimen or in atypical cases, these hyalin thrombi are not present, and cryoglobulinemic glomerulonephritis may merely show the pattern of endocapillary proliferative glomerulonephritis. Glomerular intracapillary cryoglobulin precipitates may appear rapidly, and it is likely that they can also disappear rapidly. The predominant endocapillary cells in cryoglobulinemic glomerulonephritis are monocytes and macrophages, but numerous neutrophils are not unusual. The immunofluorescence pattern in cryoglobulinemic glomerulonephritis is distinctive (particularly in type I and type II cryoglobulinemia) if the intraluminal cryoglobulin deposits (hyaline thrombi) are present. Unfortunately, as any glomerular disease, cryoglobulinemic glomerulonephritis also represents a disease spectrum and cases with little or no intraluminal cryoglobulin deposits in the glomerular capillaries occur. This is more likely if the tissue for immunofluorescence contains only a few glomeruli. The distinctive IgG- and IgM-positive globules of type II cryoglobulinemia, which usually also stain for complement, may not be evident in such cases. Electron microscopy usually reveals numerous monocytes and macrophages with unusually large secondary phagolysosomes. Ultrastructural examination at high magnification often reveals the characteristic organized microtubular substructure in the cryoglobulin deposits, but this could be missed, particularly if not enough glomeruli are examined under the electron microscope under high magnification, and

occasional cases will have no ultrastructural substructure in the immune deposits. One important differential diagnostic hint is that in cryoglobulinemic glomerulonephritis, humps are usually absent. We always consider cryoglobulinemic glomerulonephritis in the differential diagnosis if we see an endocapillary proliferative glomerulonephritis with no or only few immune complex deposits. The clinical history may be quite helpful in differentiating PSAGN from cryoglobulinemic glomerulonephritis. Similarly to PSAGN, C3 levels may be low in cryoglobulinemic glomerulonephritis, but unlike in PSAGN, the C4 levels are usually quite low in cryoglobulinemic glomerulonephritis. Cryoglobulinemic glomerulonephritis is typically associated with normal or slightly low serum C3 levels and very low C4 levels. A positive cryoglobulin test may be helpful, but unfortunately, this test is unreliable, and cryoglobulins occur in some patients with PASGN. Another useful test in the differential diagnosis is rheumatoid factor, which is detectable in most patients with cryoglobulinemic glomerulonephritis. Positive serology for hepatitis C also supports a diagnosis of cryoglobulinemic glomerulonephritis. Rarely, even the clinical history may be misleading because cryoglobulinemic glomerulonephritis may undergo spontaneous remission giving the impression of a resolving postinfectious glomerulonephritis.

Membranous Glomerulonephritis

In our experience, this is not a problematic differential diagnosis; however, in a review, Sotsiou et al. (293) described two patients with presumed postinfectious glomerulonephritis who had spike formation on methenamine silver stain, endocapillary hypercellularity with neutrophils, granular deposits of IgG and C3 along the glomerular capillaries, and elevated ASO titers. Unfortunately, no follow-up data are provided, and it is difficult to exclude the possibility that these cases in fact represented atypical membranous glomerulonephritis rather than atypical postinfectious glomerulonephritis. Three cases are reported that showed transformation of an acute proliferative and exudative glomerulonephritis into a membranous glomerulonephritis (294). These are very unusual, and the pathogenesis is debatable. Wu et al. (295) described a patient who developed PSAGN superimposed on membranous glomerulonephritis.

Diffuse Proliferative (Class IV) Lupus Nephritis

Class IV lupus nephritis shows a diffuse endocapillary proliferative pattern, frequently with the presence of glomerular polymorphonuclear leukocytes. Therefore, if immunofluorescence and electron microscopy are not available, the differential diagnosis, based on light microscopy alone, may be difficult. One has to remember that in proliferative lupus nephritis, large hump-like subepithelial deposits may be seen by electron microscopy. Still, because of the characteristic immunofluorescence and ultrastructural findings and the clinical history, the differential diagnosis is obvious in most cases.

Clinicopathologic Correlations

Many studies have been performed to correlate various clinical and pathologic aspects of PSAGN. There is no correlation between the presence of hematuria or proteinuria and the severity of the glomerular lesion. This finding is not surprising, because histologic evidence of glomerulonephritis has been noted in patients with minimal or absent hematuria and proteinuria (186) and because it is known that considerable hematuria can be present with no changes or only trivial changes in glomeruli by light microscopy.

Jennings and Earle (115) found some correlation between the light microscopic appearances of the glomeruli and various clinical parameters, certain exceptions were noted; there was a greater tendency for patients with the more severe glomerular changes to have hypertension, although this correlation was not absolute. These patients also tended to have high BUN (115). Parrish et al. (296) showed that the ratio of glomerular to tubular functions gave a good indication of the progress of the renal disease, since the renal histologic picture improved in those patients whose ratio rose during the course of the disease but remained unchanged in those whose ratio was low.

Lewy et al. (98) carried out extensive clinicopathologic correlations. They found that glomerular tuft hypercellularity showed a significant inverse correlation with creatinine clearance and a good relationship with BUN. Glomerular tuft hypercellularity did not correlate with the ASO titer, oliguria, or hypertension and also showed no significant correlation with serum complement levels. However, the greatest degree of glomerular hypercellularity was associated with the lowest levels of serum complement. There was no correlation between the number of glomerular humps by electron microscopy and the level of serum complement. Total morphologically evident tubular damage related directly to creatinine clearance and BUN. This is not surprising, since there may be a good correlation between the glomerular and tubular damage.

Haen et al. (297) showed with morphometric studies that there is a direct correlation between serum creatinine and interstitial volume. Even with severe glomerular changes, the serum creatinine level was usually not higher unless the interstitial volume was increased by 15%. Bohle et al. (138) and Hooke and Atkins (298) also found a close relationship between the severity of interstitial inflammation and the GFR. The number of glomerular humps (by electron microscopy) was associated with a more severe and protracted clinical picture (138). There was no apparent difference in the glomerular lesion or in the clinical course when patients with and without hypocomplementemia were compared. Some authors state that up to 10% to 20% of patients may have normal serum complement levels (65); others disagree (199,252). There is no doubt that large numbers of crescents are associated with oliguria and rise in the BUN and serum creatinine levels.

Several investigators have suggested that initial and/or persistent nephrotic syndrome is a harbinger of a poor renal prognosis (299,300). As noted earlier, there may be difficulty in distinguishing between exacerbations of nonstreptococcal chronic glomerulonephritis and true de novo attacks of PSAGN (301). An added problem is the lack of evidence of a streptococcal cause in many cases studied (296). Renal biopsies of patients with low creatinine clearance, microscopic hematuria, and proteinuria usually show moderate to advanced glomerulosclerosis, mesangial hypercellularity, and intense immunofluorescent staining for IgG and C3 (22). However, patients without clinical or laboratory evidence of disease can have moderate segmental mesangial sclerosis and positive glomerular immunofluorescence findings of IgG and C3 (22). As noted earlier, the studies of Sorger et al. (147,149) and others (152) indicate that the garland pattern of immunofluorescence is associated with more severe proteinuria. West and McAdams

(166) found that children with PSAGN and hypoalbuminemia had no subepithelial deposits (humps) on the paramesangial portion of the glomerular basement membrane. Children who had subepithelial deposits, not only along the peripheral glomerular capillary loops but also along the paramesangial basement membrane, had significantly higher serum albumin levels. Unfortunately, quantification of the proteinuria was not performed in this retrospective study, and the meaning of this association is unclear.

Patients older than 60 years of age tend to have a worse renal prognosis than younger adults according to some authors (2,302). When adult patients with oliguria/anuria and crescent formation are considered, the prognosis is especially poor; as many as 50% of them progress to end-stage renal failure (299,303). The prognosis for adult patients with oliguria/anuria may be related to the availability and use of dialysis and other medical support and is taken from the older literature.

Correlation of Light, Electron, and Immunofluorescence Microscopy

There is usually concordance between the light and the electron microscopic findings. The number of glomerular subepithelial deposits is directly correlated with the degree of polymorphonuclear leukocytic infiltration in the glomeruli; however, humps can be seen in sections without neutrophils (98). Those patients with the greatest extent of glomerular tuft hypercellularity generally have the most numerous humps.

There is generally good correlation between the light microscopic appearance of diffuse glomerular hypercellularity and the characteristic diffuse granular staining along the glomerular capillary walls for IgG and C3 (59). In certain cases, however, lesions thought by light microscopy to be well developed may not have glomerular staining for IgG and may show only staining for C3 (59). In biopsies in which light microscopy shows complete resolution of hypercellularity, there may be loss of staining for both IgG and C3 (59). In biopsies in which mesangial prominence persists many months after the initial biopsy, there is commonly only complement in the mesangium.

There is usually granular immunofluorescent staining along the glomerular capillary walls corresponding to the humps noted in ultrastructural studies from the same biopsy. This, however, is not always the case, and some researchers believe that the number and location of the immunofluorescent granules best match the various sites of the glomerular subendothelial deposits (153).

As noted earlier, Sorger et al. (149) have provided detailed immunofluorescence studies. They described three patterns, termed *starry sky*, *garland*, and *mesangial*. In the starry sky type, there is a granular deposition of IgG and C3 along the glomerular capillary walls and mesangium. The garland pattern consists of densely packed, sometimes confluent or continuous deposits of IgG and C3 along the glomerular capillary walls. The mesangial pattern consists of the presence of C3 in the mesangial regions. When these three patterns were compared with ultrastructural findings, the starry sky pattern corresponded, in general, to the glomerular subendothelial deposits, the garland pattern to the classic glomerular subepithelial deposits that tended to be elongated or confluent, and the mesangial pattern to electron-dense deposits in the mesangium and in a subepithelial pattern on the GBM overlying the mesangium (see Figs. 10.15 to 10.17). In summary, the correlations are good, although there are some anomalies. Chief among them is the occasional lack of concordance between immunofluorescence and electron microscopic studies.

Correlation of Morphologic Changes With Clinical Outcome

The most controversial facet of PSAGN is its long-term outcome. This is a question on which there are strong opinions and incomplete data. The difficulty in demonstrating with certainty that the glomerulonephritis in the individual patient is related to the streptococcal infection has made it difficult to interpret follow-up studies on progression to a chronic stage. Information about the correlation of morphologic changes with clinical outcome was scanty before the days of renal biopsy, although it was known that certain patients pursued a variable course ending with death owing to renal failure within a few months. Most of these are poststreptococcal cases in which crescent formation is abundant. The presence of a large number of crescents is an ominous sign. However, it is quite common to see cases of acute postinfectious glomerulonephritis with a few crescents where complete recovery is generally the rule (98). Clinical recovery has been noted in half of patients with less than 40% crescents (98) as well as in certain patients with a greater percentage of crescents (304).

Crescentic glomerulonephritis as a severe manifestation of a postinfectious episode has been noted by many researchers (66,88,111,113,295,299,304–308). The significance of crescentic glomerulonephritis in children with PSAGN remains the subject of controversy (111,112,305,309). In a comprehensive review of the natural history of glomerulonephritis, Cameron (310) described the actuarial survival of patients with severe crescentic glomerulonephritis based on the experiences of himself and Drs. Habib, Kincaid-Smith, and Morel-Maroger. He concluded that the prognosis of such patients (with all forms of nephritis) is "almost entirely dependent on the large numbers of crescents and that the prognosis normally associated with the underlying glomerular disease is no longer operative, because the prognosis of the crescent formation is so bad." He also furthered the argument that the apparently good prognosis in patients with PSAGN and extensive crescents has been misrepresented, because most of the patients in this group have had relatively minor degrees of crescent formation. In the investigation of the Southwest Pediatric Nephrology Study Group (SPNSG) (304), six patients were found to have poststreptococcal glomerulonephritis and crescent formation in 51%, 60%, 87%, 90%, 92%, and 100% of their glomeruli. The crescents were generally cellular rather than fibrocellular or fibrous, and there was a low percentage of large crescents with little evidence of chronic histologic changes, such as global glomerulosclerosis and interstitial fibrosis. In the absence of constant or progressive injury to the glomerulus, these cellular crescents can resolve without major side effects. Indeed, the five patients who had adequate follow-up in the SPNSG series had normal GFRs at last evaluation, irrespective of whether treatment was given (304).

As the above data indicate, PSAGN is usually fully reversible, even in crescentic forms. Still, long-term follow-up studies indicate that after many years, or decades, some patients who

had a history of PSAGN develop renal failure or even ESRD (293,311–315). Unfortunately, most of these studies do not specify whether the cases that show poor long-term outcome had crescents or not. Tasic et al. (316) report a pediatric patient who developed chronic renal failure 12 years following an episode of PSAGN from which the patient seemed to have recovered fully. Moroni et al. (315) followed 50 adult patients with PSAGN and found that the presence of crescents is an indicator of unfavorable long-term outcome. Interestingly, these authors found the presence of interstitial inflammatory cell infiltrate as the most important histologic indicator predicting a poor long-term outcome (315). Ardiles et al. (317) examined serum from 210 patients with PSAGN for the presence of ANCAs. They found that 9% of the patients had ANCA, which was associated with crescent formation.

The study of Roy et al. (112) suggests that the outcome is unaffected by therapeutic intervention and that such patients should receive only supportive measures to control the consequences of their renal insufficiency and hypertension until a spontaneous remission occurs. Cunningham et al. (111) noted that 7 of 13 children with PSAGN and crescentic glomerulonephritis progressed to chronic renal failure. In some of their patients, anticoagulant and antiplatelet therapy appeared to improve survival rates. Srivastava et al. (318), in a study of 43 children with crescentic glomerulonephritis, found 11 patients with evidence of poststreptococcal glomerulonephritis. Seven of these eleven children progressed to ESRD, and two additional children had chronic renal failure by the end of the study (318). Thus, the renal prognosis in this set of patients is still somewhat debatable.

Jennings and Earle (115) have suggested that the severely exudative form of PSAGN with a large number of polymorphonuclear leukocytes is the forerunner of the most severe type of PSAGN; however, the mere presence of polymorphonuclear leukocytes in the glomerular tuft does not portend a poor prognosis. Polymorphonuclear leukocytes are often present in the glomeruli of patients who recover completely (292).

Several authors have attempted to use other morphologic markers as prognostic indicators. Some suggest that the overall degree of glomerular tuft hypercellularity is related to either the degree of persistent proteinuria (319) or outcome (320), but other authors have stated that there does not seem to be a good correlation between excessive glomerular hypercellularity and outcome (98). Lesser degrees of hypercellularity also have been found to be associated with irreversible renal changes (320). There are so many exceptions to the suggested correlations that a rule of thumb probably does not exist. It is likely that several of these morphologic features taken together may be of greater prognostic value than any single finding, but this type of study has not been performed. Some investigators have ascertained that glomerular necroses, adhesions, glomerular capillary thromboses, crescent formation, and interstitial nephritis have been found more commonly in those patients whose disease progresses (302,320).

A study by Lien et al. (321) addressed the issue of obsolescent glomeruli in 57 patients (mostly adult) with PSAGN followed for 1 to 4 years. Twenty-six percent of these patients had combinations of hypertension, microscopic hematuria, proteinuria, and elevations in the serum creatinine level; 9% died. These authors raised the important point that one must exclude underlying clinically covert glomerular disease that is brought to clinical attention because of a superimposed acute postinfectious glomerulonephritis.

Vascular changes, such as arteriolar sclerosis and arterial sclerosis, have been suggested to be a harbinger of a poor prognosis (114,139). A direct correlation was noted between the presence of thickening of the vessel wall with narrowing of the lumen and the percentage of globally sclerotic glomeruli. Hypertension tended to develop in those patients with global glomerulosclerosis and morphologic evidence of vascular disease.

Ultrastructural changes, such as large and confluent glomerular subepithelial electron-dense deposits, have been thought to be indicators of a poor prognosis (319). These atypical humps have invariably been associated with renal failure following the initial attack, according to one report (319). Persistence of immunoglobulins and complement, primarily in the glomerular mesangial regions, has been considered to be evidence of continuing immunologic involvement and injury (194). Those patients who progress to a chronic stage have this feature. However, some authors have noted the final loss of immunoglobulins and complement as long as 5 years after the initial acute attack; therefore, the persistence of these immunoreactants beyond the acute stage of disease cannot be universally regarded as an infallible sign of a poor prognosis.

Linear immunofluorescence for IgG was noted in certain patients who progressed to chronic renal failure (320). Anti-GBM antibodies were searched for but were not found. The long-term study of Baldwin et al. (114) showed similar linear immunofluorescence in subsequent renal biopsies with a significant number of globally sclerotic glomeruli; renal failure had not yet developed in these patients. Whether these changes are truly specific and portend, a poor prognosis is unclear; mild linear glomerular capillary staining for IgG is a common nonspecific immunofluorescence finding, particularly in diabetic patients.

The outcomes of patients with acute postinfectious glomerulonephritis are shown in Table 10.4, but many important points need to be made before considering these outcomes. In many of the series quoted, renal biopsies were not performed; thus, histologic proof of acute postinfectious glomerulonephritis is lacking. Without pathologic categorization of nephritis, the outcome might be altered by diseases erroneously diagnosed clinically as postinfectious glomerulonephritis, such as IgA nephropathy with onset or exacerbation initiated by streptococcal pharyngitis. The criteria used for making the diagnosis of acute postinfectious glomerulonephritis were clinical and variable. Lengths of follow-up vary among the series, but they were often short. The outcome indicators used are also different; some authors used the presence of mild proteinuria and microscopic hematuria, whereas others relied on BUN and serum creatinine levels and the presence of hypertension. As Heptinstall stated (168), "It is a human failing to include as many cases in a series as possible, yet the task of assessing prognosis from published series would be made much easier if a smaller number of cases, all with a minimum follow-up period of, say, 5 or 10 years, were described."

Short-term follow-up data can give an erroneous impression, because the disease resolves more slowly in some patients than in others, with the net result that the number of patients in the latent stage is exaggerated. Studies with short-term follow-up provide fewer opportunities for some patients with

TABLE 10.4 Outcome of acute glomerulonephritis: adults, adults and children, and children only

Author	Follow-up period (years)	Population studied	No. of patients	Died in acute stage (%)	Chronic or latent stage (%)	Not traced (%)	Recovery (%)
Richter (322)	1–19	Adult	100	5 (5)[c]	15	13	62
Rudebeck (323)	>4	Adult[a]	318[b]	5 (2)[d]	9 (16)[i]	15	53
Jennings and Earle (115)	Short	Adult	36	3	36[i]	0	61
Kushner et al. (198)	<4	Adult[a]	29	0	24	0	76
Moroni et al. (315)	8	Adult	50	5	46	1	42
Pinto et al. (311)	2	Adult	69	0	30 (68)[dd]	0	70 (34)[dd]
Longcope (11)	1/2–12	Adult and child	116	6 (4)[d]	9 (34)[g]	0	49
Hayman and Martin (324)	1/2–8	Adult and child	77	9	33[h]	0	67[h]
Ellis (12)	Years	Adult and child	173	4 (4)[d]	10	0	82
Murphy and Peters (325)	2–10	Adult and child	205	13[e]	36	17[k]	34
Ramberg (326)	—	Adult and child	175	6	25	7	62
Addis (327)	Years	Adult and child	118	7[t]	20	0	73
Baldwin et al. (114,328)	2–18	Adult and child	168	5.4 (3.6)[d]	See text	—	—
Rodriguez-Iturbe et al. (70)	5–6	Adult and child[r]	120	1.3	13[s]	0	87
Nissenson et al. (93)	7–12	Adult and child[r]	722	0	See text	—	—
Garcia et al. (329)	11–12	Adult and child	71	0	21[v]	0	79
Chugh et al. (303)	2–10	Adult and child	146	14[m]	31[x]	27	28
Potter et al. (317)	12–17	Adult and child[r]	534	0[y]	3.5	0	96.5
Guild (330)	1–12	Child	34	0	18	0	82[n]
Gachet (331)	>1	Child	114[l]	7	9[i]	0	91[t]
Davis and Faber (332)	>2	Child	102	6	13[m]	0	81
Burke and Ross (333)	2	Child	90	3	3	0	94
Akerrén and Lindgren (5) (334)	—	Child	57	0	0	0	100
McCrory et al. (335)	2	Child	35	0	3	0	97
Perlman et al. (336) (337)	10	Child	62	1.6	0	0	98.4
Dodge et al. (102)	2	Child	20	0	45[o]	0	55
Lewy et al. (98)	5	Child	21	0[p]	24[q]	0	76
Schacht et al. (320)	2	Child	54	0[u]	38	0	62
	5	Child	31	0[u]	45	0	55
Travis et al. (338)	>3	Child	54	2	8	0	92[h]
Roy et al. (18)	4–12	Child	35	0	3	0	97
Drachman et al. (339)	1/2–2	Child	155	0	0	0	100
	11–12	Child	80	0	0	75	100
Popovic-Roloviz et al. (340)	5–9	Child	40	0	5[z]	85[aa]	95
	10–17	Child	88	0	6.8[bb]	69[aa]	93.2
Clark et al. (341)	5.4–22	Child	36	0	20 (persistent urinary abnormalities) 3 (hypertension)	0	80–97
White et al. (313)	6–18	Child	63	0	0[ee]	0	100
Kasahara et al. (342)	4	Child	138	0	0	0	100
Cleper et al. (314)	46	Child	36	0	0[ff]	0	100
Sarkissian et al. (40)	1	Child	474	1	5	0	97

[a]Older than 10 y of age.
[b]Seen within 3 mo of onset.
[c]Died from etiologic disease or incidental cause.
[d]Died in rapidly progressive phase.
[e]Died in acute stage or later.
[f]Died from unrelated disease; time was not given.
[g]"Quiescent" cases (latent).
[h]Percentage of those who survived acute attack.
[i]Uncertain.
[j]Some followed for <1 y.
[k]All had recovered on discharge.
[l]Those who survived the acute phase.
[m]Includes 5% who died from chronic nephritis.
[n]Includes three with orthostatic proteinuria.
[o]Of nine patients, two had persistent and seven had intermittent proteinuria.
[p]Three deaths in the initial 46 patients.
[q]Includes one death from chronic renal failure at 5 y.
[r]Mainly children.
[s]Nine percent in children, 37% in adults.
[t]By histologic outcome.
[u]Two had crescentic glomerulonephritis and became uremic.
[v]One patient with chronic renal failure.
[w]Died of uremia within 2 yr.
[x]Half progressed to renal failure.
[y]Only one patient died in renal failure 6–10 yr after the initial illness.
[z]Hypertension plus proteinuria in both patients.
[aa]Hypertension, proteinuria, or microhematuria. (All patients had normal creatinine clearances.)
[bb]From original 271 patients seen.
[cc]Three patients of the original 134 died; they were released from the study.
[dd]Thirty percent had renal insufficiency, and 48% had that or persistent proteinuria or hematuria.
[ee]Albuminuria or hematuria was present in 13% and 21% of patients, respectively.
[ff]Normal GFR with reduced renal functional reserve.

asymptomatic proteinuria to progress to the chronic stage, with hypertension and raised levels of BUN and serum creatinine, or for other patients to recover completely.

It is important to remember that selection or entry bias plays a major role in the interpretation of these series. Patients studied in the hospital represent a highly selective population, and it is likely that most mild cases may not be hospitalized or undergo biopsy. Hospitalized patients are likely to have the most severe clinical course. Renal biopsy is usually reserved for those whose clinical picture is not one of a classic or typical form of acute postinfectious glomerulonephritis. Despite these reservations, most investigators believe that the prognosis in children is good in both the epidemic and sporadic cases. The mortality rate for children in the acute stage is generally low, although some workers have noted higher death rates than others (331). These high mortality rates are usually the result of severe infection, cardiac failure, or hypertensive encephalopathy, not the nephritic process itself.

A review of 22 series confined to children noted that 0% to 45% of children were found to have latent or chronic disease, usually defined as asymptomatic or intermittent proteinuria. As mentioned previously, it is likely that short follow-up periods, highly selective admission policies, and misdiagnoses contribute to this high figure. The morphologic findings in the series, of Travis et al. (338), were described 3 or more years after the acute attack. Of the 54 children whose diagnosis of acute postinfectious glomerulonephritis was confirmed by biopsy, 1 died from a crescentic form of glomerulonephritis, 4 failed to show histologic healing, 3 had latent glomerulonephritis, and 1 had chronic glomerulonephritis. The authors thought that the three patients with latent glomerulonephritis were capable of spontaneous resolution of the glomerular process. If we take that to be true and the patient with the crescentic form of acute glomerulonephritis is excluded, then the probability of recovery from the acute attack of postinfectious glomerulonephritis would be 98%. If resolution of disease in the three with latent glomerulonephritis were not to take place, the probability of recovery would be 92%.

In a prospective study of children followed for 4 to 12 years after the onset of acute glomerulonephritis with sequential renal biopsies, healing occurred in 20% at 2 years, 46% at 4 years, 77% at 6 years, 94% at 10 years, and 97% at 12 years (86). Although there was a very high rate of healing, it can be considerably delayed. There was less than perfect correlation between the morphologic findings and the results of the Addis counts of hematuria; for example, six patients (17%) had abnormal Addis counts at a time when histologic healing and resolution had occurred (327).

A study from Japan on 138 children with PSAGN reports a 100% recovery rate including the disappearance of clinical symptoms (342). The serum complement levels were normalized within 12 weeks, the proteinuria disappeared within 3 years, and the hematuria disappeared within 4 years in all children. The authors emphasize their usage of strict criteria for diagnosing PSAGN to avoid the possibility of selection bias. They included only children who had hematuria, proteinuria, evidence of streptococcal infection, transient hypocomplementemia, and no clinical or histologic evidence of previous renal disease (342).

The patients with epidemic forms of poststreptococcal glomerulonephritis have almost uniformly shown excellent outcomes, and only a few have persisting renal abnormalities, as determined by clinical and laboratory examinations (hematuria/proteinuria) (22,93,268,337,339,343–345). This is exemplified by long-term follow-up of an epidemic in Trinidad of 760 patients, 87% of whom were younger than 15 years of age. The excellent results at 2 to 6 years (345) were surpassed in the 7- to 12-year study by Nissenson et al. (93), in which, of the 722 patients followed, persistent urinary abnormalities were present in only 0.8%, hypertension in 2.3%, and serum creatinine levels greater than 1.2 mg/100 mL in as few as 3 patients. In the 12- to 17-year follow-up of 534 patients undertaken by Potter et al. (268), only 3.5% had urinary abnormalities, 3.7% were hypertensive, and no patient had a serum creatinine level greater than 1.25 mg/100 mL. These figures did not differ from expected values in surveys of the normal population.

In an 11- to 12-year follow-up of an epidemic in children conducted by Drachman et al. (339), no persistent urinary or serologic abnormalities (BUN, creatinine) were noted. Drukker et al. (346) studied the renal sodium handling (i.e., the natriuretic response to intravenous saline loading) in 11 patients (both children and adults) several years after PSAGN and found no evidence of exaggerated natriuresis.

A few series (300,303,347) suggest that children do not do as well as generally believed and that a high proportion have at least minor clinical or laboratory abnormalities at follow-up; however, clinically significant renal failure is rare. It is also believed that patients who once had poststreptococcal glomerulonephritis in childhood have an increased propensity or susceptibility to chronic glomerulonephritis as adults (102,115,320,348). In a series of 83 children who were followed for periods of up to 17 years (with renal biopsy performed in only 36 of them), proteinuria, hypertension, and decreased GFRs were noted in 38% of the 54 children followed for 2 years or more, 45% of 31 children followed for 5 years or more, and 47% of 17 children followed for more than 10 years (347). Two of the patients, who had uremia from onset, showed progression from diffuse proliferative glomerulonephritis with crescents to proliferative and sclerosing chronic glomerulonephritis. A study of 35 patients by Rodriguez-Iturbe (20) indicated that patients followed for up to 13 years after an episode of poststreptococcal glomerulonephritis had diminished renal functional reserve capacity, as determined by a lower GFR after challenge by acute oral protein load. A study from Israel reports on the follow-up of 36, mainly pediatric, patients after an episode of PSAGN (314). The investigators calculated the renal functional reserve in these patients and found it to be significantly decreased compared to control patients, even though they had similar creatinine clearances. Interestingly, in 69% of patients who had PSAGN more than 10 years ago, the renal functional reserve was reduced compared with reduction in only 26% of the patients who had PSAGN less than 10 years ago (314). These data indicate progressive but subtle underlying injury that is not evident by measuring serum creatinine or GFR only.

Thus, these studies indicate that although uremia is rare, there is evidence of depressed renal function in some children. This finding dictates the need for continued follow-up. The following features have an adverse effect on clinical outcome: underlying renal disease, persisting proteinuria with or without the nephrotic syndrome, impaired renal function, oliguria/anuria, extensive crescent formation, atypical humps on electron

microscopy, and the garland pattern on immunofluorescence. The prognosis for children with these features is worse than for those without them (111,149,293,300,303,349). Children with the crescentic form of postinfectious glomerulonephritis may or may not have a poor renal prognosis (111,304,305,318). As we pointed out above, one has to consider the possibility that the relatively low full recovery rate in some of these publications could be explained by the possibility that in children with progressive renal disease, streptococcal infection initiated the development of C3 glomerulonephritis (260–262).

The prognosis for adults is even more controversial, and many authors consider that it is not as favorable as for children (2–4,114,236,242). The proportion of complete recoveries ranges from 53% to 76% (see Table 10.4), and death in the acute stage has been recorded in up to 9% of adults (14). A more recent paper of Nasr et al. (2,3) describes 109 elderly (≥65 years old) patients with postinfectious glomerulonephritis. The complete remission rate was only 22% after a mean follow-up of 29 months. However, only 16% of these patients had PSAGN; most of them (46%) had staphylococcal infection. Also, many of them had preexisting chronic renal disease, including diabetic nephropathy. In contrast, another recent publication from China (89) reports an 85.7% remission rate in adults with acute postinfectious glomerulonephritis. The remission rate in the 43 patients with PSAGN was higher (94.7%) than in the 21 patients (66.7%) with nonstreptococcal infection–associated glomerulonephritis (89). The good outcome is probably related to the relatively young age of patients (29 ± 14 years) and the low prevalence of underlying chronic renal conditions. It should be noted that several of the series quoted in Table 10.4 that indicated a high mortality rate in the acute stage were compiled many years ago. In those series comprising only adults, the figures for chronicity range up to 36% (13,350). The percentages might vary in part because of different durations of follow-up and uncertainty as to whether to include patients whose sole abnormality is hematuria or proteinuria. It has been suggested by Mezzano et al. (323) that there are age-related changes in the mononuclear phagocyte system fragment crystallizable receptor function in patients with poststreptococcal glomerulonephritis and that this could help explain prognostic differences between children and adult patients (351).

The studies of Baldwin et al. (114,328) and Schacht et al. (320) are of great importance in determining prognosis in a predominantly adult population. In one of their series (114) of 89 adults and 37 children, 9 patients died within the first 6 months, and 6 of them had the crescentic form of acute glomerulonephritis. Two others died from renal failure (one at 2 years and the other at 6 years); both showed extensive evidence of glomerular sclerosis at that time. Proteinuria was noted in half the patients followed from 5 to 7 years, and hypertension was seen in one fourth to one half. Subsequent renal biopsies showed subsidence of glomerular hypercellularity and an increase in the degree of glomerular sclerosis. The severity of glomerular sclerosis correlated with reductions in the GFR. Baldwin (328), in a later study, noted that 56% of renal biopsies obtained 3 years or more after the onset of the acute attack showed signs of segmental to global glomerular sclerosis of 10% or more of glomeruli (an abnormally high percentage for patients younger than 40 years of age. Of the 95 patients followed for more than 2 years in this study, 46% had proteinuria, 42% had hypertension, and 38% had reduced GFRs. Some patients died from chronic renal failure (320), which suggests that although improvement in renal function can take place after acute onset of the initial illness, chronic renal failure might nevertheless develop several years later. All the deaths were among adult patients.

In Baldwin's largest study (328), involving 168 patients who were followed for periods of up to 18 years, the author noted proteinuria or hypertension in 50% (clinical uremia occurred in 6). Thus, Baldwin maintains that an appreciable number of patients had irreversible sclerotic glomerular changes. The mechanism of such progression is unclear, although ischemia or enhancement by vascular disease was proposed as an answer. These results, however, have been widely challenged. It has been suggested that there is an inordinately high proportion of adult patients in the studies and that the patients are somewhat atypical of patients with PSAGN. Moreover, the population had a much higher incidence of the nephrotic syndrome and was clinically different from those with typical acute postinfectious glomerulonephritis. Indeed, reports from other investigators (321,329) fail to support the findings of Baldwin (328) and others and suggest that progression to chronicity is a rare event. One has to take into consideration that a proportion of adult patients may have a preexisting underlying renal condition, and the prognosis of infection-related glomerulonephritides in these patients is inferior (2,315).

In summary, acute postinfectious (mostly poststreptococcal) glomerulonephritis has an excellent prognosis in children, although the outcome of the crescentic form is less clear, especially in epidemics. Complete clinical recovery usually takes place in children. It is difficult to determine whether patients with skin infections have a different prognosis from patients with throat infections, although the prognosis for either type of infection appears good in the epidemic variety (95). Death may occur in the acute stage from infections, heart disease, or kidney failure (98,331). The outcome in adults is worse than in children. However, many infection-associated glomerulonephritides in adults are not poststreptococcal glomerulonephritis; many of them are associated with other infections such as staphylococcal infections (see subsequent section). Also, many of the infected adults have underlying comorbidities such as diabetes, hypertension, and obesity.

ACUTE POSTINFECTIOUS AND INFECTION-ASSOCIATED GLOMERULONEPHRITIS OF NONSTREPTOCOCCAL ORIGIN

GAS organisms are not the only organisms with the ability to cause acute diffuse proliferative glomerulonephritis. Various bacterial, viral, and fungal infections are thought to give rise to acute glomerulonephritis (Table 10.5), and antigens generated by these infections have been demonstrated in the glomeruli of affected patients. Many of these patients have initial signs of acute nephritic syndrome, but signs of this syndrome are less common than in those patients with nephritogenic streptococci (407,408). The glomerular diseases related to these nonstreptococcal antigens are associated with a broader spectrum of morphologic changes than typical PSAGN (2). There are also a number of patients with acute diffuse proliferative glomerulonephritis (appearing to be postinfectious) in whom no evidence of infection can be found at the time glomerulonephritis is

TABLE 10.5 Glomerulonephritis with other infections

Bacterial
Endocarditis
Shunt nephritis[a]
Deep-seated visceral abscesses[a]
Staphylococcal infections[a]
Pneumococcal pneumonia and other pneumococcal infections (352–362)
Syphilis (363)
Salmonellosis (364)
Neisseria gonorrhoeae (365)
Brucellosis (366)
Mycobacterial infection (367)
Campylobacter enteritis (368)
Nocardia (369)
Actinobacillus actinomycetemcomitans (370)
Yersinia infections (371)
Borrelia burgdorferi (372)
Bartonella henselae (362,373,374)
Propionibacterium acnes (375–380)
Q fever (*Coxiella burnetii*) (381)
Legionnaires disease (382)
Mycoplasma infection (383–386)
Viral
Varicella (387–390)
Coxsackie (391)
Cytomegalovirus (392)
Measles (393)
Mumps (394)
Epstein-Barr (395,396)
Influenza (391,397)
Hepatitis B (398)
Hepatitis C (see Chapter 8)
ECHO (391,397,399,400)
Adenovirus (391,397,401)
Parvovirus B19 (402,403)
Vaccina (404)
Herpes (399,405,406)
Schistosoma (see Chapter 5)
Malaria (see Chapter 5)

[a]Detailed references provided in text.

diagnosed. Therefore, such cases of glomerulonephritis should not be designated as postinfectious; the terminology infection-associated glomerulonephritis or infection-related glomerulonephritis is more appropriate in such patients.

Occult bacterial infections (such as infective endocarditis and visceral abscesses) can result in diffuse proliferative glomerulonephritis (409). It is likely that there are also instances in which glomerular hypercellularity is confined to the mesangial regions and in which the typical humps and immunofluorescence findings are not identified. One of the most common misdiagnosis we have noted in consultation (and even sometimes in the literature) is the erroneous interpretation of pure mesangial hypercellularity, without closure of the glomerular capillary loops, as true acute diffuse proliferative glomerulonephritis. Another common reason for the inappropriate overuse of the diagnosis of acute proliferative glomerulonephritis is that the sections for light microscopy are too thick, which leads to a mistaken perception of hypercellularity.

The epidemiology of infection-associated or postinfectious glomerulonephritis has changed considerably from decades ago. Recent studies show that the bacteria causing glomerulonephritis are often staphylococcal or gram-negative strains rather than streptococci, which predominated decades ago (3,4,68). Almost one half of the patients in recent studies were alcoholics, diabetics, or intravenous illicit drug users. The origin of infection was the oropharynx, skin, and lung (in that order of frequency). Renal biopsy disclosed signs of acute endocapillary proliferative glomerulonephritis in over one half of the patients, crescentic glomerulonephritis in one third, and a membranoproliferative pattern in almost 10% of biopsies. The glomerulonephritis persists until the infection has been eradicated, but despite therapy, the prognosis is poor (3,4,68,410).

As we already emphasized earlier in this chapter, many glomerulonephritides associated with bacterial infections other than *streptococcus* are not truly postinfectious (1). The bacterial infection causing the glomerulonephritis is frequently persistent, and the pathogenic bacteria are in the body at the time the glomerulonephritis is diagnosed. This has important therapeutic implications with respect to the use of immunosuppressive drugs. In our experience, it is a frequent mistake to consider an infection-associated glomerulonephritis postinfectious.

Glomerulonephritis Associated With Staphylococcal Infections

In the past, most glomerulonephritides associated with staphylococcal infections were secondary to endocarditis, deep-seated visceral abscesses, or ventriculoatrial shunts. In the older literature, studies have been published on only a few patients with staphylococcal glomerulonephritis in whom the glomerulonephritis was not secondary to the above conditions (120,121,131,411–414). Interestingly, in more recent years, a number of publications have drawn attention to the association of staphylococcal infection and glomerulonephritis not related to endocarditis or ventriculoatrial shunts (415–431). The earliest reports came from Japan and were subsequently followed by reports from the United States (4,13,415–431). Most of these staphylococcal organisms are coagulase-positive *S. aureus*, but rarely even coagulase-negative *Staphylococcus epidermidis* infection can be associated with acute glomerulonephritis. Many of these infections caused by methicillin-resistant strains of *Staphylococcus aureus* (MRSA) or *Staphylococcus epidermidis* (MRSE) are difficult to treat. Staphylococcal enterotoxins acting as superantigens have been implicated in the pathogenesis, and mild to prominent glomerular IgA immune complex deposits are seen, warranting the term "IgA-dominant staphylococcal infection–associated glomerulonephritis."

IgA-Dominant Staphylococcal Infection–Associated Glomerulonephritis

There is increasing focus on staphylococcal infection–associated glomerulonephritis because of the following:

1. In developed countries, the incidence of PSAGN has declined because of successful treatment of acute streptococcal infections. On the other hand, staphylococcal

infection–related glomerulonephritis is on the rise because of emerging drug-resistant staphylococcal strains and increase in nosocomial and community-acquired staphylococcal infections (2–4,68).

2. The elderly population (above 60), particularly those with underlying diabetes mellitus, malignancy, and other comorbidities, are increasingly diagnosed with infection-associated glomerulonephritis. *Staphylococcus* is the leading cause of infection-related glomerulonephritis in this population (1–4).
3. Patients with staphylococcal infection–associated glomerulonephritis frequently have active ongoing infection at the time the glomerulonephritis is diagnosed. This is different from the prototypical "postinfectious" (poststreptococcal) glomerulonephritis that develops after the infection (upper respiratory tract or skin infection with *streptococcus*) has completely resolved, either naturally or after antibiotic treatment. In glomerulonephritis of active staphylococcal infection, the infection does not resolve naturally but is commonly persistent and difficult to treat (e.g., infected foot ulcers in diabetic patients, postsurgical wound dehiscence, endocarditis, deep-seated visceral abscess, osteomyelitis). These patients frequently suffer from comorbidities, and they sometimes may have mixed (multibacterial) infections. Overt signs of infection may not be clinically evident, and sometimes the infection comes to attention only after the renal biopsy (1). There is general agreement that the prognosis in cases of "glomerulonephritis with active infection" is guarded in sharp contrast to the acute "postinfectious" glomerulonephritis in children (2–4,420,428–430).
4. IgA-dominant or codominant immune complex deposits (along with C3, occasionally with IgG) are commonly seen in *staphylococcus* infection–associated glomerulonephritis; therefore, the differential diagnosis from IgA nephropathy (and Henoch-Schönlein purpura) can be difficult. This has important treatment implications because giving immunosuppressive medications to patients infected with *staphylococcus* can have dire consequences (418,432–436).

Recent literature has described this condition under different names, such as IgA-dominant postinfectious or poststaphylococcal glomerulonephritis (in fact, most of these cases are not truly postinfectious) (426,427,429,430), staphylococcal infection–associated glomerulonephritis mimicking IgA nephropathy (428), or staphylococcal superantigen-associated glomerulonephritis (415).

Prevalence

The exact incidence and prevalence can be difficult to calculate, because bacterial culture results are unavailable in a large percentage of patients whose kidney biopsies show features of ongoing infection associated IgA-predominant glomerulonephritis. This could be because many of these patients are elderly with several comorbidities and are treated empirically with antibiotics (without culture studies) with resultant negative blood cultures. We previously reported eight patients with staphylococcal infection–associated glomerulonephritis over a period of 1 year from October 2004 to October 2005, based on the renal biopsy material at The Ohio State University (428). Over the following years, we have expanded our experience. During the period 2004 to 2011, out of 5192 native kidney biopsies, a total of 37 (0.7%) biopsies with (culture-proven) staphylococcal infection–related glomerulonephritis were seen. In addition, there were at least thirty other biopsies, with histologic features of infection-associated glomerulonephritis as well as clinical signs of infection in the patient, but no definitive culture results available (so the prevalence is probably higher). In the series by Nasr, et al. (427) among 4600 biopsy samples processed from 2000 to 2002, five cases had IgA-dominant *staphylococcus* infection–associated glomerulonephritis (0.1%). In the report by Haas, et al. (429), of the 6334 renal biopsies examined over a period of 4 years (2004 to 2007), 13 (0.2%) showed IgA-dominant infection-associated glomerulonephritis. Documented staphylococcal infection was present in 6 of 13 cases. In the report by Worawichawong et al. (430), 0.8% (7 of 905) of the biopsies fulfilled the clinical and pathologic criteria for IgA-dominant infection-associated glomerulonephritis, and 4 of 7 had proven staphylococcal infection. These patients usually have an underlying debilitating condition, such as diabetes (32% in our series of 37 patients), malignancy, severe trauma, extensive surgery, chronic infections such as Hepatitis C or severe coronary artery disease requiring catheterization, bypass arterial grafting or stent placements. Multiple simultaneous bacterial infections can occasionally be present.

Nasr et al. from the Mayo Clinic focused on infection-related glomerulonephritis in the elderly population that included staphylococcal as well as nonstaphylococcal infections (3). They report a biopsy incidence of 0.9% (93 of 10,080) over a period of 11 years from 2000 to 2010 of "postinfectious" glomerulonephritis in adults (age above 50 years). In addition to staphylococci, other infectious agents such as streptococcus, pneumococcus, pseudomonas, enterococcus were implicated (3). In 41.9% of the patients in the series by Nasr et al., the infectious agent was unknown.

The types of infection described in these publications include osteomyelitis (430), septic arthritis (412), discitis (422), pneumonia (121,427), infected leg ulcers (424), rectal abscess, other deep-seated abscesses, peritonitis, and pancreatitis (412,414,428), as well as undisclosed primary site of infection with positive blood cultures (414–416). Many of these infections were associated with MRSA (412,414–419).

Positive blood cultures are commonly found with staphylococcal endocarditis infection. However, in other sites of infection, blood cultures are often negative. Culture studies from the actual site of infection tend to be more useful. Out of the 37 cases in our series with confirmed staphylococcal infection by culture results, 19 patients had MRSA infection, 13 patients had methicillin sensitive *Staphylococcus aureus* (MSSA) infection and 1 patients had MRSE (methicillin resistant *S. epidermidis*); in the remaining patients, the exact speciation was not available. Six patients had endocarditis, five had osteomyelitis, one had septic arthritis, four had pneumonia, nine had infected leg ulcers, five had postsurgical site infection, two had skin wounds from motor vehicle accident, one had groin abscess, one patient had scrotal abscess, one had abdominal abscess, one patient had staphylococcal urinary tract infection, and three had bacteremia with unknown site of infection. Two of the patients had multiple sites of infection at the same time including endocarditis, pneumonia, and paraspinal abscess or pneumonia and abdominal abscess. One patient developed abdominal wound dehiscence after

hemicolectomy with infection of the abdominal wall, infected abdominal mesh, as well infection of the intravenous lines. The increase in the incidence of *staphylococcus* infection–associated glomerulonephritis is probably related to the increasing number of elderly diabetic patients and probably also to the increased incidence of nosocomial infections with MRSA and other staphylococci.

Clinical Presentation and Laboratory Findings The most common presentation is acute renal failure with microscopic hematuria and proteinuria. Proteinuria can be quite severe and in the nephrotic range (even above 10 g/d). Eight of the ten patients described by Koyama et al. (415) had nephrotic range proteinuria at one point during their disease course. Gross hematuria is not very common but can occur. Patients usually have active urine sediment with microscopic hematuria. In our short series of eight patients, one patient (who also had the morphologic pattern of cryoglobulinemic glomerulonephritis with IgA/IgG deposits) had a positive cryoglobulin test (428). Hypertension is common, but this may be multifactorial, due to other co-morbidities. Clinical and laboratory findings in our series of 37 patients with culture-proven staphylococcal infection–associated glomerulonephritis over a span of 8 years are shown in Table 10.6.

Serum complement levels are lowered in a small percentage of patients (up to 30% in our series), but interestingly they can also be normal. Among our 37 patients, low C3 levels were seen in only 9 patients, low C4 was seen in 2 patients (one in combination with low C3). Nasr et al. (3) report hypocomplementemia in up to 72% of the patients in their series. Low C3 is more common than low C4. History of infection in the recent past is usually present even though the specific infective agent may have not been identified at the time of the renal biopsy. In some cases, however, infection may not even be suspected. The signs of active ongoing infection in elderly patients may be masked by other comorbidities such as congestive heart failure and diabetic complications. In some instances, potential sites of infection may be overlooked, most commonly diabetic foot ulcers. Practically, all patients have at least transient staphylococcal bacteremia, which may or may not be detected on blood cultures. In our series of 37 patients with proven staphylococcal infection only, 16 (43%) had positive blood culture results. According to the largest series from Japan (417), the average duration from the detection of the infection to the glomerulonephritis is 5.4 weeks. In some cases, it is difficult to determine when the infection exactly began. This is most common in diabetic patients with chronic leg ulcers and also in patients with surgical complications and multiorganism infections. Often such patients have already received multiple antibiotics (on an empiric basis). We have encountered biopsies from diabetic patients, in whom the foot infection was so persistent that amputation of the infected limb was required to bring the infection under control and to rescue kidney function. In our experience, in diabetic patients with leg or foot ulcers, gangrene, and amputation, osteomyelitis can be a sometimes-overlooked complication.

Up to 30% of patients may present with purpuric skin rash mimicking IgA vasculitis (Henoch-Schönlein purpura) (IgAV) (418,432–436). Eight of the thirty-seven patients in our series presented with petechial skin rash (432) (Table 10.7). Skin biopsy shows leukocytoclastic vasculitis with mild IgA deposits. Kidney biopsies reveal endocapillary proliferative glomerulonephritis with varying degrees of IgA and C3 deposits, which is indistinguishable from IgAV. This is a potential diagnostic pitfall (see Differential Diagnosis section). Four of our eight patients were initially treated with high-dose steroids for presumed IgAV and atleast one patient developed sepsis.

TABLE 10.6 Clinicopathologic characteristics of the 37 cases of culture-positive staphylococcal infection–associated glomerulonephritis from 2004 to 2011 at the Ohio State University Medical Center

Clinicopathologic features	*n*	%
Age (years)	59 ± 10.6 (31–91)	
Ethnicity		
Caucasian	33	89%
African American	3	0.08%
Asian	1	0.02%
Gender		
Males	28	75%
Females	9	25%
Diabetes mellitus	12	32%
Hypertension	13	48%
Staphylococcal strain		
MRSA	19	
MRSE	1	
MSSA	13	
Staph strain unknown	3	
Mixed bacterial infection	3	
Blood culture positive	17	46%
Local wound culture positive	23	62%
Both cultures positive	2	0.05%
Low C3	8	32%
Low C4	1	
Both C3 and C4 low	1	
Complement levels not known	9	
Purpuric lower extremity skin rash	8	21.60%
Type and site of infection		
Endocarditis	6	
Osteomyelitis	5	
Cellulitis; leg ulcers	9	
Pneumonia	4	
Motor vehicle accident, multiple wounds	2	
Septic arthritis	2	
Postsurgical site infection	5	
Visceral abscess	4	
Urinary tract infection	1	
Bacteremia without known specific site of infection	3	
Multiple sites of infection	2	

Pathologic Findings

Light Microscopy

Various light microscopic patterns are observed, and the morphology of staphylococcal infection–related glomerulonephritis represents a spectrum. The light microscopic findings are

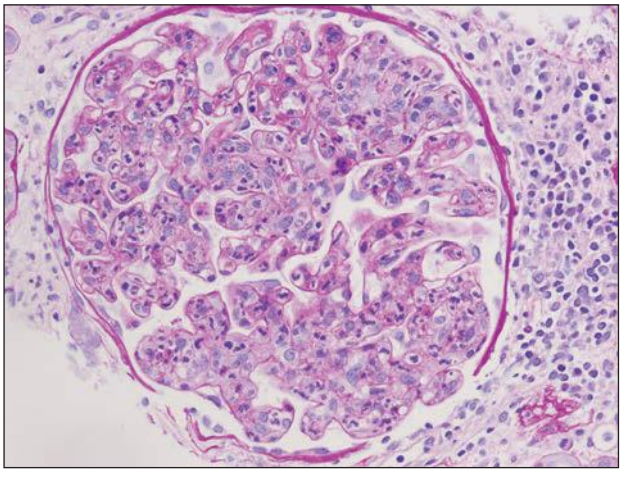
TABLE 10.7 **Clinical features and laboratory results on the eight patients with HSP-like presentation and diagnosed as *Staphylococcus* infection–associated glomerulonephritis at the Ohio State University Medical Center between 2004 and 2011**

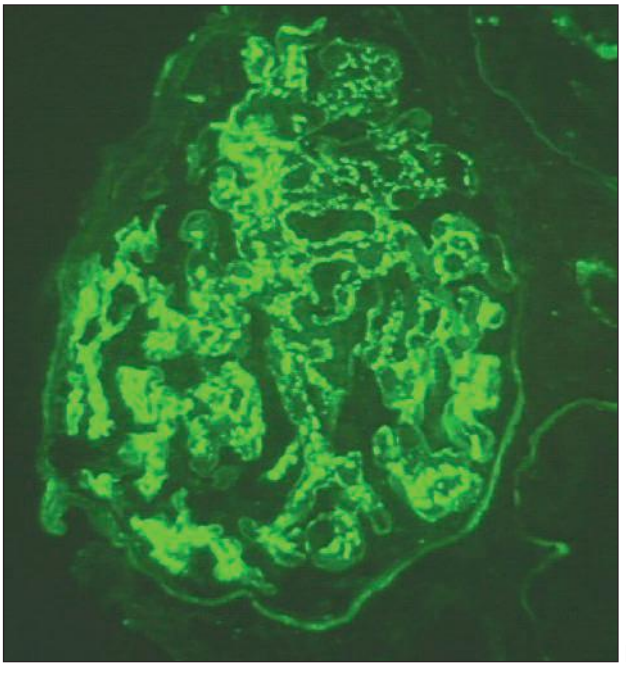
	Age	Ethnicity	Sex	Diabetes	Other comorbidities	Site of Infection	Positive cultures	Organism	Rash	Antibiotics	Corticosteroids Given	S. cr. before onset of ARF	S. cr. at biopsy	Follow-up period	S. cr. at follow-up	C3	C4	Hematuria	Proteinuria	Outcome
1	66	C	F	Present	None	Leg ulcers, osteomyelitis	Wound	MRSA	Vasculitic rash	Linezolid, Amoxicillin Clavulanate	Yes	Not known	9.7	1 mo	3.5	69*	30	>50/hpf	>200 mg/dL	CRF
2	72	C	M	Present	Prostate cancer, s/p radiation, CHF, pneumonia	Leg ulcers	Wound	MRSA	Papular/ purpuric	Yes	No	1	4.5	8 mo	1.4	Not known	Not known	3+	2+	Partial recovery
3	90	C	M	Absent	None	Groin abscess	Abscess	MSSA	Rash after antibiotics; eosinophilia	Yes	Yes	Not known	4.6	0	Dialysis	11*	Normal	Present	Present	No recovery, CRF
4	44	C	F	Absent	Dental problems	Tricuspid valve endocarditis	Blood	MRSA	Erythematous nodular bullous lesions on the legs, LCV with IgA on biopsy	Daptomycin, vancomycin	No	Not known	2	0	2	104	18	50/hpf	Urine protein/ creatinine ratio 4	No follow-up
5	48	C	M	Absent	MVA	Skin	Wound, blood	MRSA	Purpuric lesions, maculopapular vasculitic rash, LCV with C3 on biopsy	Vancomycin, piperacillin and tazobactam	Yes	0.7	1.9	1 mo	3.7	163	25	large	1.2 g/24 h	CRF
6	51	C	M	Absent	Wrist injury, swelling, pain	Osteomyelitis of the wrist	Bone	MSSA	Burning purpuric rash LE and flanks, back, upper extremities; LCV with IgA, C3 on biopsy	Vancomycin, nafcillin	Yes	0.9	2.8	8 mo	1.3	144	24	Present	Trace	Partial recovery
7	48	C	M	Absent	Colon cancer, hemicolectomy	Fistula and abdominal abscess, mesh infection	Blood	MRSE	Petechial LE rash; LCV with IgA, C3 on biopsy	Piperacillin and tazobactam, linezolid, cefuroxime	No	1	2.3	3 yr, 6 mo	2 to 5	169	43	Present	Present	CRF
8	57	C	M	Present	Obese, hypertensive	Skin wounds after working with colored mulch	Wound	MRSA; mixed infection	Vasculitic LE rash, blisters; LCV on biopsy	Multiple	No	1.2	2.8 mg/ dL	2 mo	2.3	Normal	Normal	Present	10 g/24 h	CRF

C, Caucasian; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-sensitive *Staphylococcus aureus*; MRSE, methicillin–resistant *Staphylococcus epidermidis*; S. cr., serum creatinine; LCV, leukocytoclastic vasculitis; CRF, chronic renal failure; LE, lower extremity; *, low C3 levels; exact antibiotics for patients 2, 3 and 8 not known; MVA, motor vehicle accident.

usually that of mesangioproliferative (mesangial hypercellularity without closure of the capillary loops) or endocapillary proliferative immune complex glomerulonephritis with or without crescents. The morphology may be similar to that in PSAGN or other infection-related glomerulonephritis. In our series of 37 patients, 16 cases (43%) showed enlarged glomeruli and diffuse endocapillary hypercellularity with polymorphonuclear leukocytes resembling PSAGN (2,3,427–430) (Figs. 10.25A and 10.26A). Some biopsies show a membranoproliferative (MPGN) pattern of injury with thickening and duplication of capillary loops. In other biopsies, the endocapillary hypercellularity may be focal and segmental in distribution as seen in 9 (24%) of our biopsies. Crescent formation occurs occasionally (2,3,428–430). Twelve of our thirty-seven biopsies (32%) showed crescents/necrotizing lesions of the capillary loops (Fig. 10.27). These varied from small subtle segmental necrotizing lesions (Fig. 10.28A) to large cellular crescents. Few admixed fibrocellular crescents may also be seen, but they are unusual given the acute nature of the disease. In a minority of biopsies (5 of 37), despite the presence of crescents and/or necrotizing glomerular lesions, the remaining glomeruli appeared unremarkable, a histologic pattern reminiscent of ANCA-associated glomerulonephritis. In four of five cases, the immune complex deposition also tended to be quite mild (see Fig. 10.28B). We have seen three biopsies in which, in addition to extensive endocapillary hypercellularity, few glomerular "hyalin thrombi" were evident (Fig. 10.29) suggestive of cryoglobulinemia, but these deposits did not show microtubular substructure on electron microscopic examination.

Overall, glomerular mesangial hypercellularity is common and can vary from mild segmental to prominent and diffuse. The mesangial hypercellularity may in some cases be masked by nodular mesangial matrix expansion secondary to underlying





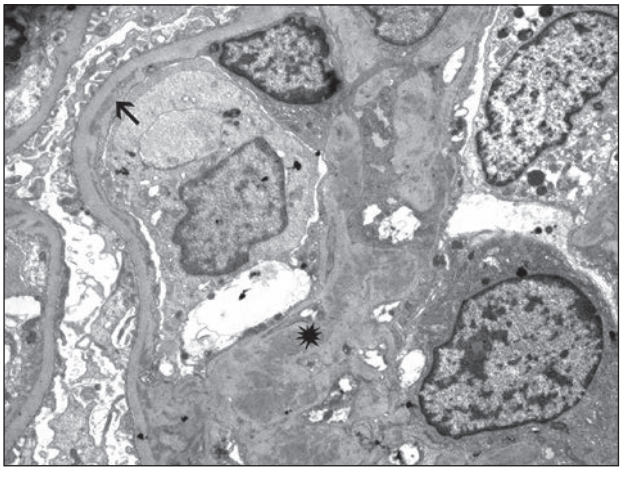
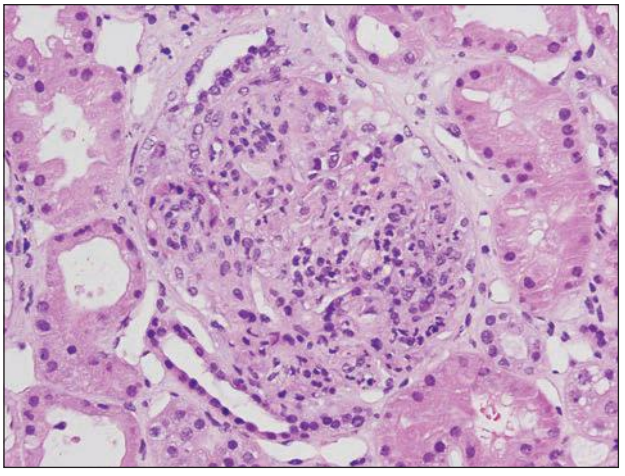
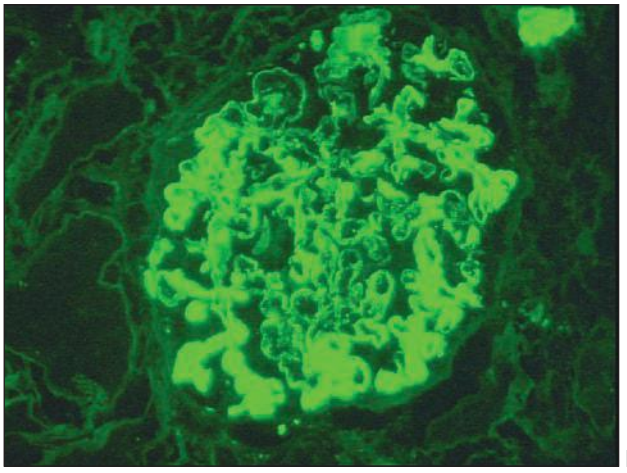


FIGURE 10.25 **A 48-year-old male with MSSA endocarditis. A:** Diffuse endocapillary hypercellularity with numerous polymorphonuclear leukocytes. (H&E, ×400.) **B:** Immunofluorescence showed bright granular C3 deposits (bright IgG, but less intense IgA were also noted) (×400). **C:** Electron micrograph showed mesangial deposits (*asterisk*) and small, scattered subendothelial deposits (*arrow*). (Uranyl acetate and lead citrate, ×44,000.)



A



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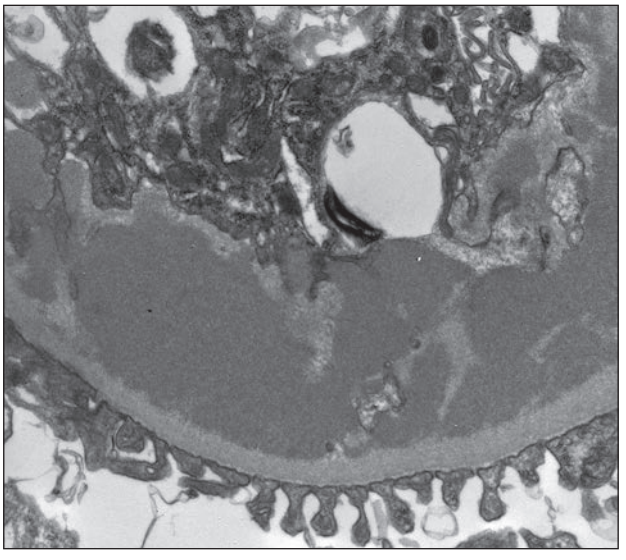

C

FIGURE 10.26 A patient with multiple infected skin wounds following a motor vehicle accident. Wound cultures were positive for MRSA and *Pseudomonas aeruginosa*. **A:** Segmental endocapillary proliferative lesion with polymorphonuclear leukocytes. (H&E, ×400.) **B:** Immunofluorescence showed massive IgA deposits (×400). Strong IgG and C3 were also present. **C:** Electron micrographs show large subendothelial immune-type deposits. (Uranyl acetate and lead citrate, ×20,000.).

diabetic glomerulosclerosis (Fig. 10.30A). Interestingly, in many patients, the histologic findings are relatively unremarkable with only mild mesangial expansion and mesangial hypercellularity (Figs. 10.31A and 10.32A) (120,121,414). Based on the literature review and on our experience, the light microscopic appearance of the glomeruli, including the degree of glomerular hypercellularity, and the clinical activity do not show a good correlation. ATN is commonly seen. Red blood cells in tubules can be present on the biopsy. Red blood cell casts may also be evident and were numerous and conspicuous in 24% of our biopsies. Interstitial inflammation tends to be quite mild in our experience. Interstitial fibrosis and tubular atrophy depend on the underlying condition of the kidney. A moderate degree of interstitial fibrosis and tubular atrophy was present in 35% of our biopsies. It was mild to absent in the remaining biopsies.

Immunofluorescence Microscopy

The most characteristic finding is the IgA dominance or codominance in the glomerular deposits, resembling the staining pattern in primary IgA nephropathy (Berger disease) or IgA vasculitis (Henoch-Schönlein purpura) (see Figs. 10.26B and 10.30B). IgA and IgG staining in *staphylococcus*-related glomerulonephritis was noted already in 1980 by Spector et al. (121). Most of the recent literature agrees that IgA is either the predominant or the codominant immunoglobulin in these deposits (1,2,4,120,121,414,418,423,424,427–430). However, occasionally, the IgA staining can be mild and segmental. Weak or absent IgA deposits (in the presence of appropriate clinical history and morphologic findings) does not exclude the possibility of *Staphylococcus* infection–associated glomerulonephritis (see Fig. 10.28B). C3 is almost always present even when IgA staining is weak (see Figs. 10.25B and 10.30C). Early components of the complement cascade, such as C1q and C4, are usually not seen. In rare instances, immunofluorescence reveals a pauci-immune pattern (no significant deposits) (336). These patients usually also have crescents and therefore mimic ANCA–associated pauci-immune crescentic and necrotizing glomerulonephritis (see Figs. 10.28B and 10.31B) (336). History of recent or ongoing infection, especially endocarditis, should be carefully investigated in such cases.

The intensity and extent of IgA immunofluorescence staining can vary widely from trace to bright. Granular IgA staining is seen predominantly in the mesangium but can also be seen scattered along segments of the glomerular capillary loops. Sometimes, the staining can be bright, but by electron microscopy, the deposits appear scant and seen only along

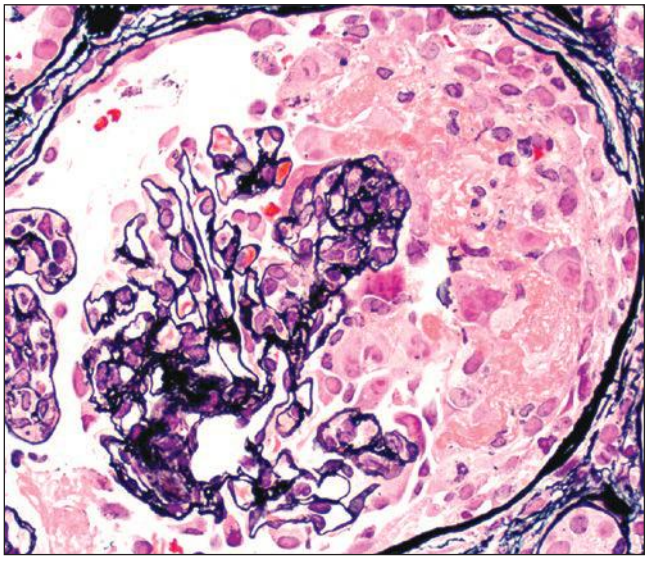

FIGURE 10.27 Biopsy of a 91-year-old female with staphylococcal pneumonia and positive blood cultures. A large cellular crescent. (Jones methenamine silver, ×400.)

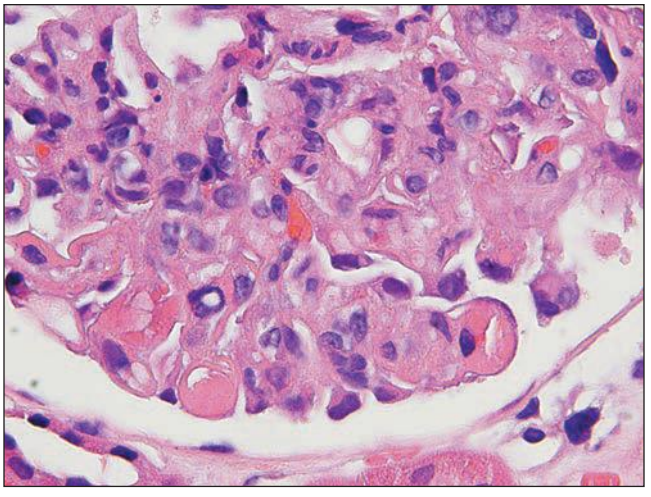

FIGURE 10.29 Hypercellular glomerulus with occasional glomerular endocapillary hyalin thrombi in a patient who developed MRSE infection following resection of a cerebellar glioma. After vancomycin treatment, the patient recovered renal function. (H&E, ×600.)

peripheral capillary loops around the expanded nodular mesangium of glomeruli in diabetic patients. IgA staining was absent in 3 of our 37 cases with *staphylococcus* infection–associated glomerulonephritis. In such cases, C3 staining alone can be very helpful. C3 tends to be bright, coarsely granular, and quite abundant (similar to that seen in PSAGN). Also, the extent of IgA immunofluorescence can vary from one glomerulus to the other within the same biopsy. Rarely, staining for all three immunoreactants IgG, IgA, and C3 can be weak (5 biopsies in our series of 37 patients). Moderate to prominent codominant granular IgG immunofluorescence was seen in 6 and mild granular IgG staining in 12 of our 37 biopsies. Smudgy IgG staining in the mesangium or linear staining along the glomerular capillary loops is often noted in diabetic patients; this IgG staining pattern is common in the kidneys with diabetic glomerulosclerosis and is considered nonspecific (the glomerular staining for albumin is similar). We encountered three biopsies with globular cryoglobulin-like glomerular capillary hyaline thrombi (without microtubular substructure on electron microscopy). In two of these three biopsies, the deposits showed strong staining for IgA and C3 with no IgG, and one of the patients tested positive for cryoglobulins. One biopsy with glomerular capillary hyaline thrombi showed strong IgG and C3 staining with no IgA; this patient was negative for cryoglobulins. Mesangial granular fluorescence for lambda light chain tends to be stronger than for kappa light chain in

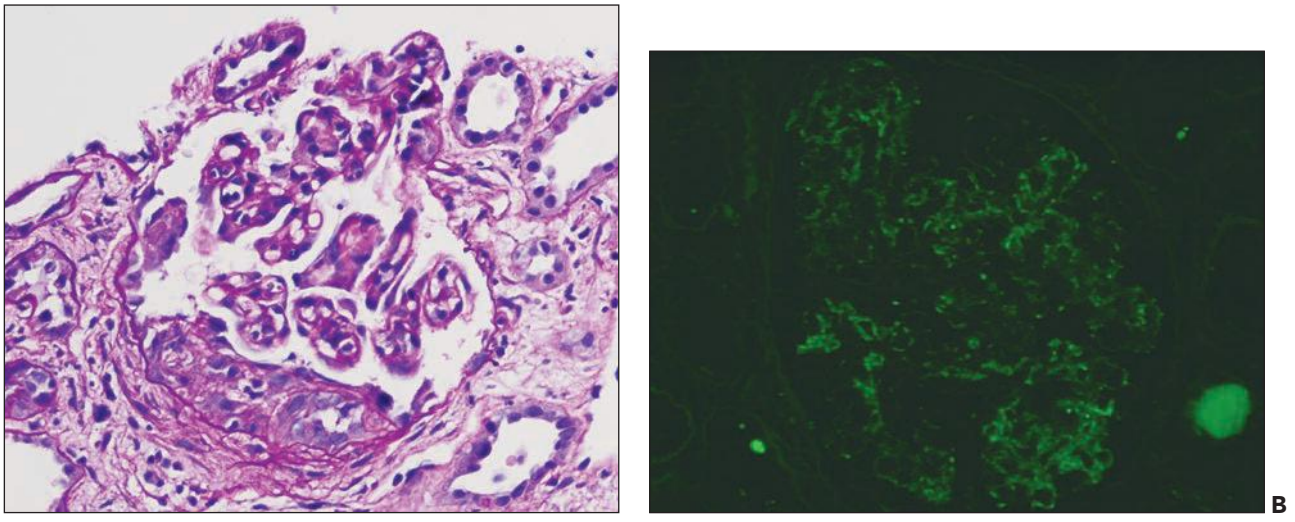

FIGURE 10.28 Renal biopsy of a 63-year-old patient with MSSA knee osteomyelitis. A: Fibrocellular crescent without relevant glomerular endocapillary hypercellularity. (H&E ×400.) **B:** Immunofluorescence showed only mild granular IgA deposits (×400). IgG and C3 were absent.

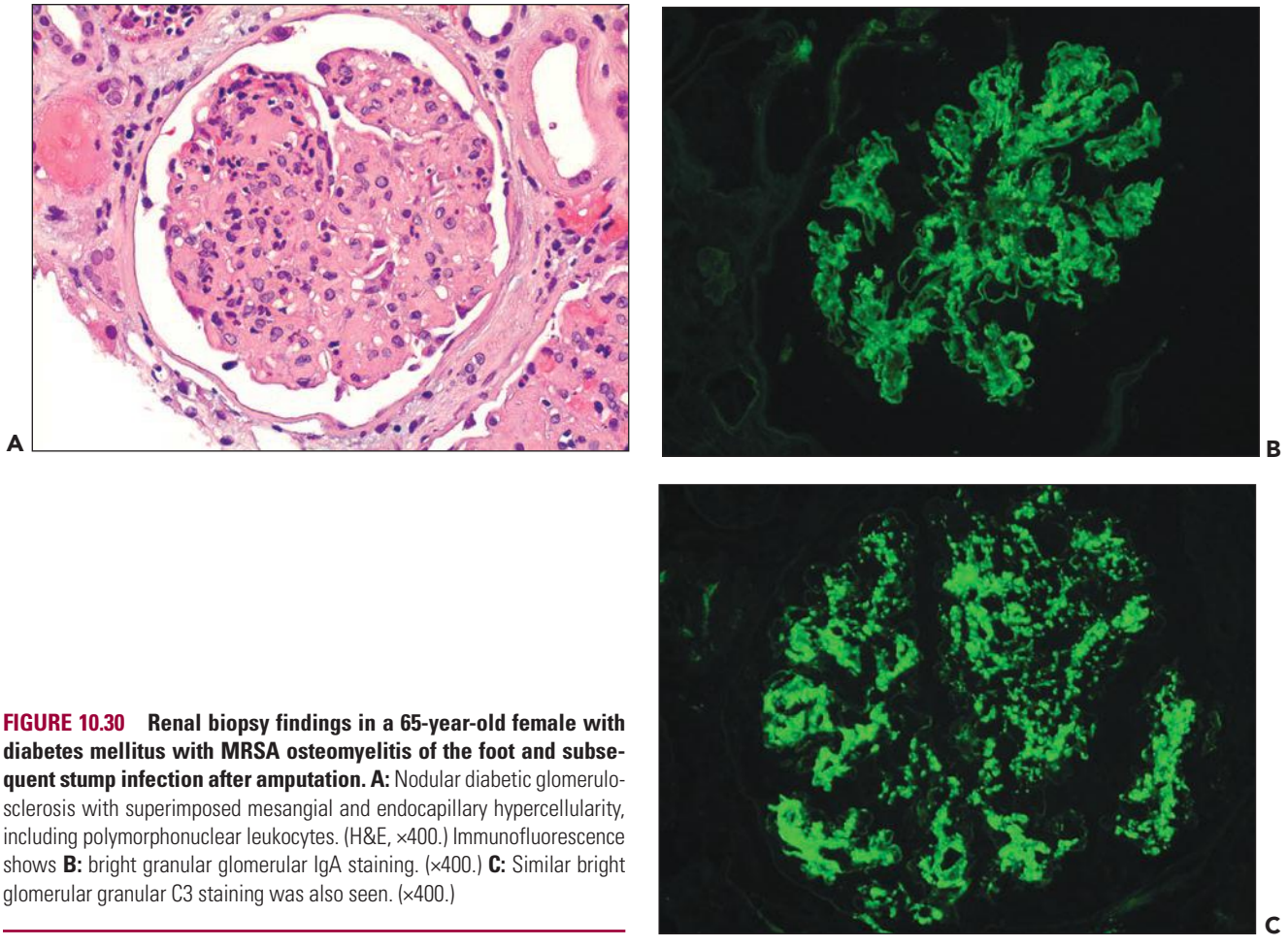

FIGURE 10.30 Renal biopsy findings in a 65-year-old female with diabetes mellitus with MRSA osteomyelitis of the foot and subsequent stump infection after amputation. A: Nodular diabetic glomerulosclerosis with superimposed mesangial and endocapillary hypercellularity, including polymorphonuclear leukocytes. (H&E, ×400.) Immunofluorescence shows **B:** bright granular glomerular IgA staining. (×400.) **C:** Similar bright glomerular granular C3 staining was also seen. (×400.)

most cases (similar to that seen in idiopathic IgA nephropathy). Immunofluorescence staining for IgM and C1q tends to be quite inconspicuous, but segmental IgG deposits (probably nonspecific) are not unusual. Bright fibrinogen staining can help to identify focal segmental necrotizing lesions or crescents.

Electron Microscopy

The degree of electron-dense immune complex deposition tends to vary from case to case. Electron-dense deposits are described in the mesangium in most publications that detail morphologic findings; however, subepithelial and occasional subendothelial deposits can also occur (2–4,420,424,428). In our experience, mesangial electron-dense deposits are present but can vary from few scattered deposits to several easily identified deposits (see Figs. 10.25C and 10.31C). These may be accompanied by small scattered intramembranous and/or subendothelial deposits (Fig. 10.32 B). Subendothelial electron-dense immune-type deposits tend to be few and small. Numerous subendothelial deposits may be seen, albeit rarely. In our series of 37 biopsies, 6 showed several subendothelial deposits, out of which 3 biopsies contained large subendothelial deposits (see Fig. 10.26C). In one of these patients, large intraluminal and subendothelial cryoglobulin-like deposits were noted but without microtubular substructure (428). "Humps" (large subepithelial deposits bulging outward from the boundary of the glomerular capillary basement membrane toward the Bowman space) may occur (Fig. 10.33), resembling PSAGN, but it is more common to see intramembranous and smaller subepithelial deposits rather than true "humps," and the latter are not a prerequisite for making this diagnosis. Some case series describe "humps" occurring very commonly in *Staphylococcus* infection–associated glomerulonephritis (2). In fact, it has been listed as one of the criteria for diagnosis (2). We emphasize, however, that these are not specific to this condition, and its absence does not exclude the possibility of infection–associated glomerulonephritis. Subepithelial humps can be seen in other diseases like MPGN, C3 glomerulopathy, and rarely lupus glomerulonephritis. Also, subepithelial humps may be seen in infection–associated glomerulonephritis caused by other pathogens as well, such as gram-negative bacteria and nonbacterial pathogens (2).

Etiology and Pathogenesis

Antibodies against staphylococcal antigens have been proposed in the pathogenesis already in the 1970s. Sato et al. (414) detected antistaphylolysin antibodies in 71 patients with acute glomerulonephritis, and in four of these patients, the staphylococcal antigen was visible in the glomerular mesangium by immunofluorescence. Polyclonal elevation of serum IgA and IgG, as well as circulating immune complexes, is frequently detected (120,414,418). One hypothesis is that staphylococcal enterotoxins act as superantigens (120,414–417,419).

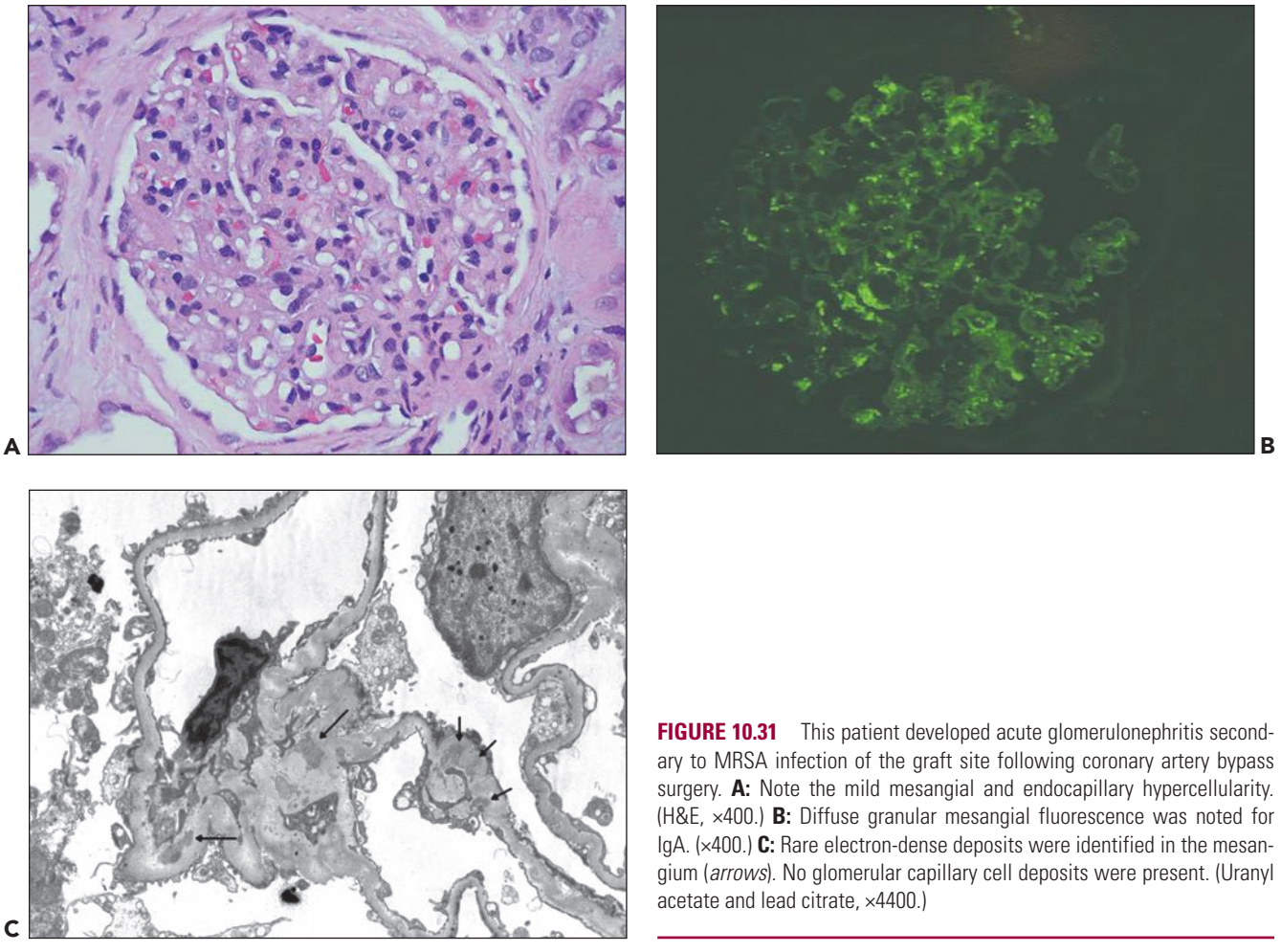

FIGURE 10.31 This patient developed acute glomerulonephritis secondary to MRSA infection of the graft site following coronary artery bypass surgery. **A:** Note the mild mesangial and endocapillary hypercellularity. (H&E, ×400.) **B:** Diffuse granular mesangial fluorescence was noted for IgA. (×400.) **C:** Rare electron-dense deposits were identified in the mesangium (*arrows*). No glomerular capillary cell deposits were present. (Uranyl acetate and lead citrate, ×4400.)

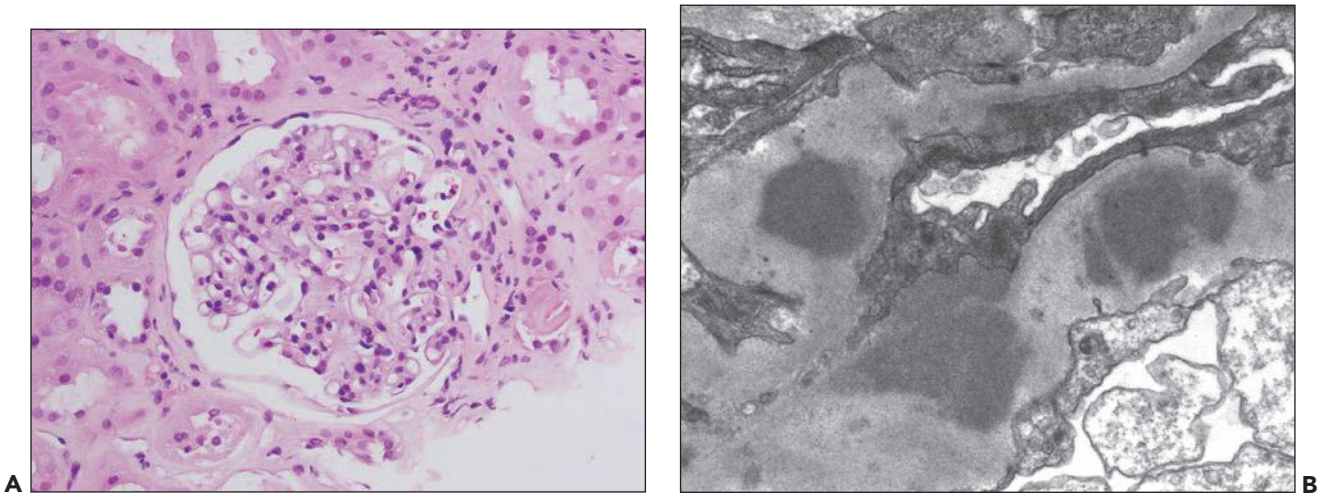

FIGURE 10.32 **Renal biopsy findings in a 66-year-old male with femoral catheter wound infection, MSSA sepsis, and endocarditis. A:** The glomeruli showed only mild mesangial hypercellularity and occasional intracapillary polymorphonuclear leukocytes. (H&E, ×400.) **B:** Electron micrograph shows prominent intramembranous and subepithelial electron-dense immune-type deposits. (Uranyl acetate and lead citrate, ×17,000.)

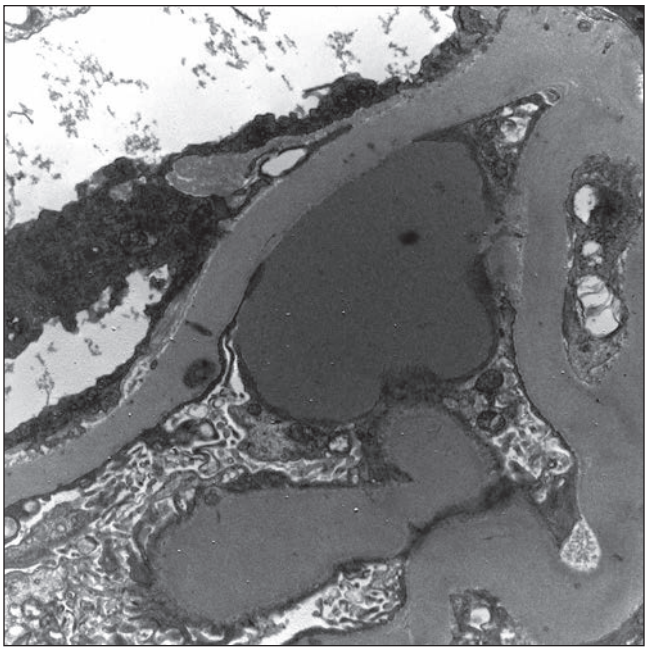

FIGURE 10.33 A patient with MRSA leg cellulitis. Large subepithelial humps. (Uranyl acetate and lead citrate, ×10,000).

The enterotoxin is usually staphylococcal enterotoxin C, A, or the toxic shock syndrome toxin-1. Superantigens can directly bind to MHC class II molecules on antigen-presenting cells without intracellular antigen processing to form peptides that can fit into the MHC molecule groove on the surface of the antigen-presenting cell. Also, the superantigen can directly bind to the T-cell receptor V beta region of a large percentage of the total T-cell population, irrespective of the antigen specificity of the receptor. These superantigens are strongly mitogenic for the T cells causing marked T-cell proliferation, and subsequent release of large amounts of lymphokines/cytokines. These cytokines, in turn, will cause polyclonal B-cell activation and immune complex formation and, eventually, glomerulonephritis. Hirayama et al. (434) in their series of six patients with staphylococcal infection–induced HSP-like (IgA vasculitis) clinical syndrome with acute glomerulonephritis have demonstrated increased number of T cells bearing specific Vβ chain of T-cell receptor (Vβ 5.2, 5.3 and 8) compared to normal controls and to patients whose *S. aureus* infection had improved. Serum levels of cytokines (ILs 1β, 2, 6, 8, and tumor necrosis factor–alpha) were also significantly higher than in normal individuals, and these normalized after staphylococcal infection had healed. They conclude that in addition to superantigens, conventional *Staphylococcus* antigens also play a role in the pathogenesis of glomerulonephritis. Staphylococcal enterotoxins acting as superantigens are also implicated in other diseases such as staphylococcal toxic shock syndrome. Minute concentration of superantigens can activate the immune system receptors because they bind with strong avidity to T-cell antigen receptors and class II MHC molecules. Koyama et al. (422) expanded this hypothesis and proposed that the *S. aureus* cell envelope antigen is a crucial pathogenetic factor in the development of IgA nephropathy. These investigators found this antigen in 68% of renal biopsy specimens from patients with IgA nephropathy. The same group from Japan developed an experimental model of IgA nephropathy in mice following biweekly immunization of the animals with antigens derived from *S. aureus* mixed with Freund adjuvants (437). Of course, these data will need further confirmation.

Differential Diagnosis

As detailed above, the morphologic findings can resemble various conditions, including PSAGN, other infection-related glomerulonephritides, MPGN type I, C3 glomerulopathy, IgA nephropathy (or IgA vasculitis), and pauci-immune ANCA-associated crescentic glomerulonephritis. The differential diagnosis is possible only if detailed clinical data, particularly bacterial culture results and serologies, are available. In PSAGN, the presence of IgA in the immune deposits is unusual; therefore, if in an infection-associated glomerulonephritis codominant or dominant glomerular IgA deposits are seen, an underlying staphylococcal infection has to be considered. The differential diagnosis from idiopathic IgA nephropathy or IgA vasculitis can be quite difficult. If no bacterial culture results are available, a *staphylococcus* infection–associated glomerulonephritis could easily be diagnosed as a primary IgA nephropathy. Of course, as indicated above, theoretically, it is possible that a subset of IgA nephropathy cases are related to staphylococcal infection (422). Also, up to 30% of patients with *staphylococcus*-related acute glomerulonephritis may develop purpuric skin lesion; therefore, the clinical presentation may mimic Henoch-Schönlein purpura (425,432–436). Adult Henoch-Schönlein purpura is a rare disease. In our experience, it is more common to see adult IgA-dominant glomerulonephritis associated with purpuric skin lesions in patients with *staphylococcus* infection. Therefore, if an adult patient presents with symptoms of IgA vasculitis and a renal biopsy shows IgA-dominant glomerulonephritis, an underlying staphylococcal infection should always be taken into consideration.

The clinical presentation can be quite helpful in making the differential diagnosis. As pointed out above, just based on morphologic findings, the diagnosis of IgA nephropathy will likely be made. However, if a patient's kidney biopsy shows IgA and C3-dominant/codominant immune complex deposits with active glomerular lesions and the patient presents with acute kidney injury, including active urine sediment, heavy proteinuria, and even the slightest signs of infection, one has to consider the possibility of an underlying *staphylococcus* infection. As pointed out above, blood cultures are frequently positive and the site/origin of infection may be quite difficult to identify. We always raise the possibility of an underlying *staphylococcus* infection if we see IgA and C3 codominant glomerulonephritis with an acute clinical presentation. Although IgA nephropathy can show exacerbations with episodic gross hematuria following upper respiratory tract infections, most of these patients do not develop acute kidney injury or heavy proteinuria, and sometimes, C3 staining is mild or even absent. In typical cases of progressive IgA nephropathy, the patients have a protracted, slowly progressive clinical course with persistent microscopic hematuria, hypertension, and gradually worsening proteinuria. Renal biopsy findings usually show a mixture of chronic and active glomerular lesions, including segmental or global glomerular sclerosis, glomerular scars, adhesions, and old fibrous crescents. In acute *staphylococcus* infection–associated glomerulonephritis, chronic glomerular lesions are

unusual, and if they are present, they may not be related to the infection (they could be secondary to diabetic nephropathy, for example).

Rare cases of pauci-immune crescentic and necrotizing glomerulonephritis have been reported in association with staphylococcal infection (417,422). In fact, the possibility that *S. aureus* infection may play a role in the pathogenesis of ANCA-associated granulomatosis polyangiitis (previously known as Wegener granulomatosis) has been proposed (431). Fortunately, such cases are rare, but the clinical management can be quite problematic because if a pauci-immune crescentic and necrotizing glomerulonephritis is secondary to *staphylococcus* infection, treatment with cyclophosphamide and steroid may be contraindicated.

MPGN, particularly MPGN type I, may be difficult to differentiate, particularly because *S. epidermidis* infections can "cause secondary MPGN" (see section on ventriculoatrial shunts). Fortunately, in most instances, the obvious clinical history of infection, fever, and positive cultures make the differential diagnosis relatively easy. A subset of MPGN cases would now be classified under the recently described entity C3 glomerulopathy, in which C3 deposits are the predominant finding on immunofluorescence staining with absence of immunoglobulin components. As mentioned above, IgA staining can be weak to absent in few cases of *Staphylococcus* infection–associated glomerulonephritis, but these tend to have strong staining for C3. Such cases may be confused with the disease entity of C3 glomerulopathy. Rarely, hyaline thrombi resembling cryoglobulin deposits can be seen in association with bacterial infections, and the patients may have mixed type III cryoglobulinemia. This should be differentiated from noninfectious causes of cryoglobulinemia.

Clinical Course and Outcome

In contrast to children with postinfectious glomerulonephritis, in whom complete remission occurs in the vast majority of patients, the prognosis in adults with staphylococcal infection–associated glomerulonephritis is much more guarded. A significant proportion of adults does not recover and have persistant renal dysfunction or progress to ESRD. Persistent renal dysfunction develops in 8% to 54% of patients and progression to ESRD in 4% to 33% of patients as described in several case series (2–4,315,410,428). Poor prognostic indicators in adults include older age, higher serum creatinine at biopsy, tubulointerstitial scarring, and presence of underlying debilitating conditions (2,3,428–430). The goal of treatment should be eradication of the infection and management of additional comorbidities that these elderly patients commonly have, such as diabetes, hypertension, congestive heart failure, and surgical complications (2,167,410). Appropriate antibiotics (for methicillin-resistant or methicillin-sensitive *staphylococcus*), surgical debridement of the infected wounds, or infection sites such as cellulitis, osteomyelitis, are important (421,438). In severe cases of diabetes, even amputation of the infected lower extremity may be required to bring the infection under control. Some antibiotics (such as high doses of vancomycin) used for staphylococcal infections can themselves be nephrotoxic and can cause acute tubular injury and interstitial nephritis. In such instances, it can be difficult to determine the cause(s) of the renal dysfunction. Antibiotic levels, especially vancomycin levels in the blood, may have to be monitored, and the antibiotic may have to be changed to reverse the drug-induced nephrotoxicity. The role of immunosuppressive therapy in adult patients with ongoing *Staphylococcus* infection–associated glomerulonephritis is highly controversial and considered contraindicated in most instances. There are no randomized prospective clinical trials on the role of steroids in this condition. The available data are based on retrospective studies. Steroid use is common in patients with accompanying leukocytoclastic vasculitic skin rash because it can mimic IgA vasculitis (Henoch-Schönlein purpura) (432–435). Sometimes, the rash may even disappear following administration of steroids. However, the patients subsequently may develop sepsis without improvement in renal function (432). Despite few case reports describing good results after the use of steroids in adults with infection-associated glomerulonephritis (with or without crescents) and renal dysfunction (308,349), none of the case series with statistical analyses have found a beneficial effect of steroids on outcome (2–4,315,410,428,432). Based on the absence of any proven benefit and the potential risk of sepsis, immunosuppressive therapy is not recommended in most adults with staphylococcal infection–associated glomerulonephritis.

Glomerulonephritis Associated With Other Infectious Agents

Pneumococcal infections may cause acute proliferative glomerulonephritis (352–362) as well as other morphologic patterns (352,354,355), such as pure mesangial proliferative glomerulopathy. The clinical signs are hematuria, proteinuria, edema, and renal insufficiency. Glomerular subepithelial humps are found, and C3 and pneumococcal antigens can be detected in the mesangial regions and along the glomerular capillaries by immunofluorescence (354,355). Properdin also has been found to be present in a similar distribution (352), and C3, C3 proactivator, and pneumococcal antigen are sometimes evident focally along the TBMs (355). In view of these findings, it was suggested that the alternative pathway of complement activation had been stimulated by the pneumococcal polysaccharide. Complete recovery has been noted.

Meningococcal infections may cause acute proliferative glomerulonephritis (358,359). Patients with this infection may not have clinical evidence of glomerulonephritis, but they undergo biopsy because of laboratory evidence of circulating immune complexes. Immunofluorescence and electron microscopic studies reveal changes similar to those noted in typical PSAGN.

There are many other causes of acute infection–associated glomerulonephritis (see Table 10.5). Proliferative glomerulonephritis has been reported in patients with pneumonia owing to *Klebsiella* and *Mycoplasma* organisms (360,383–386). This disease may manifest in the form of hematuria, proteinuria, or renal insufficiency, but it may also be clinically occult (360,383–386). *Klebsiella* capsular polysaccharide antigens, immunoglobulins, and complement have been demonstrated in the glomerular capillaries and in the mesangial regions of a patient with focal proliferative glomerulonephritis and pneumonia caused by *Klebsiella* organisms (360). In this case, the eluate of the glomerular-bound IgG had antibody specific to *Klebsiella*. Similar evidence of diffuse proliferative glomerulonephritis, with mycoplasma antigen, immunoglobulin, and complement deposition along the glomerular capillary wall and mesangium, was noted in a patient with pneumonia caused by

Mycoplasma organisms (383). In *Mycoplasma*-associated glomerulonephritis, renal biopsy most frequently shows diffuse endocapillary proliferative glomerulonephritis with low serum complement levels and primarily mesangial immune complex deposition (383–386). One patient had findings of characteristic glomerulonephritis. *Mycobacterium gordonae*– and *Coxiella burnetti*–associated glomerulonephritis also has been reported (367,381).

Bookman et al. (373) reported three patients with *Bartonella henselae* endocarditis–associated crescentic and necrotizing glomerulonephritis. The patients all had crescentic and necrotizing glomerulonephritis mimicking a vasculitis; however, they had mesangial or subendothelial immune complex deposits by electron microscopy and C3 deposits on immunofluorescence. A very similar case was presented at the 2004 meeting of the American Society of Nephrology in St. Louis, MO, by Dr. Helen Liapis (Fig. 10.34). These cases may mimic crescentic glomerulonephritis secondary to a vasculitis; however, the correct diagnosis is important to make because treatment is antibiotics instead of immunosuppression.

Salmonella typhi has been noted to trigger glomerulonephritis with glomerular deposition of immunoglobulins and complement (364,439), although the clinical evidence of glomerular disease has usually been slight. Various protozoan and viral organisms can produce glomerulonephritis, although the glomerular changes by light microscopy are not as marked as those in classic acute postinfectious glomerulonephritis (see Table 10.5).

Viruses have been incriminated in the evolution of acute immune complex–mediated glomerulonephritis (391,397, 401,440–443). Smith et al. (391) prospectively studied 240 previously healthy military personnel with nonstreptococcal upper respiratory tract infections to find evidence of asymptomatic glomerulonephritis. Nine patients were found to have red blood cell casts in the urine and focal or diffuse mesangial hypercellularity (with mesangial deposits of C3) on renal biopsy. Five of these nine patients had serologic evidence of viral infection with adenovirus or influenza A or B, and four of nine had hypocomplementemia. Subsequent renal biopsies showed histologic improvement or loss of immunofluorescent staining.

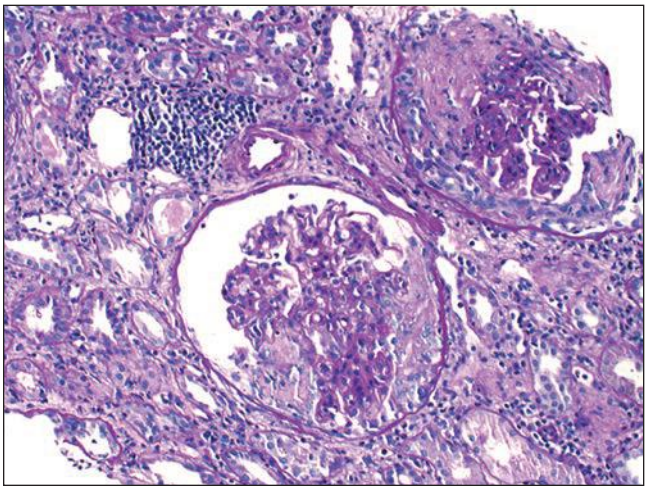

FIGURE 10.34 Glomerular crescent formation in a biopsy taken from a patient with *B. henselae* endocarditis. Immunofluorescence in this patient showed IgG-, C3-, and C1q-positive mesangial and glomerular capillary deposits. Electron microscopy confirmed mesangial deposits and the presence of subendothelial and intramembranous deposits along the glomerular capillary loops. (PAS, ×200.) (Courtesy of Dr. Helen Liapis).

POSTSTREPTOCOCCAL AND OTHER INFECTION-RELATED GLOMERULONEPHRITIDES SUPERIMPOSED ON DIABETIC NEPHROPATHY

In the United States, diabetic nephropathy has become the most common cause of ESRD. Therefore, the incidence of glomerular disease superimposed on diabetic nephropathy is also on the rise. Because diabetic patients are susceptible to infections, they also develop infection-related renal diseases more commonly. In our biopsy material, an increasing proportion of adult infection-related glomerulonephritides occur in diabetic patients and many of them have underlying diabetic nephropathy. The same tendency is reported in the literature (2–4,68,427,444–446). Nasr et al. (4) studied 86 adult patients with postinfectious glomerulonephritis. Twenty-five (29%) of them had diabetes and 16 (18.6%) had diabetic nephropathy with diabetic glomerulosclerosis. The same authors later published 109 elderly patients with postinfectious glomerulonephritis and found that 49% of them were diabetic (3). Haas (446), at the Johns Hopkins Hospital, found some ultrastructural evidence (subepithelial deposits in the glomerular mesangial notch region) of postinfectious glomerulonephritis in 23 of 104 kidney biopsy specimens with the primary pathologic diagnosis of diabetic nephropathy (22% of all biopsies with diabetic nephropathy). Although this number represents the high end of the spectrum, one must not underestimate the significance of the problem. It is quite possible that in many cases of unexplained deterioration of renal function in patients with underlying diabetic nephropathy, an undiagnosed postinfectious glomerulonephritis may be in the background. A large study from Italy by Mazzucco et al. (445), describing 393 renal biopsies from diabetic patients, reports 37 biopsies with postinfectious glomerulonephritis. Twenty six of these biopsies were from patients who had evidence of diabetic nephropathy and only eleven of them from patients who had no histologic evidence of diabetic nephropathy (445). Most of these cases represent PSAGN; however, any kind of infection, particularly staphylococcal infections, may induce a proliferative glomerulonephritis superimposed on diabetic nephropathy (427).

The diagnosis of infection-associated glomerulonephritis superimposed on diabetic nephropathy may not be easy because the underlying changes of diabetic glomerulosclerosis may alter the typical histologic manifestations (Fig. 10.35). Some degree of mesangial hypercellularity may occur in diabetic nephropathy. One has to look carefully for intracapillary accumulation of inflammatory cells, which is frequently not diffuse in infection-associated glomerulonephritis superimposed on diabetic glomerulosclerosis. Immunofluorescence frequently shows various nonspecific staining patterns in diabetic nephropathy, including linear staining for albumin and IgG along the glomerular and TBMs and smudgy or coarsely granular, frequently somewhat

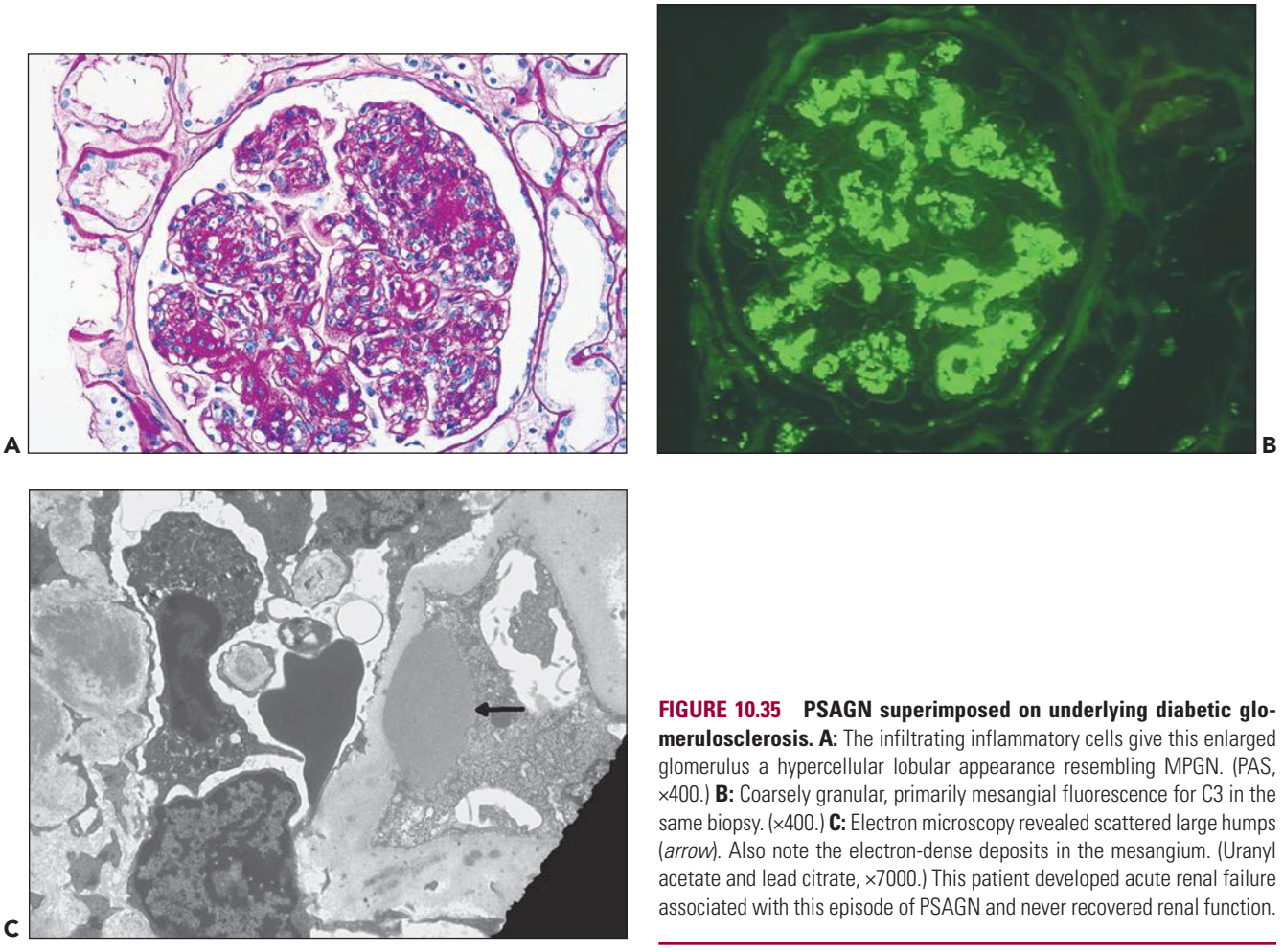

FIGURE 10.35 PSAGN superimposed on underlying diabetic glomerulosclerosis. A: The infiltrating inflammatory cells give this enlarged glomerulus a hypercellular lobular appearance resembling MPGN. (PAS, ×400.) **B:** Coarsely granular, primarily mesangial fluorescence for C3 in the same biopsy. (×400.) **C:** Electron microscopy revealed scattered large humps (*arrow*). Also note the electron-dense deposits in the mesangium. (Uranyl acetate and lead citrate, ×7000.) This patient developed acute renal failure associated with this episode of PSAGN and never recovered renal function.

segmental, fluorescence for C3. Therefore, using immunofluorescence alone may not be sufficient to make the diagnosis. One has to review carefully the electron micrographs in search for subepithelial humps as well as mesangial, intramembranous, and subendothelial deposits. Unfortunately, in many biopsies with diabetic glomerulosclerosis, electron-dense deposits, representing hyalin change, are abundant and can be difficult to differentiate from true immune complex deposits. As also indicated earlier, Haas (136) emphasizes careful electron microscopic studies to diagnose a so-called incidental healed postinfectious glomerulonephritis. In his opinion, subepithelial deposits in the mesangial notch region (between folds of the glomerular basement membrane overlying mesangial regions) are of particular diagnostic value. The importance of this finding needs further confirmation. We encounter occasional subepithelial deposits in mesangial notch regions. Such deposits frequently (but not always) have a microspherical substructure (Fig. 10.36) and, in our opinion, represent a nonspecific degenerative change with no proven diagnostic specificity.

The prognosis of postinfectious glomerulonephritis in patients with underlying diabetic nephropathy appears to be much worse than that of postinfectious glomerulonephritis without any underlying renal disease. In the study of Nasr et al. (4) on adult postinfectious glomerulonephritis, 9 of 11 patients (81.8%) with underlying diabetic glomerulosclerosis progressed to ESRD. Their extended study on a larger number of elderly patients showed similarly dismal outcome; 55% of patients with diabetic glomerulosclerosis progressed to ESRD during the short follow-up period in contrast to the 19% progression rate in patients without diabetic glomerulosclerosis (3). As pointed out above, it is not uncommon that an otherwise relatively mild postinfectious or infection-associated glomerulonephritis may represent the last "hit" to the kidney with underlying diabetic nephropathy. Because of the prominent microvascular disease, frequent hypertension, cardiac disease, and other complications of diabetes, renal function in these patients may never recover.

GLOMERULONEPHRITIS ASSOCIATED WITH DEEP-SEATED VISCERAL ABSCESSES

Clinical Features

Whitworth et al. (447) and Beaufils et al. (447,448) first described the association of glomerulonephritis and visceral suppuration in the absence of infective endocarditis. The temporal association between deep-seated infection and glomerulonephritic immune-type lesions suggests an etiologic relationship between these two conditions. Serum cryoglobulins and circulating

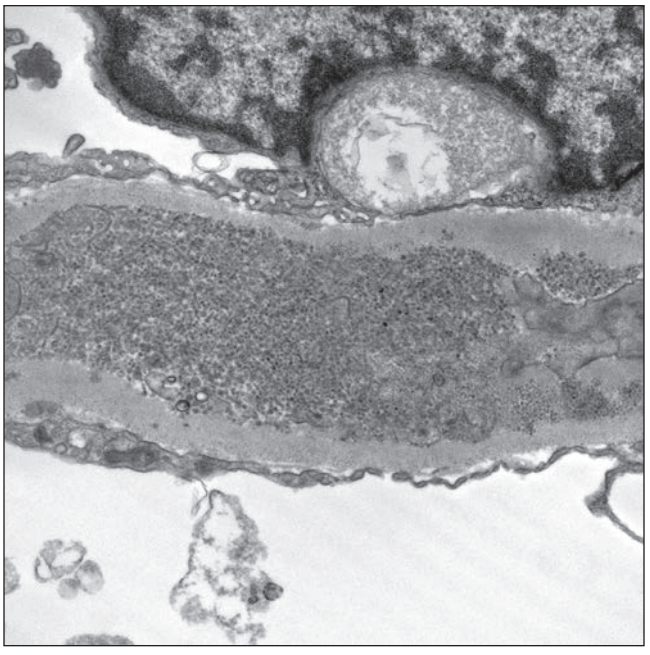

FIGURE 10.36 Deposits in mesangial groove regions with microspherical substructure represent a common ultrastructural finding, particularly in diabetic patients. The pathologic and clinical significance of such deposits is unclear. (Uranyl acetate and lead citrate, ×20,000.)

immune complexes are often present (447,448) and usually disappear when the infection is cured. Hypocomplementemia is not generally a feature unless infective endocarditis is also present (380); however, the data suggest activation of the alternative pathway of complement activation.

Deep suppurative infections are caused by either gram-positive or gram-negative organisms; as noted previously, bacterial endocarditis also can be present. Bacteremia may not be documented in all patients. Two patients with *Entamoeba histolytica* liver abscess–related proliferative immune complex glomerulonephritis have been reported (449,450). A recent case report describes MPGN with glomerular C3 and IgG deposits in a patient with nocardial cerebral abscess (451). Most cases are owing to intrathoracic abscesses, but wound infections, subphrenic abscess, abscess of the appendix, abdominal abscess, rectal abscess, septic abortion, cutaneous abscess, mediastinitis, osteomyelitis (including mastoiditis), and infection of valvular and vascular Dacron prostheses have all been reported (120,411,423,448,452–454). Lung abscesses were most commonly noted in those patients with the crescentic form of the disease (447). In our experience, *staphylococcus* infection–associated osteomyelitis in diabetic patients is becoming a more and more common disease underlying a glomerulonephritis. The duration of the deep-seated abscess ranges from a few weeks to a few years (409,448). The morphologic picture correlates somewhat with the duration of the preceding infection. Those patients with infection of less than 2 months' duration had only mesangial hypercellularity, whereas patients experiencing more than 2 months of infection had either acute diffuse glomerulonephritis with crescents or crescentic glomerulonephritis (408,448).

The patients are febrile and generally quite ill. Microhematuria is present in all patients, and gross hematuria is noted in approximately half of them. Proteinuria is usually present and may be marked. Hypertension is found in about one fourth of patients, and oliguria is evident in almost half. Rapid progression of renal insufficiency can occur (408,447). Some three fourths of patients require dialysis. Extrarenal manifestations include purpura, arthralgia, and cutaneous necrosis, especially if there is cryoglobulinemia.

Pathologic Findings

A number of morphologic patterns have been noted, including crescentic glomerulonephritis (447), MPGN with or without crescents (409,444,447,448), acute diffuse endocapillary proliferative glomerulonephritis (411,423,427,454) with or without crescents (409,448), and mild mesangial hypercellularity (121,413,421). Immunofluorescence staining for immunoglobulins and complement is positive in the glomeruli in a granular pattern. As pointed out earlier, if the abscess is secondary to staphylococcal infections, the immunofluorescence may reveal predominant or codominant IgA fluorescence, in addition to C3 and occasionally IgG. In other cases, the predominant immunoreactant is usually C3 with some IgG. Electron microscopy most commonly demonstrates glomerular mesangial deposits; glomerular subepithelial deposits have been noted in patients with *S. aureus* infection–associated glomerulonephritis (427–430). Small intramembranous and subendothelial deposits may also occur. Magil (454) reported eight patients with remote visceral infections who all had diffuse proliferative glomerulonephritis; the sites of infection included the lung, blood, and retroperitoneal space. Histochemical staining with the α-naphthyl acetate stain for nonspecific esterase showed numerous intraglomerular monocytes/macrophages (fewer than are seen with cryoglobulinemia but more than are evident in other types of proliferative glomerulonephritis, such as systemic lupus erythematosus or cases of MPGN).

Prognosis and Outcome

Deep-seated abscess–associated glomerulonephritis is not postinfectious glomerulonephritis, and the treatment should focus on the eradication of the infection (1,438). When there is complete eradication of the deep-seated infection (through surgical means and/or aggressive antibiotic treatment), renal function generally recovers (409,447). Subsequent renal biopsies show morphologic evidence of healing, with only mild residual mesangial hypercellularity, capillary wall thickening, and a few globally sclerotic glomeruli (409,447). If the infection cannot be controlled, the glomerulonephritis persists (as demonstrated on subsequent biopsies) and patients progress to renal failure (409,447). Incomplete therapy (delayed or suboptimal) results in moderate to severe renal insufficiency that may require dialysis. Persistent microhematuria or proteinuria may be found in those who otherwise appear to have recovered normal renal function (409,447).

GLOMERULONEPHRITIS ASSOCIATED WITH INFECTIVE ENDOCARDITIS

Infection of the heart valves historically has been divided into *subacute bacterial endocarditis*, which usually affects a previously damaged heart valve that is susceptible to bacterial organisms

of low virulence, and *acute bacterial endocarditis*, which usually affects a previously normal heart valve that is infected by a virulent bacterial organism. Infection of a rheumatic heart by organisms of the *Streptococcus viridans* group is an example of the former, whereas *S. aureus* infection in an intravenous drug abuser is an example of the latter. The natural history of glomerulonephritis owing to infectious endocarditis has been dramatically influenced and altered by the advent of antibiotic therapy and changing epidemiologic patterns. Although some authors have discontinued use of this subdivision of terminology (subacute and acute), we retain it in this chapter for historical purposes.

Glomerulonephritis in Subacute Bacterial Endocarditis

Renal complications of subacute bacterial endocarditis include glomerulonephritis, renal infarction, abscesses, and therapy-related or therapy-induced tubulointerstitial nephritis and acute tubular epithelial injury. We shall consider only glomerulonephritis here. *Embolic nonsuppurative focal nephritis* was the name given by Löhlein at the turn of the century (454) to the renal lesions noted in seven patients with subacute bacterial endocarditis. Baehr (455) and Bell (456) described glomerulonephritis at autopsy in patients with subacute and acute endocarditis. The lesion in subacute endocarditis was characterized by a number of glomeruli with segmental or local necrosis, often also with segmental hypercellularity or sclerosis. Polymorphonuclear leukocytes and nuclear fragments also were present. Thus, different stages of segmental lesions appeared to be represented. Most of the glomeruli were histologically normal.

The term *focal embolic nephritis* implied that the renal disease was caused by embolization of infectious material. Although most investigators do not accept this pathogenetic mechanism, a few authors have described embolization of infectious material to glomeruli in endocarditis (457). Because it is now apparent that the mechanism is virtually always immunologic, the term *focal and segmental proliferative, necrotizing, or sclerosing glomerulonephritis* is preferred. The most common organisms leading to this pattern are the *S. viridans* group and coagulase-negative staphylococci, including *S. epidermidis*, although *Actinobacillus actinomycetemcomitans*, *Streptococcus mitis*, *Haemophilus influenzae*, *Neisseria gonorrhoeae*, enterococci, and *Chlamydia psittaci* have all been reported.

Glomerulonephritis associated with subacute bacterial endocarditis is becoming rare because of the declining incidence of subacute bacterial endocarditis, but the true incidence is difficult to determine because most reports do not come from prospective and consecutive examinations of clinical and morphologic material from unselected patients.

Clinical Presentation

Renal involvement occasionally is the initial manifestation of subacute bacterial endocarditis, especially when the diagnosis of endocarditis is not considered or when blood cultures show negative results. However, the clinical findings of renal involvement may be mild and are usually overshadowed by the cardiac features and the effects of systemic infection. Gross hematuria may be present, but the microscopic hematuria is more commonly noted. Hematuria may persist or resolve, only to appear again on several occasions. Gross hematuria may be caused by renal infarctions rather than by glomerular lesions (168). Proteinuria (mild) and granular casts may be detected in the urine. The nephrotic syndrome and hypertension are unusual. Depression in serum complement level is frequent but not always present, nor is it specific to renal involvement (458–462). Before the era of antibiotic therapy, hypocomplementemia was noted in 90% of patients with diffuse glomerulonephritis and 60% of patients with focal glomerulonephritis in subacute bacterial endocarditis. Most patients appear to have activation of the classic complement pathway (463).

When the BUN and serum creatinine are elevated, the renal lesion is more likely to be the diffuse form of glomerulonephritis rather than the focal form (367,455,464–466). Focal glomerulonephritis may occur in the absence of any clinical renal involvement (466). Uremia was present in approximately 5% to 10% of patients with endocarditis in the era before antibiotics (467). Following the introduction of antibiotics, this figure fell to 3% to 4% (467). No uremic deaths were found in penicillin-treated patients with fatal subacute bacterial endocarditis in the series of Spain and King (468). Among the 52 untreated patients in the same series, 8 patients with diffuse glomerulonephritis and 1 patient with focal glomerulonephritis had uremia.

Glomerulonephritis is common in patients with subacute and acute endocarditis with high titers of ANCA and may be crescentic (336,469–473). Such cases can be problematic for diagnosis because the glomerulonephritis may be "pauci-immune" with few or no detectable glomerular immune complex deposits (336). Differentiating such ANCA-positive endocarditis-associated crescentic glomerulonephritis cases from pauci-immune crescentic glomerulonephritis associated with small vessel vasculitis can be very difficult. From the management point of view, the correct diagnosis is crucial because treatment options are quite different. The differential diagnosis is complicated even more by the fact that, rarely, ANCA-associated small vessel vasculitis may cause cardiac valvular involvement (ANCA-associated noninfectious endocarditis) (472). The ANCA in subacute and acute endocarditis is usually antiproteinase 3 (Pr3-ANCA) (472), but dual ANCA positivity (antiproteinase 3 and antimyeloperoxidase) has also been reported (473). Rarely, ANCA and crescentic glomerulonephritis may be the first manifestation of infectious endocarditis (474). A recent review of the literature by Uh et al. (475) indicates that after successful treatment of the endocarditis, the titers returned to normal in 10 of 15 patients with available follow-up. Some authors advocate immunosuppression, in addition to antibiotics, but this is controversial. The review of Uh et al. (475) indicates that two of the six patients treated with immunosuppression died.

Pathologic Findings

Gross Pathology

The kidneys are either normal size or enlarged. The largest kidneys are in patients who have widespread or diffuse glomerulonephritis. There are petechial hemorrhages and red blood cells within tubular lumens that can be seen as red dots on the surface of the kidney (hence the description "flea-bitten") (471); two thirds of the 30 patients studied by Heptinstall (168) had this appearance. Either fresh or healed renal infarcts were identified in 57% of the cases; the infarcts were either single or multiple and were of a size suggesting obstruction of arcuate or large interlobular arteries.

Light Microscopy

The infarcts noted grossly show various ages. They are sterile and are not different from any other type of sterile infarct.

Glomeruli

A number of light microscopic glomerular patterns are noted. Focal and segmental glomerulonephritis is often present (210,455,456,459,465,468,476). This type of lesion was noted in 50% to 84% of patients studied (349,465,468). Bell (456) found diffuse proliferation in over half his patients and focal glomerulonephritis in 18%. Diffuse glomerulonephritis often had more destructive focal segmental lesions. As mentioned above, crescents may occur, sometimes associated with ANCA (129,336) (Fig. 10.37).

Acute or chronic lesions are observed. A*cute*, or *fresh*, *lesion* consists of fibrinoid necrosis or intracapillary thrombosis confined to one or two glomerular lobules. Polymorphonuclear leukocytes and nuclear debris may be present. There is usually segmental hypercellularity in the affected segment, but it is not always present. Cellular crescent formation may be evident. The active segmental lesions are indistinguishable at the light microscopic level from other forms of focal segmental proliferative or necrotizing glomerulonephritis. A few authors have reported organisms in some of the involved segments (455), but this is very unusual. It is important to remember that even in the focal and segmental form of glomerulonephritis (by light microscopy), there are widespread (diffuse global) deposits throughout all glomeruli when they are studied by electron microscopy or immunofluorescence.

Chronic sclerotic lesions are usually situated at the periphery of one or several lobules. There is usually an adhesion or synechia between the sclerotic region and the Bowman capsule. There may be an adjacent fibrocellular crescent. Layers of fibrotic capsular bands encircling the involved glomerular tufts may be noted, but this is not a specific change. This advanced, or scarred, lesion is most common in those cases of longer duration and is the exclusive lesion found in Libman's healed, or bacterial-free, stage (477). The focal segmental sclerotic change may be difficult to distinguish from idiopathic focal segmental glomerulosclerosis (478).

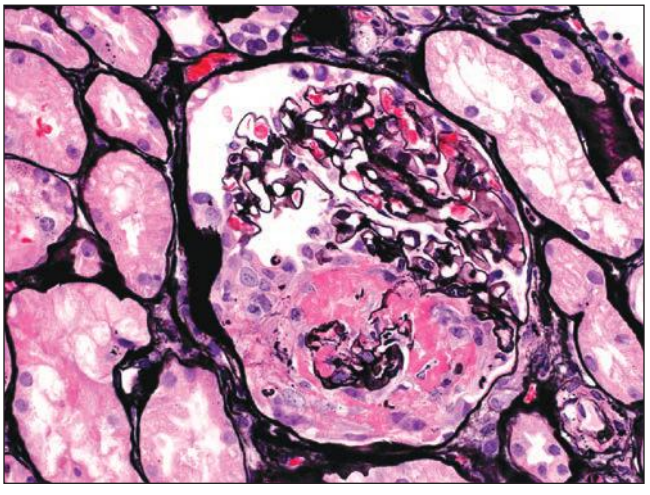

FIGURE 10.37 A segmental necrotizing glomerular lesion (Jones methenamine silver stain, ×400) in a 62-year-old male subacute bacterial endocarditis caused by *S. viridans*. ANCA serology was negative. (Courtesy of Dr. Christopher Larsen.)

The focal and segmental glomerular changes are evenly distributed throughout the kidney. Baehr (455) noted that in his patients, 2% to 75% of the glomeruli were involved. In more than 70% of patients, the segmental glomerular lesions affected from 10% to 40% of the glomeruli (455,464,479,480). Among 15 patients with focal and segmental glomerulonephritis in the series of Heptinstall (168), 15% or more of the glomeruli had lesions in 6 patients, 5% to 14% were affected in 7, and less than 4% were involved in 2. Villarreal and Sokoloff (206) described patients in whom more than 95% of glomeruli were affected. These authors noted the difficulty in distinguishing widespread glomerulonephritis caused by endocarditis from chronic glomerulonephritis when the lesions show evidence of "advanced healing."

Acute diffuse endocapillary proliferative glomerulonephritis also may be encountered (456,459,461,462,479,481). By light microscopy, it may be indistinguishable from typical PSAGN. There may be segmental necrosis, thrombosis, or sclerosis superimposed on the generalized hypercellularity (461,462). Crescents also may be present, but they are generally not so numerous as to warrant the designation of *crescentic glomerulonephritis* (146,461,471,482).

Baehr and Lande (479) have noted greater incidence of generalized diffuse glomerular changes in the so-called bacteria-free stage, and most of the patients studied by Gutman et al. (461) who had repeated negative results on blood cultures showed widespread glomerular involvement. However, diffuse glomerulonephritis can be seen in patients with positive blood cultures, and not all patients with negative cultures have the diffuse lesion. Bell (456) noted diffuse proliferative glomerular lesions in 65% of his patients. The exact incidence of this pattern is difficult to determine because most series are small and the large series are based on autopsy findings. Most studies were performed many years ago when the value of thin sections was not appreciated, and many of the sections shown in these articles were quite thick, thereby exaggerating the cellularity of the glomerular tufts. Marked focal segmental glomerular hypercellularity with closure of the capillaries may coexist with mild diffuse global hypercellularity (456,461,483).

Another glomerular pattern noted is membranoproliferative (mesangiocapillary) glomerulonephritis (484,485). Most of the older studies are not detailed, and it is not possible to determine the precise characteristics of the lesion. The finding of membranoproliferative pattern is not surprising, considering that it is one of the most commonly encountered lesions in patients with shunt nephritis, which also is caused by a nidus of persistent bacterial infection in contact with the circulation.

Interstitium

There is interstitial inflammation regardless of the type of glomerulonephritis, and it can be present even in treated patients with quiescent disease (146).

Tubules

There is acute tubular injury and/or tubular atrophy commensurate with the degree of glomerular damage. Tubular casts (granular and red blood cell) are common.

Arteries

Arterial intimal thickening may be present (146). It may be noted in quite young individuals, and the cause is uncertain.

Immunofluorescence Microscopy

Immunofluorescence microscopy studies in both the focal and the diffuse forms of glomerulonephritis usually show widespread glomerular distribution of immunoglobulins and/or complement, even in the normal-appearing glomeruli. The glomerular staining is located in the mesangial regions and along the glomerular capillary walls. Morel-Maroger et al. (466) described a series of patients, most treated with antibiotics, and reported diffuse granular immunofluorescence along the glomerular capillaries for C3 and, in some patients, for IgG, IgM, and IgA in the mesangial regions. Other investigators have reported a granular pattern for immunoglobulins and C3 along the glomerular capillary walls (459,465) and in the mesangial regions (168,459) cite a case in which most glomeruli were normal by light microscopy although others showed segmental sclerosis. There was mesangial IgG, IgM, and C3, with less intense granular staining along the glomerular capillary walls. Immunofluorescence studies in the diffuse glomerulonephritic form, as noted, show diffuse granular deposition of immunoglobulins and C3 along the glomerular capillary walls and in the mesangial regions (461,462,486). Perez et al. (481) described granular deposition of IgM and C3 in the glomeruli in addition to bacterial antigen demonstrated by the corresponding antiserum. A recent case of proliferative glomerulonephritis with "full house" immunofluorescence in a patient with subacute endocarditis was reported from Taiwan. The patient did not have systemic lupus erythematosus and gradually recovered renal function following treatment with penicillin and gentamicin (487). Rarely, few or no immune complex deposits are seen. This is problematic in patients who are ANCA positive, because differentiation from ANCA-positive small-vessel vasculitis is difficult (336,472).

Electron Microscopy

Ultrastructural studies show discrete electron-dense deposits in the mesangial regions, often very near the endothelium of the glomerular capillary. Boulton-Jones et al. (459) and others (461) have reported glomerular subendothelial and mesangial deposits. Nast et al. (488) encountered immune complex deposits not only within glomeruli but also in the splenic venous sinus basement membranes, substantiating the systemic nature of the immune complex deposition in this disorder.

Etiology and Pathogenesis

Löhlein (476) was the first to describe the renal changes in this condition when he reported seven patients with endocarditis in some of whom organisms of the *S. viridans* group were cultured. He observed streptococci in an embolus in an artery that had led to infarction. This finding suggested to him that the glomerulonephritis was caused by bacterial emboli. This idea was further supported by Baehr (479,489), who noted bacterial emboli in the glomeruli in 5 of 25 patients. The segmentally scarred (sclerotic) lesion was thought to represent a later lesion resulting from healing of the necrotic lesion. Bell (456) considered that the acute glomerular lesion was an intracapillary thrombus that in the larger, but not the smaller, lesions led to necrosis of the glomerular capillaries. Thörig et al. (457) came to the same conclusion after induction of bacterial endocarditis by intravenous injection of live streptococci into rabbits with nonbacterial thrombotic endocarditis.

Longcope (175) suggested that the glomerulonephritic lesion was immunologic rather than infectious. Bell (456) did note in 1932 that "the fact that a certain duration of the infection is necessary suggests that immune bodies may play a role in the formation of the glomerular lesions." It is now apparent that both focal and segmental glomerulonephritis and acute diffuse glomerulonephritis are manifestations of an immunologic reaction and that glomerular immune complexes or ANCA play the major role in the pathogenesis of glomerular injury. Bacterial cultures from kidneys show no growth. It is now recognized that focal glomerulonephritis can be seen in diseases in which there are no sources of emboli, such as systemic lupus erythematosus and microscopic polyangiitis. Patients with known true septic emboli do not generally have this type of glomerular response.

Williams and Kunkel (490) demonstrated depression in the level of serum complement in patients with subacute infective endocarditis. Subsequently, patients with focal or diffuse glomerulonephritis owing to infectious endocarditis also were noted to have hypocomplementemia (462,481,490). The degree of complement depression is directly correlated with the severity of renal involvement. Persistent hypocomplementemia is associated with a failure to control the infection and prevent continuing renal insufficiency (483), whereas normalization of the serum complement takes place with successful antibiotic therapy and the return of renal function (463).

Circulating immune complexes have been found in patients with infectious endocarditis (458,459,462,490). High levels of circulating immune complexes have been noted in patients with less virulent bacteria, right-sided cardiac involvement, and hypocomplementemia. Many of these patients also had extracardiac manifestations of endocarditis (458,460). Circulating immune complexes are persistent or rise when it is not possible to control the infection (460,461,486). Successful antibiotic therapy leads to falling levels of circulating immune complexes (458). Rheumatoid factor also may be present (470), and the titer falls quickly after successful antibiotic therapy (470).

Mixed cryoglobulinemia has been identified in the serum of most patients with infectious endocarditis (460). The levels of cryoglobulinemia (like the levels of rheumatoid factor and circulating immune complexes) fall with control of the infection (460). However, the level of serum cryoglobulinemia (and rheumatoid factor) is not directly correlated with the presence or absence of renal involvement (460).

Some studies have shown that the eluate from a kidney with focal glomerulonephritis caused by infectious endocarditis reacted specifically with bacteria cultured from the patient's blood (465,488). Immunofluorescence studies have demonstrated bacterial antigens in glomerular deposits in endocarditis owing to streptococcal infection (481). It is uncertain, however, whether the glomerular deposits form locally, with the binding of circulating antibodies to planted (possibly bacterial) or native glomerular antigens, or result from the deposition of circulating immune complexes. In summary, in patients with subacute bacterial endocarditis, there is much evidence in support of an immune complex pathogenesis of glomerulonephritis with glomerular immunoglobulin and complement deposits. ANCA may have a pathogenic role in patients with a

paucity of immunoglobulin and complement in glomeruli and circulating ANCA.

Effect of Treatment on Renal Lesions

Most studies indicate that there is partial to total resolution of the renal disease after successful antibiotic therapy (467); however, repeated biopsies are generally not performed. Treatment with antibiotics alone has resulted in renal recovery with loss of proteinuria, circulating immune complexes, and cryoglobulinemia (482). Observations on the incidence of glomerulonephritis in the early years of antibiotic therapy are few and contradictory. Spain and King (468) studied 77 patients with subacute bacterial endocarditis: 52 were not treated, whereas 25 were given penicillin, with treatment starting on average within 1 to 2 months after the clinical onset of the disease. The incidence of focal glomerulonephritis was reduced by half. Diffuse glomerulonephritis was noted in a third of untreated patients, but no case of diffuse glomerulonephritis was noted in the treated patients. Great numbers of sclerotic or healed lesions were identified in the treated group. The efficacy of antibiotic treatment with regard to glomerular damage is, therefore, apparent and has been confirmed by others (146,438,477,482).

Glomerulonephritis in Acute Infective Endocarditis

Antibiotic therapy and prophylaxis, the decline in rheumatic fever, and the marked increase in intravenous drug abuse have all altered the picture of infective endocarditis (483). The routes of infection, types of organisms, and clinical manifestations have undergone major changes. Although the frequency of infection with organisms of the *S. viridans* group has diminished (468), *S. aureus* has become a major cause of bacterial endocarditis (336,483). Infection with this organism has a strong likelihood of causing glomerulonephritis, especially in patients who are intravenous drug abusers. *S. aureus* is the etiologic agent in more than a third of the fatal cases and is responsible for more than half the cases of all types of endocarditis-associated glomerulonephritis in recent series (336,460,463,483). Glomerulonephritis may develop in intravenous drug abusers with *S. aureus* infections following a clinical illness of only 1 week (463). More recently, other microorganisms, including *B. henselae* (373) and *Enterococcus*, have been reported in association with glomerulonephritis (470). With the growing prevalence of intravenous drug abuse, right-sided endocarditis is becoming more common. In fact, in a recent series from referral centers in Little Rock, Arkansas, and the Mayo Clinic, 28% of patients with endocarditis-related glomerulonephritis had tricuspid valve involvement (336).

Irrespective of the infecting organism, glomerulonephritis is uncommon in patients with acute bacterial endocarditis when it is defined as infective endocarditis lasting less than 6 weeks. However, a study by Neugarten et al. (483), conducted at a large metropolitan hospital from 1965 to 1979, found glomerulonephritis in 22% of patients with infective (mostly acute bacterial) endocarditis. Glomerulonephritis was focal in 8% and diffuse in 14% of patients. Before the advent of antibiotics, glomerulonephritis appeared to occur less frequently in cases of acute than in those of subacute bacterial endocarditis (455,456,464,479,480,483). Bell, earlier on (456), noted an incidence of 7% for focal glomerulonephritis in patients with what he termed the *primary acute form* (i.e., those forms that seemed to begin as a bacteremia) and of 6% in patients with the *secondary acute form* (his expression for those patients in whom bloodstream bacterial invasion comes from a known focus, such as acute endometritis or lobar pneumonia). The incidence of focal glomerulonephritis in the subacute form was 53%. Bell (456) found diffuse proliferative or exudative glomerulonephritis in 29% and 33% of patients with primary and secondary acute forms, respectively. Patients with infections caused by organisms of the *S. viridans* group of less than 6 weeks' duration did not have focal glomerulonephritis. The experiences of other workers are similar (168).

The combination of acute infective endocarditis and diffuse glomerulonephritis is usually the result of infection by coagulase-positive staphylococci (*S. aureus*). Largely as a result of drug addiction, however, other organisms are being seen more frequently. They include coagulase-negative staphylococci (*S. epidermidis*) and *Pseudomonas aeruginosa*. A wide range of other bacterial and fungal organisms has been found in those patients. Pulmonary hemorrhage as an initial symptom (at first clinically confused with Goodpasture syndrome) has been reported (490). A study from Birmingham, England, examined 20 renal biopsy specimens and 42 autopsy specimens from patients with endocarditis (470). Interestingly, only 9 patients in the renal biopsy group had acute glomerulonephritis and, according to those authors, 6 of them did not have immune complex deposits, but only crescent formation and necrosis (a pauci-immune pattern). The second most common morphologic pattern in the renal biopsies was acute interstitial nephritis. The most common findings in the autopsy material were localized infarction (19 cases), acute tubular damage (8 cases), glomerulonephritis (7 cases), and cortical necrosis (6 cases). Unfortunately, the morphologic description of the biopsies and of the autopsy specimens is not detailed, and no ultrastructural studies were performed (470). In the section on subacute endocarditis, we briefly addressed the diagnostic challenge in patients with pauci-immune crescentic glomerulonephritis related to endocarditis (336,472). Several of those patients are ANCA positive, and they can be misdiagnosed with small vessel vasculitis. Treating a patient with infectious endocarditis with immunosuppressive medications can have disastrous consequences.

Clinical Presentation

Diffuse proliferative glomerulonephritis is well documented in patients with acute endocarditis caused by coagulase-positive staphylococci (*S. aureus*) (461,490–493). The clinical picture may be dominated by the underlying infectious process, but oliguria may herald the onset of renal involvement. There is often a nephritic process with red blood cells and casts in the urine. Gross hematuria may stem from glomerulonephritis, renal infarction, or drug-related interstitial nephritis. Proteinuria is also often noted, but the nephrotic syndrome is unusual (438,490). Most of the patients have been intravenous drug abusers with *S. aureus* infections. The BUN level is often elevated, and the serum complement level is diminished (461,493). Hypertension is unusual; when it is found, it may have been present before the acute onset of infective endocarditis (485,493).

These laboratory findings may show considerable resolution or improvement (within days to weeks) after the institution

of antibiotic therapy. Renal insufficiency may be relatively mild or may lead to the need for dialysis (483). The degree of renal insufficiency does not correlate with the clinical duration of infective endocarditis. In most patients, the serum creatinine level reaches its peak at or just into the beginning of successful antibiotic therapy and soon declines with therapy. Patients who show signs of renal failure fare less well than those in whom it is absent (483). One group (494) has suggested that addition of plasmapheresis and steroids aids in renal recovery, but additional studies are needed to confirm these findings. The problem of ANCA positivity (usually antiproteinase 3) can provide a differential diagnostic dilemma. The prevalence of ANCA in patients with infective endocarditis is unknown, but it is very well documented (336,472–474). In patients with infectious endocarditis, in addition to ANCA, other autoantibodies, such as rheumatoid factor, cryoglobulins, ANA, and anticardiolipin antibodies, may be observed (472).

Although a transient worsening of renal function may occur before recovery (495), mild to moderate renal insufficiency almost always resolves with proper antibiotic therapy (461,495). Even severe renal failure may heal with antibiotic therapy, although it may take weeks or months to achieve (37). Subsequent biopsies have shown almost complete morphologic resolution in those patients with clinical recovery; the only renal parenchymal changes noted were persistence of mesangial sclerosis and the presence of globally sclerotic glomeruli.

Occasionally, renal insufficiency may persist despite proper antibiotic therapy and dialysis (459,483). Marked residual morphologic changes have been noted long after apparent cure (459). Progressive renal failure and uremic deaths have been reported occasionally even today, when antibiotics are commonly administered (459,483). This is not a typical outcome, and once infectious endocarditis has been effectively treated, complete renal healing should take place. There may be persistent proteinuria or hematuria in some patients despite effective therapy (146,483–485). Some ANCA-positive patients are given immunosuppressive therapy. In our opinion, this should be avoided or done very carefully. Uh et al. (475) reviewed the literature and found that two of six ANCA-positive patients with subacute bacterial endocarditis who were immunosuppressed died.

Pathologic Findings

Light Microscopy

Acute diffuse proliferative glomerulonephritis is the pattern of injury observed most often with acute bacterial endocarditis. The light microscopic features of acute diffuse proliferative glomerulonephritis are a proliferation of endocapillary cells as well as an infiltration by mononuclear and polymorphonuclear leukocytes (Fig. 10.38). Crescents are often evident, but they usually affect less than 50% of glomeruli (Fig. 10.39). The light microscopic changes closely resemble those already described in patients with acute postinfectious (poststreptococcal) glomerulonephritis.

Immunofluorescence Microscopy

Immunofluorescence methods show granular deposits of IgG and C3 along the glomerular capillary walls and, often, in the mesangial regions (455,491–493). In *staphylococcus* infection–induced endocarditis, IgA staining may also be seen. Sometimes, the mesangium is predominantly involved, with less conspicuous deposits along the capillary walls (461,493). Immunofluorescence studies have confirmed the presence of bacterial antigens in the glomerular deposits in patients with infective endocarditis owing to *S. aureus* (491,493); staphylococcal antigens were also demonstrated along TBMs in some patients (491). As pointed out, a proportion of patients have few or no glomerular immune complex deposits.

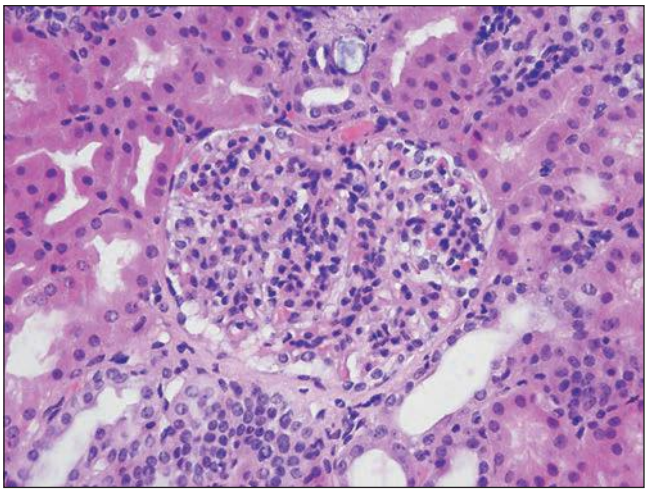

FIGURE 10.38 A proliferative/hypercellular glomerulus from a biopsy taken from an 8-year-old girl with presumed staphylococcal endocarditis. She also had pneumonia, and by the time of blood cultures, she was already on vancomycin and gentamicin. All glomeruli showed similar prominent proliferative changes, but she fully recovered with antibiotic treatment. (H&E, ×400.)

Electron Microscopy

Ultrastructural studies always show discrete electron-dense glomerular deposits, and subepithelial (including humps) and intramembranous deposits are the most common (483,484, 491–493) (Fig. 10.40). Glomerular subendothelial deposits

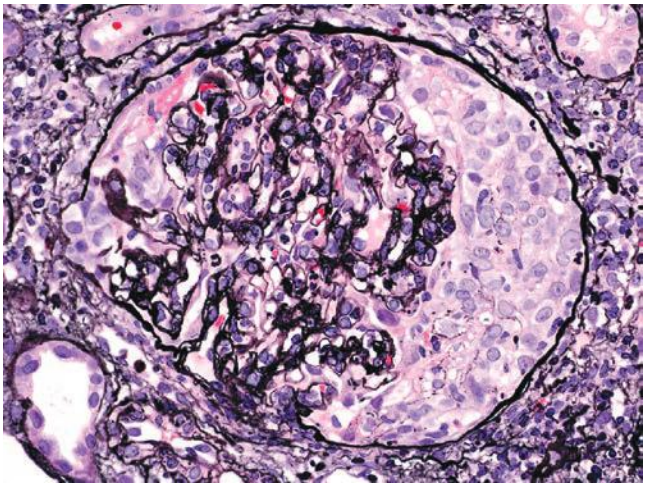

FIGURE 10.39 Cellular crescent (Jones methenamine silver stain, ×400) in a 30-year-old patient with acute MRSA endocarditis. ANCA serology was negative. (Courtesy of Dr. Christopher Larsen.)

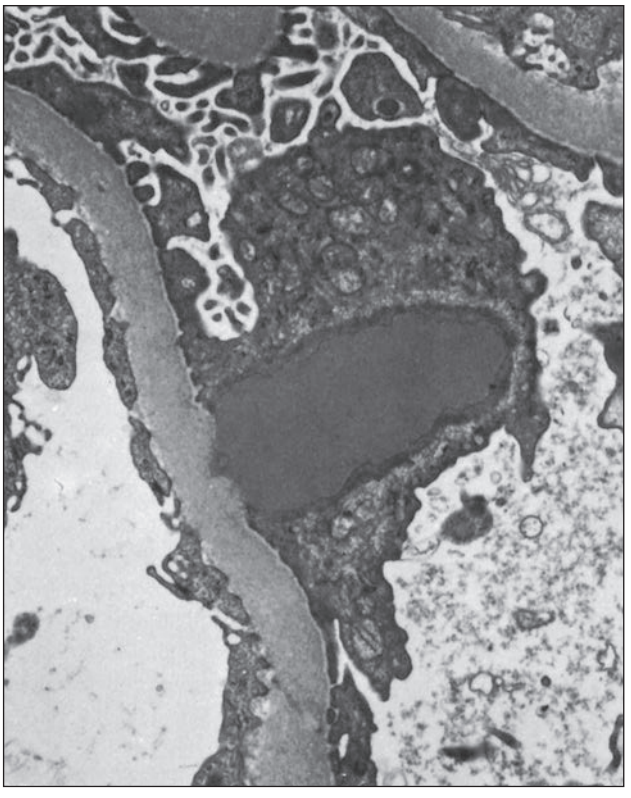

FIGURE 10.40 Electron micrograph shows a hump on the epithelial side of the glomerular capillary basement membrane from a patient with coagulase-positive staphylococcal endocarditis. The hump is covered by a dense zone in the epithelial cytoplasm. (×11,000.) (Courtesy of Dr. G. Striker. From Gutman RA, Striker GE, Gilliland BC, et al. The immune complex glomerulonephritis of bacterial endocarditis. *Medicine* 1972;51:1.)

(483) and mesangial deposits also occur (483,484). Mesangial deposits often predominate in later biopsies studied months after the initial onset of the disease (461). In some of these studies (461), glomerular subepithelial humps did not disappear on subsequent biopsy as they do in classic PSAGN. The persistence of these humps suggests either that immune complexes containing staphylococcal antigens disappear more slowly than those of streptococcal origin or that the source of the antigen has not been completely eliminated.

Etiology and Pathogenesis

Immunofluorescence and electron microscopic findings, along with the depression of serum C3, suggest an immune complex etiologic source and pathogenesis. The continued antigenemia (i.e., bacteremia) probably provides a propitious background for the development of these immune complexes. Most of the cases of infective endocarditis now seen stem from drug addiction (455,492). Narcotic addicts are particularly vulnerable to infective endocarditis (483). Between 40% and 78% of intravenous drug abusers with acute endocarditis owing to *S. aureus* have glomerulonephritis (463,483). The reason for the high incidence in this group is not known, but it may be related to existing antibodies to staphylococcal antigens or to the nonimmune activation of the alternative complement pathway by staphylococcal cell wall antigens.

Hypocomplementemia is noted in 70% of patients with acute bacterial endocarditis and diffuse glomerulonephritis. The incidence in patients with focal glomerulonephritis and acute endocarditis is not known. There appears to be a high rate of activation of the alternative complement pathway in patients with *S. aureus* endocarditis and glomerulonephritis (463). Several pieces of evidence suggest that there may be nonimmune activation of the alternative complement pathway by staphylococcal cell wall antigens in acute endocarditis caused by *S. aureus*. These include an inability to find evidence of circulating immune complexes in some of these patients (463,483), an absence of prolonged illness before evidence of glomerulonephritis, and deposition of complement without accompanying immunoglobulins in immunofluorescence studies. Other organisms have been associated with endocarditis, such as *Neisseria gonorrhoeae* (365) and *Coxiella burnetii* (496). Griffin et al. (490) reported the case of a patient with pulmonary renal syndrome whose renal biopsy showed signs of acute proliferative and exudative glomerulonephritis with a membranoproliferative pattern; large glomerular subendothelial deposits and focal glomerular capillary thrombi were noted. The patient had mixed (type III) cryoglobulins (490).

GLOMERULONEPHRITIS WITH INFECTED VENTRICULOATRIAL SHUNTS AND CENTRAL VENOUS CATHETERS

Infection of ventriculoatrial shunts (inserted for the relief of hydrocephalus) may lead to glomerulonephritis (375–379, 489,497–510). This finding was first described by Black et al. (498) in two children with the nephrotic syndrome and gross hematuria in whom bacterial colonization of a ventriculoatrial shunt had developed. The infecting organism is usually a coagulase-negative staphylococcus (*S. epidermidis*) that has been introduced either intraoperatively, probably from a skin source, or as a result of transient bacteremia to which the shunt is exposed. *S epidermidis* accounts for approximately 75% of shunt infections (505). The exact way in which the shunt becomes infected is not clear (377,497). Coagulase-negative *staphylococcus* sometimes forms a biofilm around the catheter tips in vivo, which is thought to shield the organism from the effects of antibiotics (378). Other reported organisms include *Listeria monocytogenes* (503), peptococcus (509), *Corynebacterium bovis*, *Bacillus subtilis*, micrococcus, diphtheroid species, and gram-positive anaerobic rods, such as *Propionibacterium acnes* (375–379,505–507,511).

Between 6% and 27% of ventriculoatrial shunts have evidence of bacterial colonization (375,509), and low-grade bacteremia may persist for years before the onset of clinical symptoms (497). Cultures of the blood and cerebrospinal fluid may be sterile, and bacterial identification may be achieved only on removal of the shunt (497). Clinically overt glomerulonephritis occurs in approximately 4% to 5% of infected patients (377). The true incidence is not known and would require prospective urinalysis to identify patients with subclinical renal involvement. The latent period between shunt placement and the onset of clinical symptoms ranges from 1 month to 15 years (mean, 4 years). Renal involvement is noted almost exclusively in patients with ventriculoatrial or

ventriculojugular shunts. Renal symptoms in patients with ventriculoperitoneal shunts are uncommon, but they have been reported and are similar to those seen with ventriculoatrial shunts (499,511,512). Ventriculoatrial shunts have been almost totally replaced by ventriculoperitoneal shunts as a form of therapy for hydrocephalus.

Although shunt nephritis is becoming a rare diagnosis, we encounter occasional patients with glomerulonephritis associated with infected central venous catheters (513–515). Although the published cases are still limited, this glomerulonephritis appears very similar to shunt nephritis. The most common pathogen is *S. epidermidis*, colonized to the central venous catheters. Patients have symptoms of acute glomerulonephritis with low serum complement (C3) levels. The morphologic findings are those of an immune complex glomerulonephritis with an MPGN pattern with C3 containing mesangial and glomerular capillary deposits with or without IgG and IgM. Crescents may occur (see below) (513–515).

Clinical Presentation

The clinical features include anorexia, anemia, malaise, and fever (all probably the result of the bacteremia). Fever is noted in more than four fifths of patients. Most of the patients are children, although cases among adults have been reported (age ranges from 2 months to older than 50 years). Patients usually show signs and symptoms of bacteremia and sepsis, although renal involvement may be the first manifestation (375). Serum C3 levels are low in 85% to 94% of patients (505). Purpura, arthralgias, lymphadenopathy, hepatosplenomegaly, hypergammaglobulinemia (IgA, IgM, and IgG), and anemia are common. Less common manifestations are leukocytosis, leukopenia (499), thrombocytopenia (502,516), elevation of the erythrocyte sedimentation rate (375), cryoglobulinemia, and hypertension. Just like patients with infectious endocarditis-associated glomerulonephritis, some patients with shunt nephritis may be positive for ANCA (anti–proteinase 3 antibodies) (511). Renal findings include edema, hematuria (gross in half of patients), and proteinuria (375,489,502–505,509,512,517,518). The proteinuria may be pronounced, and the nephrotic syndrome has been described in about half of patients. One patient even had 38 g of proteinuria per 24 hours (504). Acute oliguric renal failure has been noted (509). Apparent recovery takes place in most patients whose infected shunts or central venous catheters are removed (375,497,499,502,504,505,513–515), although there may be persistent proteinuria or hematuria (499,505). Death may result from complications following removal of the shunt or from the original neurologic disease for which the shunt was inserted (502).

Pathologic Findings

Light Microscopy

Renal biopsies typically show evidence of diffuse proliferative glomerulonephritis or the pattern of MPGN (Fig. 10.41) (501,503,505,509,519). Polymorphonuclear leukocytes are often present within glomeruli. There is typically an increase in the amount of mesangial matrix (498,499,504), and one reported case was referred to as *lobular glomerulonephritis* (499). There is almost always accentuation of the lobular pattern. Crescents may be present (499,501,514). A membranoproliferative glomerulonephritic pattern is found in approximately one half of patients, diffuse (nonlobular) proliferative glomerulonephritis in about one third, and pure mesangial proliferative glomerulonephropathy in the remainder. Focal segmental proliferative glomerulonephritis and crescentic glomerulonephritis have been noted, but less commonly (497).

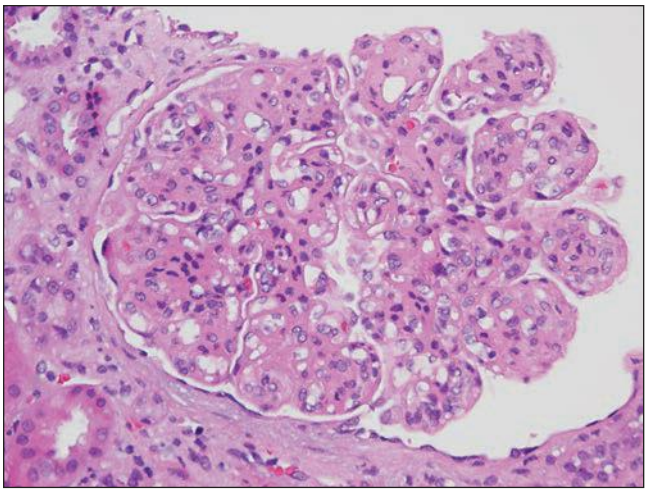

FIGURE 10.41 A lobular hypercellular glomerulus from a biopsy of a patient who had *Propionibacterium acnes*–infected ventriculoperitoneal shunt. (H&E, ×400.)

Immunofluorescence Microscopy

Immunofluorescence shows a granular to coarse broken linear pattern along the glomerular capillary walls and in the mesangial regions (497–499,501,503,504,509). Peripheral glomerular capillary wall immunofluorescent deposits are noted in more than four fifths of patients, whereas mesangial deposits are seen in slightly more than one half. IgG, IgM, C3, and the early complement components (C1q and C4) are present. IgG is found in about two thirds of patients (497), but IgM is sometimes the predominant immunoglobulin (377,499,520). It was found in 84% of patients in one study (497). IgA, usually less intense than IgG or IgM, is present in less than one half of cases (497). Bacterial antigens have been demonstrated (377,499,520). IgM and C1q have been described in peritubular capillaries (499), and immune complexes have been found along the TBMs.

Electron Microscopy

Ultrastructural studies demonstrate discrete electron-dense immune-type deposits on the subendothelial portions of the glomerular capillary walls and in the mesangial regions (499,501,503,504). Glomerular intramembranous and subepithelial deposits also have been detected, but they are rare (497,509). Increased mesangial matrix and circumferential mesangial cell interposition with creation of a new inner basement membrane–like material also can be identified. Subsequent renal biopsy, after successful treatment, reveals complete disappearance of the deposits found by electron microscopy and immunofluorescence techniques (518).

Etiology and Pathogenesis

There is evidence that the renal disease is caused by immune complex deposition. As noted previously in the case of other infectious diseases, there is frequently a depression of the serum complement level (375,499,503,504). Decreases in serum C3

levels are noted in more than 85% of patients (505). Half of patients with acute glomerulonephritis have reduced levels of C4, indicative of activation of the classic complement pathway. Evidence of activation of the alternative pathway is noted in only a few patients (499,503,516). Patients with shunt infections without glomerulonephritis do not have hypocomplementemia. Serum levels of C3 and C4 generally normalize after effective therapy (i.e., antibiotic therapy or shunt removal) (497,516). If therapy is inadequate and the glomerulonephritis persists, the serum complement level remains depressed (516).

Cryoglobulinemia has also been noted (503,509). Cryoglobulins are able to activate the classic complement pathway in vitro (503). Circulating immune complexes and rheumatoid factors are found in most patients (521). Circulating immune complexes, serum cryoglobulins, and serial titers of antibody to bacterial antigen all abate with removal of the shunt, control of the infection, and remission of the glomerulonephritic process (522). IgG, IgM, and C3 are present in the cryoglobulins, and there was evidence in one study of the presence of both antibody to the bacterial organism and the bacterial antigen (503).

Clinical Course and Outcome

Serial renal biopsies have been performed before and after removal of the shunt; complete resolution of the glomerulonephritic process has been confirmed (518). The only residual may be mild mesangial hypercellularity (523) or focal global glomerular sclerosis (523). In most patients, the immunofluorescent and electron microscopic deposits completely disappear (504,523). However, disease in patients in whom crescentic glomerulonephritis develops may not resolve despite adequate therapy (523,524). Occasionally, patients with underlying MPGN with crescent formation may also show a steady decline (514,524). Full clinical recovery with normalization of the serum and urine abnormalities is noted in about two thirds of patients, sometimes within a month or two (519); renal disease persists in the remaining third, as manifested by proteinuria, microhematuria, hypertension, or renal insufficiency. Rarely, complete clinical recovery can take place after several months of proteinuria or hematuria (485). Delay in diagnosis and treatment may prevent complete recovery (500) and lead to irreversible renal insufficiency (489).

The glomerulonephritic process may develop as long as 5 years after the apparent colonization of a shunt and the onset of low-grade bacteremia (498,502,509,522). In some of these reports, culture of the blood and of cerebrospinal fluid obtained from the shunt was found to be sterile, and identification of a bacterial infection was possible only on removal of the shunt or central venous catheter (497,513); in other cases, the organism was erroneously regarded as a contaminant (375) or the infection was thought to have been controlled by antibiotic therapy (502). If the shunt infection is not treated properly and the bacteria persist, mild renal involvement may progress to severe renal impairment (501,523). Later renal biopsies in these cases have shown an increase in glomerular tuft hypercellularity, crescent formation, sclerotic glomeruli, and the number of glomerular electron-dense deposits (501). As noted earlier, eradication of the bacteremia (usually by removal of the shunt or the catheter) leads to subsidence of the glomerulonephritis. Although removal of the shunt or catheter is almost always needed to permanently eliminate the infection (497,501), remission of bacteremia and kidney disease has been achieved by antibiotic therapy alone (377,504).

In summary, infected ventriculoatrial shunts and central venous catheters may lead to immune complex glomerulonephritis with the morphologic pattern of type I MPGN, although other phenotypes of immune complex glomerulonephritis are seen less frequently. It is of considerable interest that there can be complete clinical cure following eradication of shunt infection. In contrast, most patients with the idiopathic form of type I MPGN progress inexorably toward ESRD (525–528).

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CHAPTER 11

Arthur H. Cohen • Cynthia C. Nast

Renal Injury Associated With Human Immunodeficiency Virus Infection and Therapy

It was within 3 years of the initial description of the acquired immunodeficiency syndrome (AIDS) that the first reports of renal involvement appeared (1–3) and documented various forms of glomerular disease. Since that time, myriad publications have provided ample evidence that the kidneys may and do harbor varied serious and pathogenically diverse lesions and manifest numerous clinical syndromes in human immunodeficiency virus (HIV)-infected patients (4–21). It has become apparent that some of the lesions may be directly related to HIV infection of the kidney, some may be the result of immunologic responses to the virus, some may be indirect manifestations of viral infection not within the kidneys, still others evolve from the opportunistic infections and neoplasms that characterize AIDS, and others may be the consequences of various therapies or hemodynamic derangements. It has also become apparent that a few types of nephropathy may occur in asymptomatic HIV-infected individuals and that the more serious manifestations of HIV infection are not always necessarily present in patients with renal disease.

In this chapter, we consider in detail those lesions that are unique to (or virtually limited to) HIV infection and those lesions that are associated with various reasonably consistent diseases common to HIV infection and AIDS or their complications, and we discuss in less detail lesions that are seen in patients with AIDS but that are covered more comprehensively in other chapters. It has been estimated that ≤60% of patients (10,22) with AIDS will manifest clinically significant kidney dysfunction, whether acid-base or electrolyte disturbances or parenchymal damage. Based upon racial and geographic considerations, the nature of the lesions varies considerably. It is important to note, however, that, as documented by autopsy studies (23,24), different statistics with regard to renal abnormalities

emerge. That is, postmortem examinations of consecutive and unselected patients have indicated that many of the lesions encountered in renal biopsy series are rarely observed in autopsies. That information has shed some doubt on the clinically derived statistics, although it may well be that our clinical colleagues' experience is more accurate. As of 1999, HIV-related renal disease was the third leading cause of end-stage renal disease among African Americans 20 to 64 years of age. However, due to effective treatment, this risk has declined by 40% to 60% accompanied by a threefold increased survival on dialysis (25). In addition, some investigators have suggested that, while HIV-associated nephropathy (HIVAN) was once considered the major renal lesion in HIV infection, it is likely that all other pathologies are collectively almost as or more common in the era of highly active antiretroviral therapy (HAART) (26).

HIV-ASSOCIATED NEPHROPATHY

The seminal report in March 1984 by Rao et al. in Brooklyn, New York (3), of focal segmental glomerulosclerosis in a group of black intravenous heroin abusers with AIDS, represented the first formal awareness that some patients with AIDS may show signs of renal disease. Before the end of that year, Pardo et al. in Miami (2) and Gardenswartz et al. in New York City (1) also reported clinically significant parenchymal renal disease, especially glomerular lesions, in patients with AIDS. In all three reports, the major glomerulopathy was described as focal and segmental glomerulosclerosis. Over the course of the next 5 or 6 years, detailed aspects of the clinical manifestations and epidemiologic considerations were made known, and comprehensive pathologic descriptions were written and refined (5,27–37). Since then, considerable attention has been directed to elucidating pathogenetic aspects of the disorder now known as HIV-associated nephropathy (HIVAN). The condition has reasonably characteristic clinical manifestations, striking racial predominance, and exciting and intriguing pathologic features.

HIVAN is a pan-nephropathy, with regularly occurring glomerular, tubular, and interstitial changes. As is described in detail later, the glomerular lesion is the collapsing variant of focal segmental glomerulosclerosis; the tubular abnormalities include cellular degeneration and necrosis, as well as cystic dilation, and the interstitium is edematous and often infiltrated by lymphocytes. Thus, while many other glomerulopathies and parenchymal lesions have been described in HIV-infected patients, it is only the one discussed in this section that should be termed HIVAN, based upon proposed pathogenetic mechanisms and historical considerations (29,38). All other lesions should be known by their commonly accepted appellations, with further indication of their existence in an HIV-infected individual. It makes no sense to consider all renal lesions in patients with HIV as HIVAN (37,38); certainly, we do not designate all forms of renal injury in patients with diabetes mellitus as diabetic nephropathy.

Clinical Features

Although the use of HAART appears to have an impact on the presentation and course of HIVAN (26), this description will pertain to the untreated patient. The effects of therapy are described below. HIVAN typically appears with the acute onset of heavy proteinuria (often ≥20 g/d) and progressive renal insufficiency. Hypoalbuminemia is usual, and proteinuria is nonselective. Renal failure may occur acutely, and some patients may have mild renal insufficiency. In contrast to other nephropathies with massive proteinuria, there is no or little peripheral edema, and blood pressure is often normal, even with advanced renal insufficiency (4,9,10,22,37,39). Most patients have had HIV infection for several years and have low CD4 counts. In the HAART era, more patients present earlier and with higher CD4 counts. The progression to end-stage renal disease may be quite rapid; in some series, the time from onset to dialysis may be as little as a few weeks to a few months (27,33,37). This progression is often irrespective of the clinical manifestations of HIV infection. It appears that black patients have a more severe course than either Hispanic or non-Hispanic white patients (40–42).

Imaging studies have consistently noted normal-sized or, more commonly, enlarged kidneys not only initially but also during the course of the disease, including end-stage kidney disease (9,43). Nephromegaly is so characteristic that an astute clinician can strongly suspect HIVAN on the basis of the clinical and laboratory features in conjunction with enlarged kidneys.

Although the initial reports documented this entity in patients with full-blown AIDS, with the advent of serologic testing for HIV, it has become evident that this nephropathy can manifest at any stage of HIV infection (26,28–30,43,44). In patients who are otherwise asymptomatic for HIV infection, this nephropathy may be the initial manifestation, and the renal pathologist may be the first physician to diagnose HIV infection based upon the biopsy findings (28–30,45,46). At the present time, although it is a common clinical practice to include HIV testing in the work-up of patients with renal disease, renal biopsy continues to represent the diagnostic method of detecting HIV infection in a small number of patients.

Patients with HIVAN acquire HIV infection by any of the modes of transmission (29,30). It was initially thought that intravenous drug abuse was an important and even necessary cofactor (3,11,17,43). However, many reports have documented the existence of this nephropathy in children with perinatal transmission of the virus, adults with heterosexual transmission, male homosexuals without intravenous drug abuse, and patients with HIV infection from contaminated therapeutic blood products (8,9,19,29,47).

From the first reports, it has been abundantly clear that there is a striking racial predominance—80% to 85% of reported patients are black. First pointed out by Bourgoignie et al. (48) in 1989 in a review of the literature, this racial imbalance has been amply supported by all published series (49). Bourgoignie et al. (39) convincingly documented their own experience; in 1989, in Jackson Memorial Medical Center in Miami, 67% of HIV-infected patients were white (both Hispanic and non-Hispanic), yet 88% of HIVAN patients were black. The incidence and prevalence of this lesion in Africa are unknown, although it clearly occurs in native Africans; several reports from Europe have described this nephropathy in Africans and residents of the Caribbean islands who seek treatment at European medical centers (15,50). Reports from Africa indicate the emergence of HIVAN and other renal diseases in patients with longer duration of illness, perhaps reflecting the effect of anti-HIV therapy (31,51–53). It is of interest to note that Pakasa et al. (54) described an increasing incidence of focal segmental glomerulosclerosis, including the collapsing variant (see Chapter 6) in Kinshasa, Zaire, although specific information about HIV status was not known in most patients. Few reports have documented rare cases in Hong Kong and India, among a small number of Asian countries describing their experience (55,56).

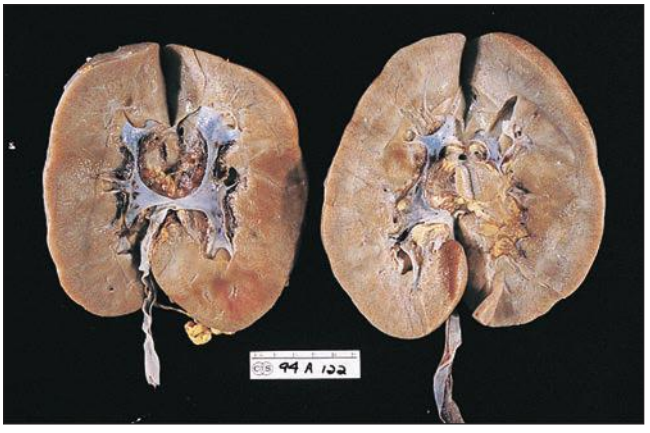

FIGURE 11.1 Gross appearance of the kidneys with HIVAN. The organs are enlarged, and each weighs 390 g, with a cortex of ample quantity. These kidneys are from a patient with end-stage dialysis-dependent renal failure.

The racial predominance also explains the geographic and other seemingly anomalous aspects of epidemiology that have become evident. For example, for the first several years following the awareness that some AIDS patients had coexisting focal segmental glomerulosclerosis, reports denying the existence of "AIDS-associated" glomerulopathy appeared in the medical literature in both the United States and Europe (57). However, it soon became obvious that the medical centers with this view treated very few or no black patients; with experience with a more racially heterogeneous patient population, some doubters became believers and proponents (31)

Pathology

Gross

The kidneys are generally enlarged, even at end stage (Fig. 11.1). In adults, the mean combined kidney weight has been documented to be as high as 500 g (58). In children, the mean weight is usually 1.20 to 1.30 times normal (22). The capsular surface is smooth. The cortex is enlarged and is more pale than the medulla. The parenchyma is swollen. Small cysts, 0.5 to 1.0 mm, are occasionally observed in the cortex or at the corticomedullary junction; they correspond to massively dilated tubules. As a rule, unless hypertension or chronic renal disease existed before the onset of HIVAN, grossly discerned scarring is not a feature.

Light Microscopy

There are prominent coexisting changes of glomeruli and tubules, often with an important interstitial component. The lesions of glomeruli are most typically, but not always, of the collapsing variant of focal segmental glomerulosclerosis (59). Because HIVAN has both clinical and pathologic manifestations of tubulointerstitial as well as glomerular involvement, the designation "nephropathy" rather than focal and segmental glomerulosclerosis is appropriate. As we view the glomerular abnormalities, they represent predominantly the early lesions of focal segmental glomerulosclerosis ("shift to the left" in the morphogenesis) (29,38,60). Initially, there are hypertrophy and hyperplasia of visceral epithelial cells; these alterations may affect only a few cells of a single lobule (Fig. 11.2A) or virtually all epithelial cells in a glomerulus simulating a crescent (Fig. 11.2B). Parietal epithelial cells have

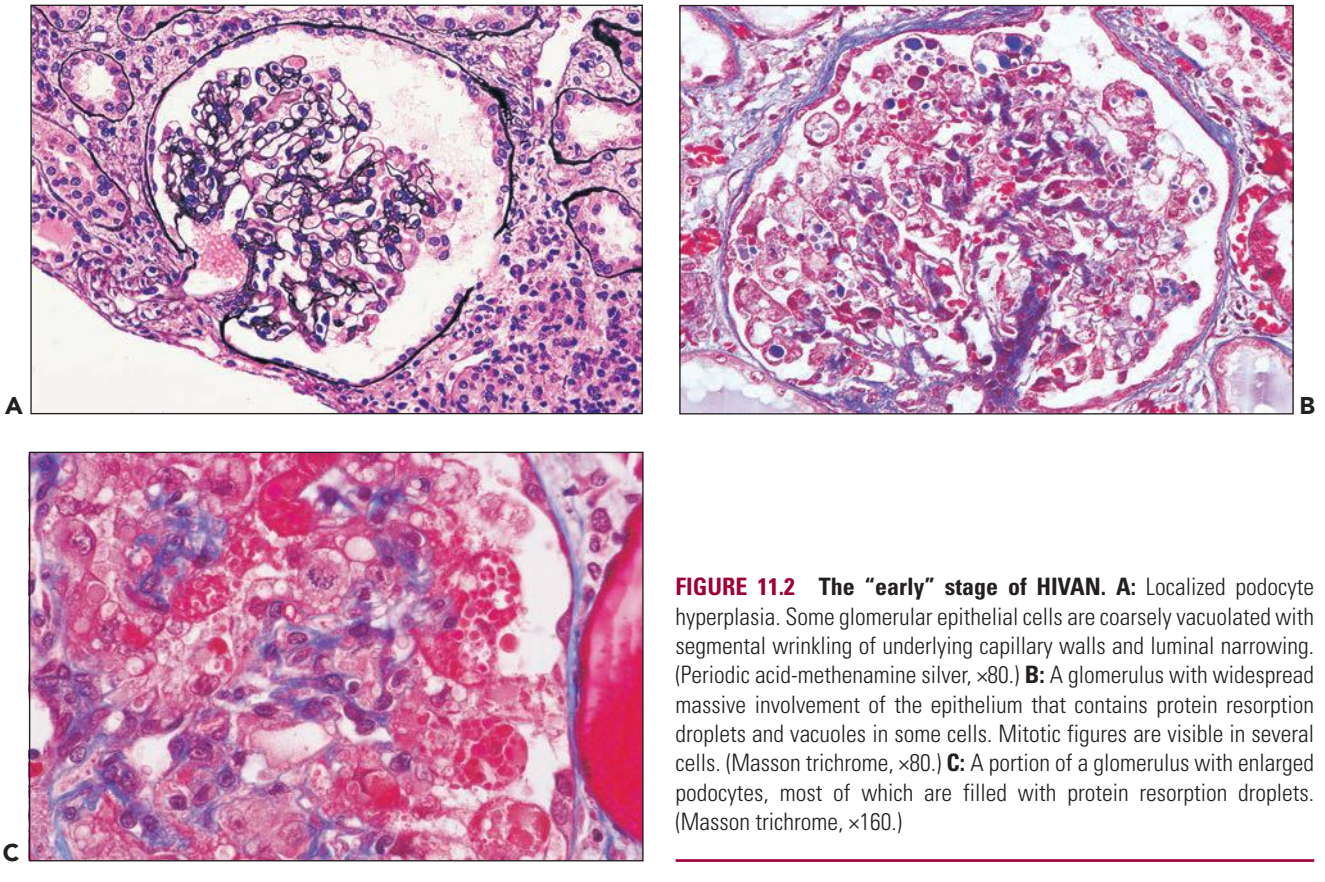

FIGURE 11.2 The "early" stage of HIVAN. A: Localized podocyte hyperplasia. Some glomerular epithelial cells are coarsely vacuolated with segmental wrinkling of underlying capillary walls and luminal narrowing. (Periodic acid-methenamine silver, ×80.) **B:** A glomerulus with widespread massive involvement of the epithelium that contains protein resorption droplets and vacuoles in some cells. Mitotic figures are visible in several cells. (Masson trichrome, ×80.) **C:** A portion of a glomerulus with enlarged podocytes, most of which are filled with protein resorption droplets. (Masson trichrome, ×160.)

been shown to contribute to the glomerular epithelial cell hyperplasia in collapsing glomerulopathy (61). Mitotic figures are usually present in some epithelial cells. The abnormal cells may be coarsely vacuolated and characteristically contain many cytoplasmic protein reabsorption droplets (Fig. 11.2C). Capillary walls in affected segments may be wrinkled or collapsed and lumina narrowed. There is relative dilation of the urinary space with segmental or more extensive involvement. As the lesion evolves, there is further narrowing or obliteration of lumina, resulting in solidification of the tufts (Fig. 11.3). In some glomeruli, typical segments of sclerosis develop, with lumina containing foam cells, insudative lesions, or both (Fig. 11.4). In advanced lesions, the visceral epithelial cells remain numerous and enlarged with protein resorption droplets and cytoplasmic vacuoles; the cells are typically arranged as a crown over the solidified tuft or a portion thereof (Fig. 11.5) (5,9,22,29,30,38,58).

There are constant and varied abnormalities of the tubules. Cells display degenerative features, with diminished or absent brush border staining of proximal tubular cells, flattening of cells in many segments of the nephron, and sloughing of cells into the lumina (Fig. 11.6). These changes may be focal or, more commonly, widespread (29,30,38). Lumina of tubules, in all segments of the nephron, are characteristically filled with a precipitate of plasma protein (Fig. 11.7), staining pale or negative with periodic acid-Schiff (PAS) and fuchsin positive with Masson trichrome. Tubular lumina are dilated, some only modestly and others massively, forming microcysts that may be visible on gross examination. Some tubules are so markedly dilated that they dwarf adjacent glomeruli (Fig. 11.8). Bowman spaces, also dilated and in direct continuity with dilated proximal tubules, contain the same precipitate (Fig. 11.9). The luminal precipitates, whether in greatly or slightly dilated tubules, have a scalloped periphery at the interface with apical portions of epithelial cells. Some of the luminal precipitates may contain more densely staining casts, crystals, or desquamated cells or cellular debris. In addition, some nondilated tubules contain typical hyaline casts composed of Tamm-Horsfall protein; as expected, these are strongly PAS positive. Other changes of tubular epithelium include the accumulation of numerous protein reabsorption droplets in proximal cells (Fig. 11.10) (29,38).

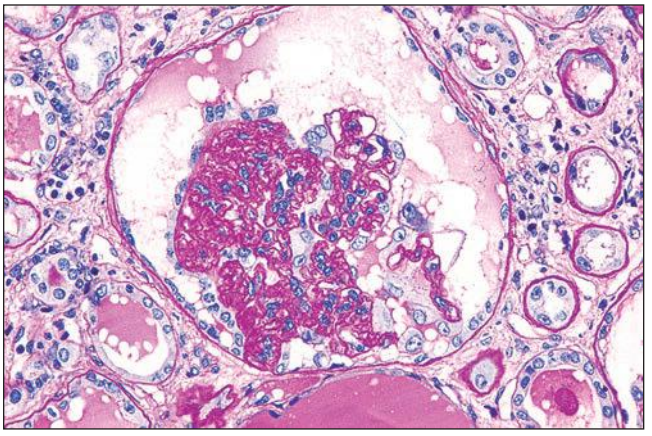

FIGURE 11.4 Glomerulus with advanced changes including segmental collapse and solidification of the tufts with a capsular adhesion and few enlarged podocytes. (PAS, ×80.)

The interstitium is edematous and contains a variable infiltrate of lymphocytes, with fewer plasma cells and monocytes (29,30,38). Interstitial fibrosis and tubular atrophy are present as the disease progresses; alternatively, these features may be related to other chronic changes (e.g., hypertension and nephrosclerosis) antedating the development of HIVAN. There are no consistent accompanying alterations of arteries, arterioles, or veins. Hypertension as an integral feature of HIVAN is unusual. Vascular changes of nephrosclerosis are most commonly associated with preexisting hypertension.

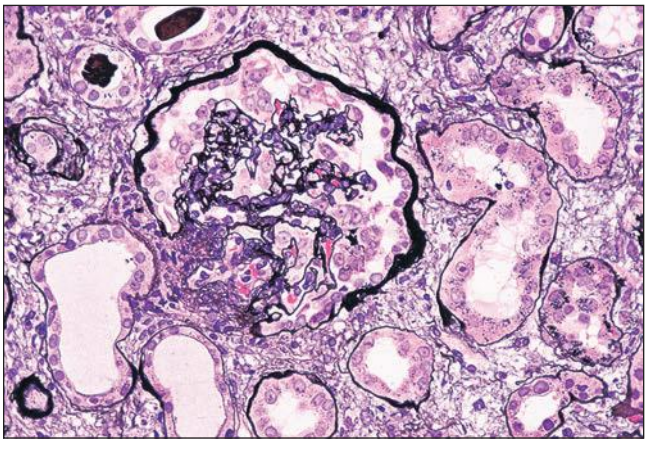

FIGURE 11.3 A glomerulus shows more advanced changes than in Figure 11.2. Portions of tufts are solidified because of capillary wall collapse. The epithelial cells are diffusely hyperplastic and exhibit changes similar to those in the earlier figures. (Periodic acid-methenamine silver, ×80.)

Immunofluorescence and Immunohistochemistry

The immunofluorescence findings in glomeruli are as would be expected for focal and segmental glomerulosclerosis, including the collapsing variant. In glomeruli with segmental sclerosis, immunoglobulin M (IgM), C3, and C1q are typically found in capillary walls in a coarsely granular to amorphous pattern with a segmental distribution, corresponding in location to the abnormal segments (27,28,36). "Noninvolved" glomeruli usually show negative results on immunofluorescence, although IgM and C3 have been documented in mesangial regions in a granular pattern and with a diffuse distribution in some reports. Most commonly, albumin, but also IgA, IgG, or both, is present in visceral epithelial cells as protein resorption droplets (29,30,38) (Fig. 11.11). Similarly, albumin, with lesser amounts of IgG, IgA, complement, and both light chains, is found in proximal tubular cells as protein resorption droplets. In our study of the composition of the precipitates ("casts") in dilated tubular lumina, we documented the presence of all plasma proteins sought (IgG, IgA, IgM, C1q, C3, albumin, both light chains) but not Tamm-Horsfall protein

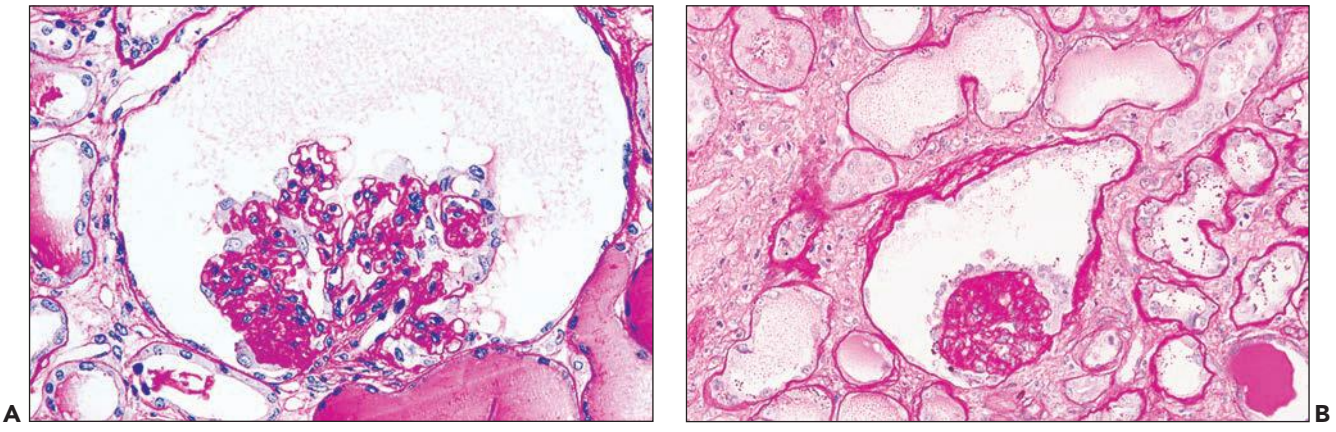

FIGURE 11.5 Glomeruli with advanced collapse/sclerosis and dilated Bowman spaces filled with precipitate of plasma proteins. A: Few patent glomerular capillaries and podocyte abnormalities persist. Note precipitates in the tubular lumina. (PAS, ×80.) **B:** A solidified glomerulus covered by a row of podocytes in a moderately dilated and fluid-filled Bowman space. (PAS, ×80.)

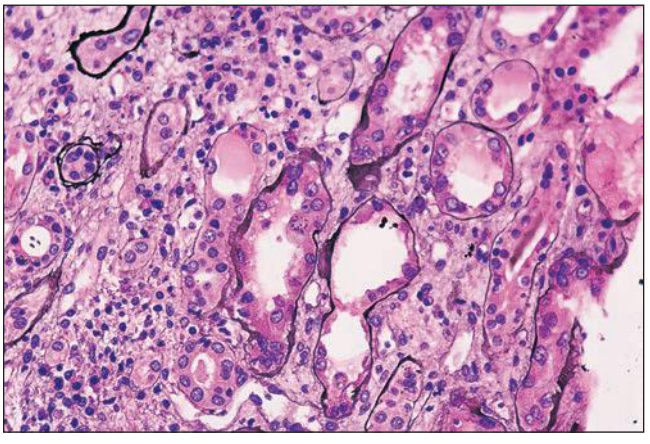

FIGURE 11.6 Tubular changes. There is irregular flattening of the epithelium with associated foci of tubular basement membrane denudation. Cells of proximal tubules lack brush borders. The interstitium is edematous, with a leukocytic infiltrate. (Periodic acid-methenamine silver, ×80.)

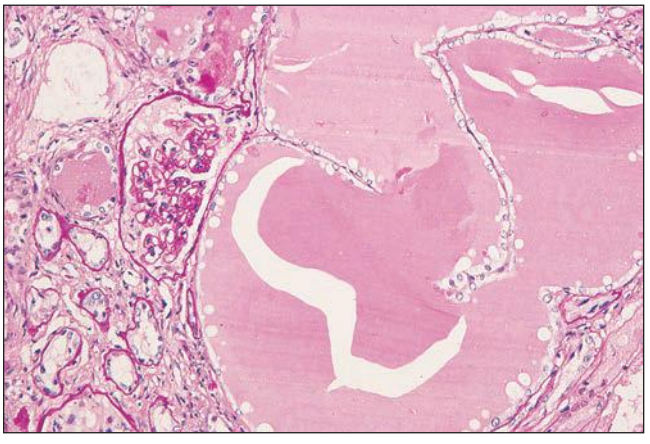

FIGURE 11.8 Massive dilation of tubules filled with plasma protein. This is from the autopsy of the patient whose biopsy is depicted in Figure 11.7; he died 3 months after the biopsy. (PAS, ×16.)

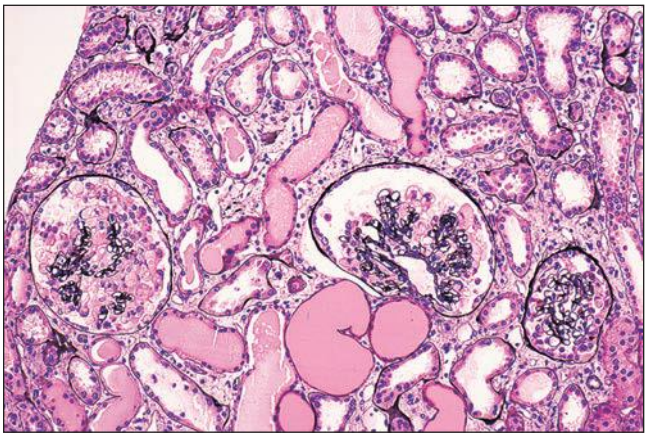

FIGURE 11.7 Many tubules are filled with a pale-staining luminal precipitate; some are also slightly dilated. Note glomerular changes. (Periodic acid-methenamine silver, ×40.)

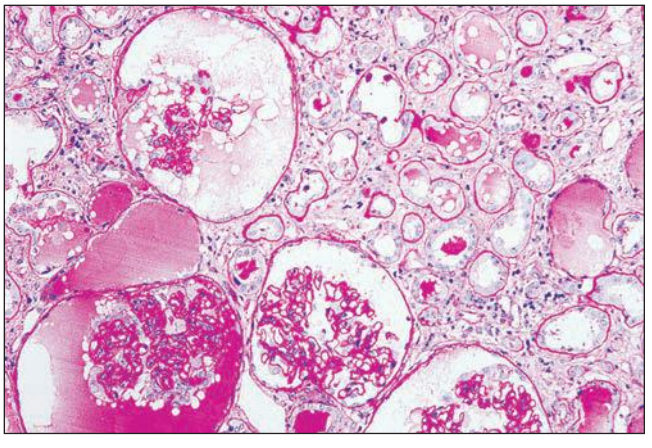

FIGURE 11.9 Tubules with moderate luminal dilation and proteinaceous precipitates. Note the Bowman spaces of glomeruli are similarly affected. (PAS, ×40.)

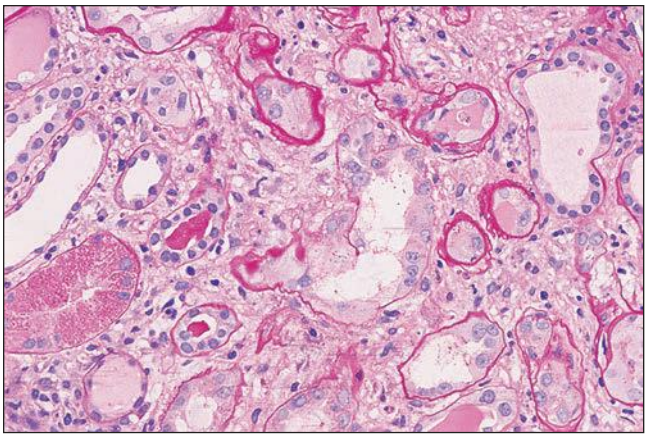

FIGURE 11.10 There are acute tubular cell injury and tubules that have undergone atrophy. In addition, there are numerous protein reabsorption droplets in many cells of the lower left proximal tubule. (PAS, ×80.)

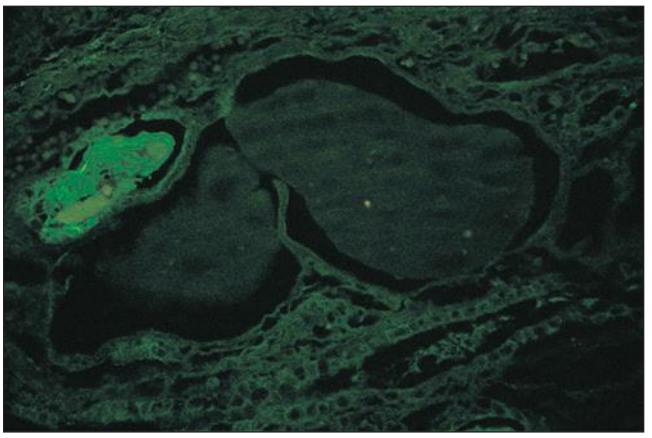

FIGURE 11.12 Immunofluorescence staining of tubular casts. The positive cast is composed of Tamm-Horsfall protein, while the large negative casts are not (anti-Tamm-Horsfall protein, ×80).

(Fig. 11.12), strongly suggesting their origin to be of the glomerular filtrate. In contrast, typical tubular hyaline casts are composed of Tamm-Horsfall protein, IgA, variable IgM, and both light chains, findings typical for these casts in other settings (62).

Cell marker studies have elucidated the composition of the leukocytic interstitial infiltrate. In the study by D'Agati et al. (30), there were both CD4 and CD8 cells, with a markedly reduced CD4/CD8 ratio (0.23 to 0.77, mean 0.35), similar to findings in the peripheral blood. In contrast, Rey et al. (63), studying mostly patients with full-blown AIDS, identified the infiltrating cells to be predominantly T cells, with both CD4 and CD8 cells present in a ratio of approximately 1.0, considerably different from the situation with circulating blood, which had markedly diminished numbers of CD4 cells and more numerous CD8 cells. These authors documented expression of major histocompatibility complex class II molecules (HLA-DR) on these cells as well as on parenchymal cells (endothelial, glomerular mesangial, and visceral epithelial cells). T cells were rarely identified in tubules or glomeruli. B cells and macrophages represented a minor component of the infiltrate. This study indicates that while AIDS may be associated with considerable CD4 lymphopenia, some organs may harbor a disproportionate number of these cells. Bodi et al. (64) documented that approximately 50% of interstitial leukocytes were macrophages, approximately 3% were B cells, and the remainder were T cells; it is not clear from their report what manifestations of HIV infection the patient population exhibited, making comparison with the other two studies difficult. It is of interest to note that Rey et al. (60,63) found the infiltrate in HIVAN to differ from that of idiopathic focal segmental glomerulosclerosis, which is characterized by considerably higher CD4/CD8 ratios.

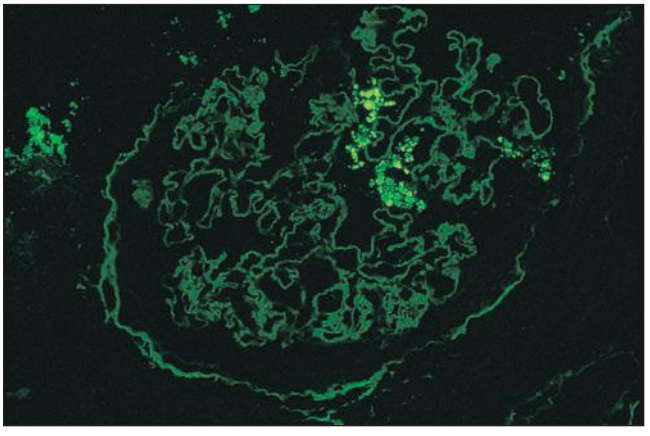

FIGURE 11.11 Many glomerular podocytes contain protein resorption droplets stained for albumin. (×80.)

Electron Microscopy

The ultrastructural findings reflect two distinctive processes and features: the basic electron microscopic features of the glomeruli and tubulointerstitium in focal segmental glomerulosclerosis/collapsing glomerulopathy (65–67) and the fine structural abnormalities of HIV infection (28,30,38,45,62,68,69). Each is discussed separately.

In the case of glomerulopathy, the abnormalities are dominated by pronounced changes in visceral epithelium and mirror very well the features of light microscopy (27,28,36). In affected glomeruli or segments thereof, these cells are often massively enlarged and contain one or more dense, round, secondary lysosomes (Fig. 11.13A); in addition, large and irregular single membrane-bound and seemingly empty vacuoles are present (see Fig. 11.13B). The vacuoles are often responsible for bizarre and irregular shapes assumed by these cells. The vacuoles may be exceedingly large, larger than the caliber of the underlying capillary lumen. The foot processes are usually completely effaced. The epithelial cell cytoplasm is not infrequently partially or completely detached from the basement membrane (Fig. 11.14A); at a later stage, after repair, the cell is separated from the original basement membrane by thin layers of presumably new basement membrane material (Fig. 11.14B).

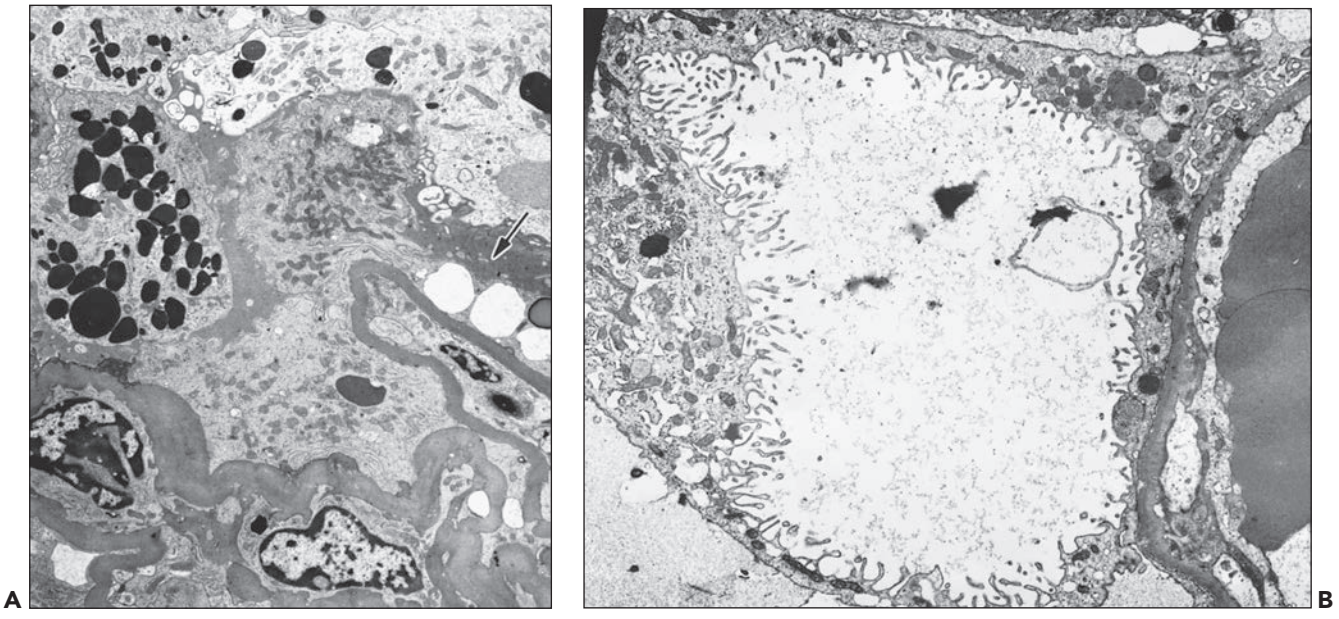

FIGURE 11.13 Electron microscopic appearance of glomerular podocytes. A: The cells are enlarged and numerous. Most have one or more dense lysosomes (protein resorption droplets). Small vacuoles are visible in one cell (*arrow*). Basement membranes are slightly wrinkled. (×6000.) **B:** Bizarre epithelial "bleb," or vacuole, with irregular microvillous lining. (×6930.)

Basement membranes display varying degrees of wrinkling with luminal narrowing (29,38). Endothelial cells may be swollen. With advancing lesions, capillary lumina may be completely obliterated by basement membrane material. Less commonly, monocytes with considerable cytoplasmic lipid (foam cells) fill the lumina, often in association with degeneration and detachment of endothelial cells. With further progression, plasma protein insudates, in the form of extracellular electron-dense masses, often with incorporated lipid and debris, occlude the lumina (38). Electron-dense deposits are usually absent, although small deposits in the mesangium are present in glomeruli with mesangial IgM and C3 deposits.

There are several ultrastructural abnormalities associated with HIV infection; it should be recognized that they are not limited to the kidneys but are widespread in many organs (68–70). Thus, their presence does not define the kidney changes as being indicative of HIVAN but as occurring in an HIV-infected patient. That is, there is a prevalent misconception that when these ultrastructural abnormalities are present in the kidneys, they are indicative only of HIVAN or a lesion

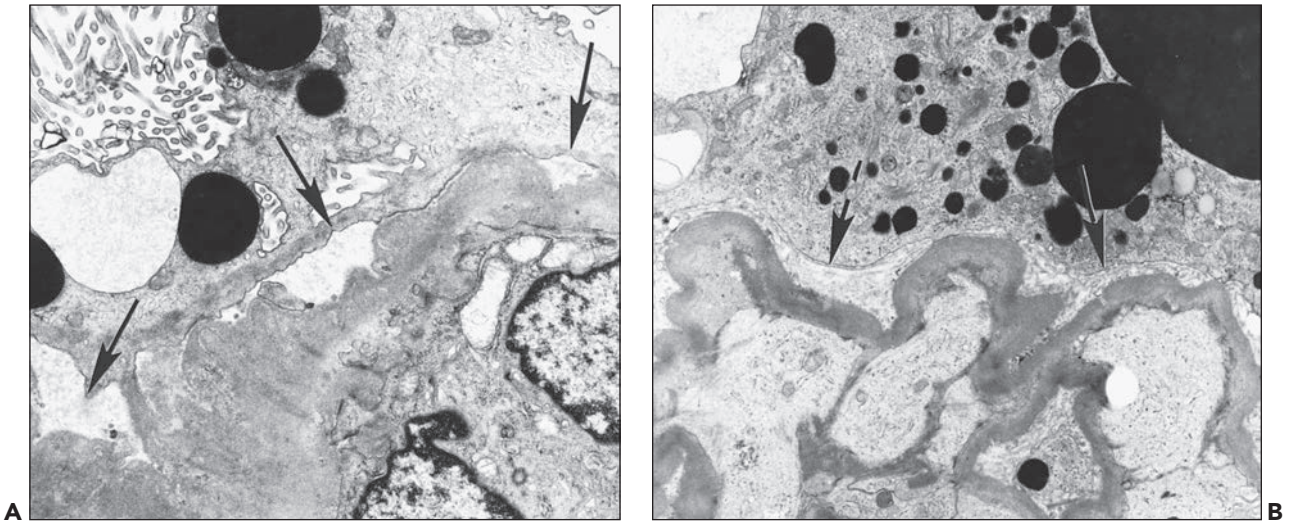

FIGURE 11.14 Podocyte detachment. A: The cytoplasm is lifted from the underlying basement membrane in three foci (*arrows*). Note the cytoplasmic lysosomes and vacuole. (×9075.) **B:** Later lesion, with the epithelial cell separated from basement membranes by thin layers of new basement membrane material (*arrows*). There is a moderate degree of capillary wall collapse. (×6800.)

directly related to HIV infection. However, they are indicative only of HIV infection and are present in the kidneys with other lesions, ranging from IgA nephropathy perhaps integrally related to HIV to, for example, diabetic nephropathy in an HIV-infected patient.

The most common abnormality is the tubuloreticular structure (Fig. 11.15A), consisting of reticular aggregates of branching tubules, approximately 25 nm in diameter, within cisternae of the endoplasmic reticulum or the nuclear envelope (68,69). These cytoplasmic structures, also known as tubuloreticular inclusions or interferon footprints, are primarily found in endothelial cells of glomeruli and peritubular capillaries and, to a lesser degree, in arteries, arterioles, and veins; in addition, they may be present in lymphocytes and monocytes (Fig. 11.15B), whether in the interstitium or in vessel lumina. They are typically large and numerous. Tubuloreticular structures are considered to be induced by cellular exposure to interferon-alpha. They are also an integral feature of cells in patients with systemic lupus erythematosus and in patients who are treated with interferon-alpha and may be found in patients with other viral infections (71). In addition, tubuloreticular structures may be identified, although in small numbers, in other forms of renal disease. Therefore, these structures are not specific to HIV infection.

Another ultrastructurally defined lesion, cylindrical confronting cisternae, is emphasized as an important and regularly occurring abnormality (28,69), but it is infrequently noted in renal tissue. These cisternae are long cylinders of fused membranous lamellae also known as test tube– and ring-shaped forms (Fig. 11.16); they almost always occur in cells with tubuloreticular structures, mainly in lymphocytes and monocytes. Confronting cylindrical cisternae are not unique to HIV infection; they also have been documented in multiple sclerosis, systemic lupus erythematosus, and in association with interferon-alpha therapy. Nuclear alterations are not uncommon. Perhaps, the most typical are nuclear bodies; these are nuclear inclusions, with diverse morphologic characteristics, consisting of dense or pale granular or fibrillary aggregates (Fig. 11.17). They are usually divided into five different types based upon structure (68) and are found most often in tubular and interstitial cells, including leukocytes and fibroblasts, where they are frequently quite numerous in a single nucleus.

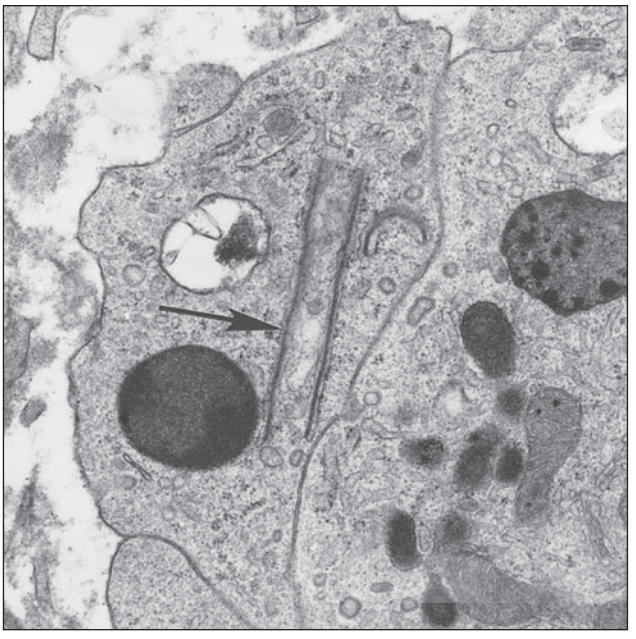

FIGURE 11.16 Confronting cylindrical cisternae (*arrow*) in the cytoplasm of an interstitial monocyte. (×19,450.)

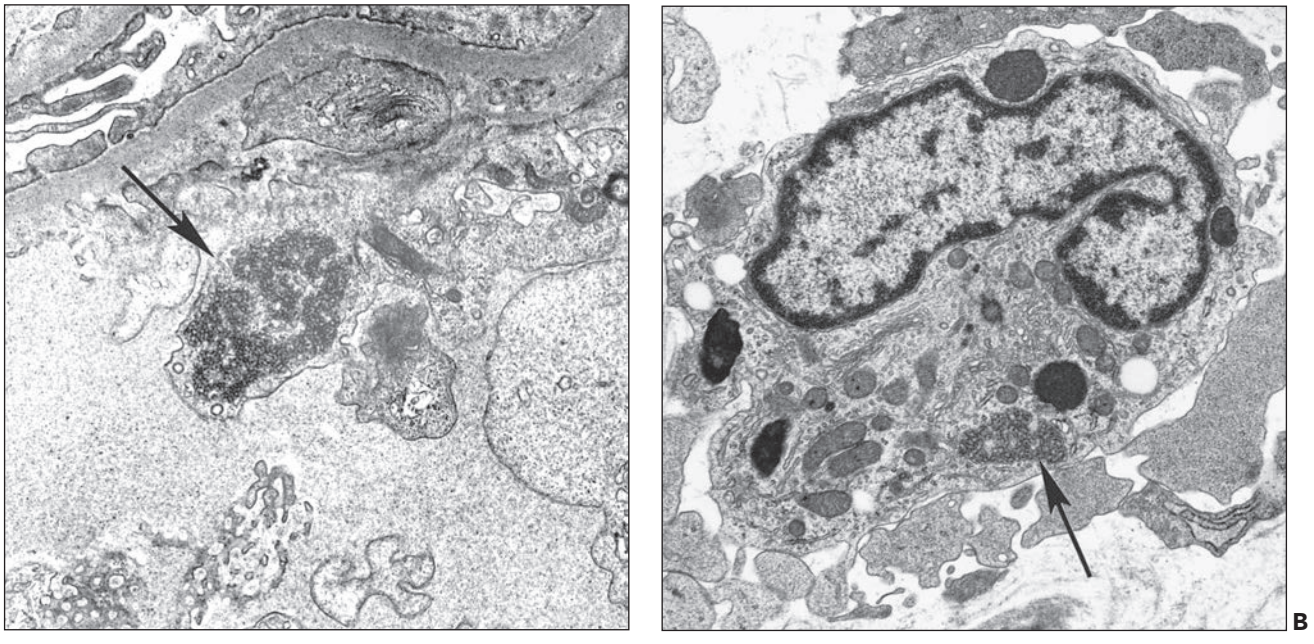

FIGURE 11.15 **Tubuloreticular structures. A:** Moderately large structure (*arrow*) is visible in a glomerular endothelial cell. (×11,345.) **B:** A small tubuloreticular structure is present in an interstitial monocyte (*arrow*). (×13,610.)

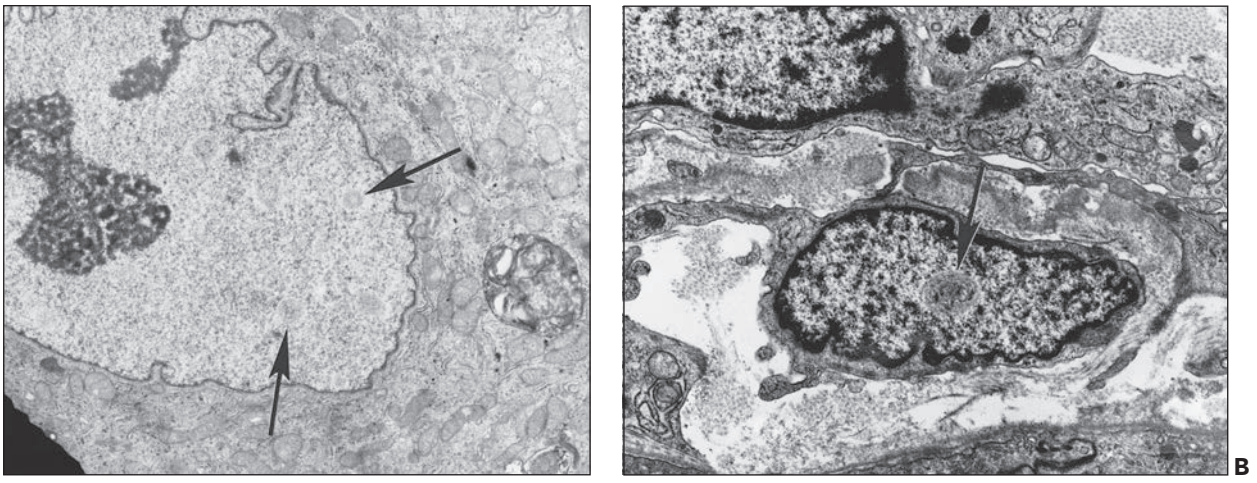

FIGURE 11.17 Nuclear bodies. A: A tubular epithelial cell with six type I nuclear bodies (*arrows* point to two). (×6800.) **B:** An interstitial cell with a single type III nuclear body (*arrow*). (×9980.)

The type III variant is most commonly present (30,38). Nuclear bodies are not specific to HIV infection; they had been described many years before the onset of the AIDS epidemic. Their composition and function are unknown; they may occur in association with viral infections. At the present time, this group of structures no longer generates the same interest as earlier.

More pronounced nuclear changes also may be present, including granular transformation of nuclei and, less commonly, granulofibrillar transformation. In the former case, the nucleus is completely or partially replaced by a coarsely granular material often associated with disruption of a portion of or the complete nuclear membrane (Fig. 11.18). Concomitant alterations of cytoplasm and organelles, especially mitochondrial swelling, are not uncommon. It should be noted that this change is not an artifact of inadequate fixation, for nuclei and cytoplasm of adjacent cells are not similarly abnormal. This alteration typically affects tubular and interstitial cells (28,36); it is more frequently found in interstitial cells in our experience (38).

Another more dramatic and perhaps related lesion is granulofibrillar transformation of nuclei; the chromatin is replaced by material with a coarse or fine granularity, with interspersed bundles of pale-staining filamentous ("fibrillar") structures

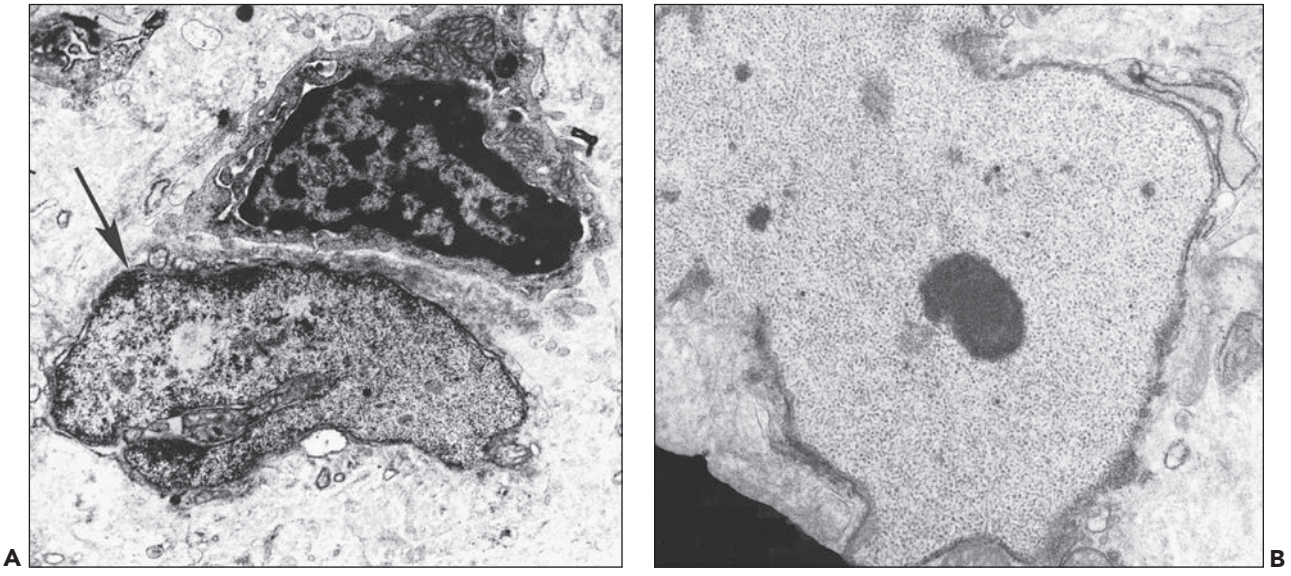

FIGURE 11.18 Granular transformation of a nucleus. A: A nucleus with early granular change (*arrow*). Compare this to the adjacent normal nucleus. The abnormal nucleus also contains several nuclear bodies, while the cell has an indistinct cytoplasmic membrane and dilated mitochondria. (Biopsy specimen, ×9076.) **B:** A nucleus with more advanced and extensive granular change. (Biopsy specimen, ×13,610.)

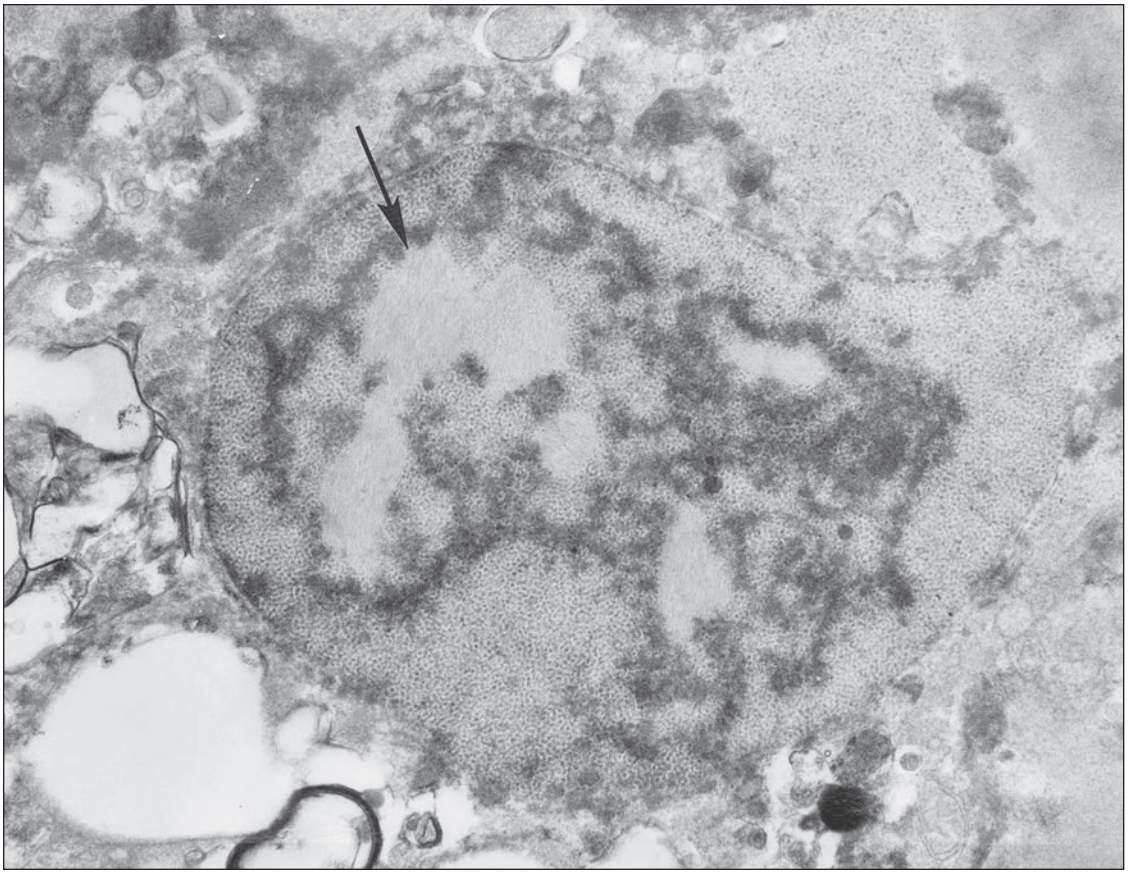

FIGURE 11.19 Granulofibrillar transformation of a nucleus. The granular change coexists with masses of pale-staining fibrils (*arrow*). (Postmortem specimen, ×20,500.) (From Cohen AH, Nast CC. Pathology of the kidneys. In: Nash G, Said J, eds. *The Pathology of AIDS and HIV Infection.* Philadelphia: WB Saunders, 1992.)

(Fig. 11.19). While granular transformation is readily seen in biopsy material, it should be noted that granulofibrillar transformation seems to be restricted to postmortem specimens (38,68,69). The nature of the transforming material is not known in either instance. The specificity of granular transformation to HIV infection is not known; we have noted it occasionally in renal biopsies from patients with systemic lupus erythematosus, among other disorders. While cytomegalovirus (CMV) and other viruses have been identified in renal tissue in HIVAN and represent coexisting disease rather than having pathogenetic importance in this disorder, the HIV agent has not yet been described in any renal cell.

The tubular casts of plasma protein are of medium density, with a finely granular to homogeneous appearance, without fibrils typical of Tamm-Horsfall protein (62), and without cytoplasmic or other debris. The casts look the same, regardless of the nephron segment in which they are located (29). Morphologic tubular cell manifestations reflecting acute tubular necrosis and tubular reabsorption of protein are similar to those seen in other nephropathies. The interstitial changes, likewise, are not different from those found in other disease contexts.

The light microscopic features, especially of the collapsing form of focal segmental glomerulosclerosis with tubular cell changes, tubular luminal protein precipitates, and cystically dilated tubules—in conjunction with the ultrastructural findings (particularly, but not exclusively, numerous, large, and widespread tubuloreticular structures)—are a fairly unique combination of findings. Observed together, these are highly suggestive of HIVAN, and HIV infection should be confirmed by testing for HIV with polymerase chain reaction (PCR) or for HIV antibodies serologically. The differential diagnosis includes patients treated with interferon, which can induce a picture of collapsing glomerulopathy with tubuloreticular structures (72). This constellation of findings allows the renal pathologist to suggest a diagnosis of HIV infection in a patient not previously known to harbor the virus (27–29,44–46). It should be emphasized that the diagnostic criteria must include electron microscopic evaluation as collapsing glomerulopathy clearly occurs in non–HIV-infected persons, some of whom may have other immunodeficiency conditions; if light microscopy alone is used, diagnostic specificity is lost. Thus, incompletely studied renal specimens are likely to provide misleading information.

In the HAART era, tubuloreticular structures are much less commonly found (21,73). Some specimens may be devoid of them, and fewer tubuloreticular structures are present in those biopsies that harbor them. Although the consequence of

these features is that they have a reduced role in pathologic diagnostic specificity, the pathologist is very likely to be aware that the patient is HIV infected at the time of the renal biopsy. Additionally, since the introduction of HAART, the prevalence of the typical morphologic changes of HIVAN has decreased, while the "classical" (non-collapsing) forms of focal segmental glomerulosclerosis have increased likely due to effectiveness of HAART in abrogating the collapsing glomerulopathy of HIVAN (74,75). Over the last several years, the noncollapsing morphology is the leading cause of glomerular disease in HIV-infected individuals followed in one large institution in Paris (26).

Natural History

Untreated, this nephropathy has a uniformly dismal prognosis, with or without clinical manifestations of AIDS. In 1989, Carbone et al. (27) described rapid progression to renal insufficiency in all patients (HIV asymptomatic, AIDS-related complex, AIDS), from the initial clinical presentation to dialysis in 10.9 weeks. The median survival time from diagnosis of renal disease to death was 4.5 months. In asymptomatic patients, it was 9.7 months; in those with AIDS-related complex, it was 3 to 6 months; and in those with AIDS, it was 1.9 months. This rate was not appreciably different from the initial experience of Rao et al. 5 years earlier (3). Some reports have indicated a better outcome in patients treated with zidovudine (35,76,77) although this is not uniformly true (78).

Examination of renal tissue some time after the initial pathologic diagnosis of HIVAN, either with a second biopsy or at autopsy examination, indicates progression of the glomerular and tubulointerstitial damage. We have noted marked solidification of collapsed tufts, commonly with persistent enlargement and vacuolation of visceral epithelial cells of the vast majority of glomeruli at autopsy, in as little as 3 months following a biopsy that disclosed exclusively glomerular epithelial hypertrophy and hyperplasia with early capillary wall collapse in a patient who experienced rapid decline to end-stage renal disease. Concomitant massive tubular dilation, not present on biopsy, was also evident in the postmortem specimen. Few studies have assessed morphologic progression in the face of corticosteroid therapy. Briggs et al. (79) reported the case of a patient with combined typical HIVAN and thrombotic microangiopathy who was treated with prednisone (60 mg/d) and experienced initial improvement in renal function; following tapering of prednisone, renal function deteriorated. A second biopsy showed "substantial" reduction of interstitial inflammation, with fewer T cells and macrophages/monocytes. The glomerulopathy was unchanged (as was proteinuria), and vascular thrombotic microangiopathic lesions were absent.

Since the introduction of HAART, data indicate that, as HIV-infected patients are living longer, the incidence of kidney involvement with progression to end-stage renal disease is increasing. Some treatment modalities have an effect on the incidence and progression of HIVAN. Patients with HIVAN treated with angiotensin-converting enzyme inhibition show delayed progression to end-stage renal disease. Antiretroviral therapy has been reported to result in dramatic improvement in HIVAN and longer time to renal failure (80), and HIVAN is considered an indication for HAART administration (81). Furthermore, few isolated case reports (82) have described considerable improvement in renal function and proteinuria as well as microscopic pathology in some patients with biopsy-documented HIVAN (83,84).

Etiology and Pathogenesis

Since its initial description, the pathogenesis of HIVAN has been a source of considerable interest and investigation. Although many diverse theories have been proposed, it seems very likely that HIV genome or protein in the renal epithelium is responsible for the development of this nephropathy (13,20,21,85). In an attempt to explain the simultaneous occurrence of the striking abnormalities in glomerular visceral and tubular epithelium and their functional consequences as manifestations of a single renal injury, we studied renal biopsy specimens for HIV nucleic acid with in situ hybridization using a cDNA probe and with a peroxidase-labeled antibody to p24 core protein (86). HIV genome was documented in many glomerular visceral and tubular epithelial cells in HIVAN; in contrast, in kidneys from HIV-infected patients with immune complex glomerulonephritis and in AIDS patients without renal disease, genome was documented in only isolated glomerular and tubular epithelial cells in very few tissue samples. The immunohistochemical part of the study indicated that this method was not very sensitive, for in only 1 of 11 biopsies with HIVAN was p24 identified in glomerular epithelium; tubular cells were positive in 10 of 11. These results suggested a role of direct HIV infection of these cells in the initiation, progression, or both of HIVAN. Originally discounted because other studies (87–89) could not reproduce the results in different settings, evidence over the last decade, using more sophisticated techniques, has confirmed the basic concept that HIV genome is an important, indeed necessary, factor in renal epithelium in the genesis of this disorder (83,90–93).

The methodologic problems associated with the immunohistochemical detection of HIV antigen in tissue sections were reviewed extensively by Nadasdy et al. (94); these investigators carefully documented the pitfalls of identifying viral protein in fixed and paraffin-embedded kidney and other tissue specimens. Kimmel et al. (95) documented HIV DNA by PCR in microdissected kidney biopsies; viral genome was identified in glomerular and tubular cells in HIVAN and also in other glomerulopathies in HIV-infected patients.

On the other hand, support for the finding, and perhaps the significance, of HIV genome/protein in renal epithelium comes from transgenic mouse models. Investigators at the National Institutes of Health established a line of HIV transgenic mice using a noninfectious proviral transgene lacking gag-pol (96–98). Some of these animals develop a morphologic lesion virtually identical to HIVAN, including focal segmental glomerulosclerosis with abnormal visceral epithelial cells, microcystic tubular dilation, and increased accumulation of components of the extracellular matrix. Proteinuria and renal failure are evident. Furthermore, viral RNA is found in the kidneys, at least early in the disease. The mice are not CD4 depleted and do not experience opportunistic infections, suggesting that HIV gene products alone are sufficient to induce HIVAN (96–98). Although detailed immunohistochemical studies have not been reported, renal abnormalities with

striking similarity to HIVAN have also been documented in cats with feline immunodeficiency virus (99). A report describes focal segmental glomerulosclerosis in rhesus monkeys with simian AIDS (100).

The pioneering work of Barisoni et al. (101) documented abnormal maturation and differentiation of podocytes in collapsing glomerulopathies, including HIVAN. As these dysregulated cells have the ability to proliferate (one of the major glomerular cellular abnormalities in HIVAN), and lose markers of maturity, the direct effect of HIV on these cells has been extensively studied. Bruggeman et al. (91) showed that HIV-1 mRNA and DNA were present in glomerular visceral and parietal epithelial cells and tubular cells in biopsies from HIV-infected patients with HIVAN. Circularized DNA, a marker of recent infection and active replication, was also present. Other studies by Marras et al. (92) extended the concept that renal epithelial cells are permissive to HIV-1 infection and viral replication by demonstrating that HIV quasi-species evolve in renal epithelial cells as a separate compartment, independent from peripheral blood mononuclear cells. In a landmark report on a single patient, Winston et al. (83) described the development of HIVAN in a patient with recent infection, HIV-1 mRNA in renal epithelium, improvement in clinical manifestations, and renal morphology with HAART, but persistence of viral RNA in the kidney indicating this organ to be a reservoir for HIV infection. Although the role of HIV in the genesis of HIVAN is accepted, a brief report by Izzedine et al. (102) described this nephropathy in an infected patient with an undetectable proviral DNA load in both plasma and kidney tissue. The HIV gene(s) responsible for podocyte and tubular epithelial cell abnormalities has been investigated using transgenic and infectious animal models (103). Current evidence supports that *nef* induces many of the molecular changes underlying the abnormal podocyte phenotype (104,105). In animal models and in man, *vpr* appears to play a synergistic role in the development of nephropathy, including the tubulointerstitial lesions (106,107). In susceptible mouse strains, the genetic loci conferring susceptibility to HIVAN encode transregulators of podocyte gene expression, suggesting a transcriptional network that involves NPHS2, the gene encoding podocin (108). Additional lines of investigation are centered on the role(s) of cytokines, including transforming growth factor–beta (TGFβ) (109) and basic fibroblast growth factor (bFGF) (110), and the role of HIV type 1 regulatory gene products or envelope in affecting cells either directly or indirectly through abnormal regulation of growth factors and other soluble mediators (9,111). The HIV transactivating protein tat, released by infected cells, can be taken up by and stimulate many cells, among which are bone marrow–derived macrophages, to up-regulate production of TGFβ (111,112). The levels of this cytokine protein and mRNA are elevated in peripheral blood mononuclear cells, plasma, and tissue. It has been documented to have an antiproliferative effect in lymphoid cells and proliferative effects on endothelium. Furthermore, TGFβ has cellular proliferative activity and also promotes glomerulosclerosis (113,114). We have found increased expression of TGFβ and the proteins induced by it in glomerular and tubular cells in renal biopsies of HIVAN, suggesting the possible role of TGFβ in the genesis of this renal disorder (109). Shukla et al. (115) documented that TGFβ increases expression of an HIV gene (LTR) in transfected cultured human mesangial cells, suggesting a possible mechanism of action of TGFβ in promoting increased viral transcription. Yamamoto et al. (114) and Kimmel (90) described higher levels of TGFβ in kidney tissue from patients with HIVAN and also idiopathic collapsing glomerulopathy in comparison to a wide variety of other renal diseases. Other considerations include chemokine coreceptors for HIV and their relationship to disease development. Conflicting data make meaningful interpretation at this time difficult (90). bFGF has been shown to colocalize with glomerular extracellular matrix in kidneys from the transgenic mouse model of HIVAN; furthermore, bFGF low-affinity binding sites were increased, especially in the interstitium (110). Both of these factors point to the role of bFGF in this disorder. It is of interest to note that rats treated with fibroblast growth factor type 2 develop glomerular changes, especially of visceral epithelial cells, that are very similar to those of HIVAN (116).

Although they have not been studied as intensively, other cytokines, including interleukin (IL)-1, IL-6, tumor necrosis factor–alpha, and granulocyte-macrophage colony–stimulating factor, can be dysregulated by HIV and may be important in HIVAN. Bodi et al. (64) documented increased apoptosis in tubules but not in glomeruli in HIVAN, suggesting the possible role of this process in the initiation or progression of tubulointerstitial damage, perhaps induced by HIV peptides. Thus, it is accepted that HIV infects circulating and renal monocytes and lymphocytes as well as renal epithelium (including podocytes, parietal cells, and tubular cells), that cytokine production can be induced by viral gene products, and that both viral gene products produced by infected renal epithelial cells and cytokines produced locally or systemically act on renal epithelial cells to mediate the glomerulosclerosis and tubulointerstitial scarring.

Genetic factors in patients may have an important role in pathogenesis; polymorphisms in the MYH9 and APOL1 genes that are linked with African ancestry carry increased risk of developing HIVAN as well as focal and segmental glomerulosclerosis (117). Carrying two APOL1 risk alleles explains approximately 35% of HIVAN cases. In a more recent study, among 60 HIVAN patients who were successfully genotyped for APOL1 risk allele variants, 37 carried two APOL1 risk alleles and 18 carried one risk allele variant; only 5 had neither risk allele (118). These data indicate that APOL1 risk alleles confer a considerable risk for the development of HIVAN. Interestingly, the finding that HIVAN has similar clinical and pathologic features in patients with and without APOL1 gene variants (118) suggests that other risk factors also are involved (119).

IgA NEPHROPATHY

Reports of IgA nephropathy in HIV-infected patients first appeared in the late 1980s and early 1990s (120–127). Most of the early as well as later articles collectively describe relatively few patients, perhaps 25 or so, although it is likely that this form of glomerulopathy is more prevalent in HIV infection

than the literature would suggest. The clinical manifestations and the pathologic aspects of this type of glomerulopathy do not appreciably differ from IgA nephropathy in individuals without HIV infection; it is possible that the HIV agent may be directly implicated in its immunopathogenesis (7).

Clinical Features

Similarly to IgA nephropathy, the manners of presentation are quite varied, although hematuria and low-grade proteinuria are most common. However, rapidly progressive glomerulonephritis, acute nephritic syndrome, nephrotic syndrome, and renal insufficiency, which is occasionally irreversible, have also been described (7,128). Both children and adults are affected (7). Unlike the case of HIVAN, the vast majority of patients are white, including Hispanics, although isolated Asians and blacks are described (7,50,129). Many of the reports emanate from Europe. It is somewhat surprising, considering the large and growing HIV-infected population and the very high incidence of IgA nephropathy in Asia, that, as of this writing, no descriptions of this combination of diseases have appeared from that area of the world. It was initially thought that IgA nephropathy is a disorder of asymptomatic HIV infection; however, articles have since indicated that patients with any manifestation of HIV infection may be affected. Two of the reported patients had Schönlein-Henoch purpura with nephritis (122,130).

Several surveys of consecutive autopsies of patients dying from AIDS have yielded conflicting results regarding the prevalence of glomerular mesangial IgA deposits. Béné et al. (131) in Vandoeuvre, France, documented only one case among 54 patients (1.85%) with glomerular IgA deposits; the patient had hepatitis B virus–associated cirrhosis, and the authors concluded that the deposits were related to cirrhosis rather than "true" IgA nephropathy. On the other hand, Beaufils et al. (120) in Paris described IgA glomerular deposits in 9 of 116 patients with AIDS (7.75%); although 2 patients had been exposed to hepatitis B virus and 3 to hepatitis C virus, cirrhosis was absent in all of them, and only 1 had "chronic hepatitis." Only one patient had microhematuria; proteinuria was absent in all patients. All but one patient were white, while the last was Asian. The results of this study indicate a high prevalence of IgA deposits in patients with AIDS; it does not, however, indicate a high prevalence of IgA nephropathy in this population (120). Furthermore, because of the study's design, it does not provide information concerning IgA nephropathy (or even IgA deposits) in HIV infection, regardless of the manifestation of this viral infection. Nevertheless, it does indicate that a very high percentage of patients with AIDS may harbor mesangial IgA deposits; 7.75% is a much higher percentage than is found in the general population in Paris.

Pathology

The basic findings do not differ from those of IgA nephropathy outside the context of HIV, with one exception. The reader is referred to Chapter 12 for a detailed discussion of the pathologic aspects of IgA nephropathy. The major differentiating point between IgA nephropathy in HIV infection in contrast to the situation outside HIV infection concerns ultrastructural findings. As discussed in the Electron Microscopy section of HIVAN, there are numerous tubuloreticular structures in endothelial cells, lymphocytes, and monocytes in patients not on HAART. Furthermore, the other ultrastructural features of HIV infection also may be present. Thus, IgA nephropathy with these abnormalities may be the first indication of HIV infection in a person not known to harbor the virus (7).

Natural History

Because of the small number of patients reported and the frequent lack of follow-up information, there are inadequate data to provide meaningful information regarding the course and prognosis of the disease; it is likely that it is the same as IgA nephropathy in non–HIV-infected patients. In one small series, patients developed malignant hypertension with higher frequency than non–HIV-infected individuals (132).

Etiology and Pathogenesis

IgA nephropathy is an immune complex–mediated glomerulonephritis in which the antigen is seldom identified. However, in the context of HIV infection, work by Kimmel et al. (124) has provided interesting and provocative information. They described two patients with IgA nephropathy; one had circulating immune complexes containing IgA idiotypic antibodies reactive with IgM anti-HIV p24, and the other had antibodies reactive with IgG anti-HIV gp41. In the first patient, the eluate of glomerular deposits contained IgA/IgM/p24. In another study, this same group of investigators documented, in a single patient, circulating IgA reactive with p24, gp41, gp120, and gp160 HIV antigens; they also described IgA complexed to p24 in glomerular eluate. These findings strongly suggest a direct role of HIV antigen(s) in the genesis of this glomerulonephritis.

Other supportive evidence is provided by Katz et al. (122). They described elevated levels of circulating IgA, IgA-containing circulating immune complexes, and IgA-rheumatoid factor in four patients; although a variety of HIV antigens were complexed to IgA in the circulation, p24 and gp41 antigens were not identified in the glomerular deposits in the three biopsies tested. The results of these studies are certainly commensurate with other findings that, in HIV-infected patients, polymeric IgA rheumatoid factor is present (133), serum IgA levels are elevated, and IgA binds to collagen and other matrix components, even in the absence of IgA nephropathy (134). As suggested by van Es et al., it is likely that serum IgA in patients with AIDS is of marrow origin (135).

OTHER GLOMERULOPATHIES

Many glomerulopathies other than HIVAN and IgA nephropathy have been described in HIV-infected patients (Table 11.1). Most of them are immune complex mediated; their incidence in renal biopsy series is dependent on age and geographic and racial factors. Furthermore, the types of lesions may be associated with the coexistence of other infections, especially (but not limited to) hepatitis B (136,137) and hepatitis C (139,141).

TABLE 11.1 Glomerulopathies reported in HIV infection

Glomerulopathies	References
HIV-associated nephropathy—collapsing glomerulopathy/focal segmental glomerulosclerosis	See text
Diffuse mesangial hypercellularity	(2,19,41)
Minimal change disease	(6,19,40)
IgM nephropathy	(40)
Membranous glomerulonephritis	
Hepatitis B virus	(136–138)
Other	(139,140)
Membranoproliferative glomerulonephritis	
Hepatitis C virus	(141–143)
Other	(141,143)
IgA nephropathy	See text
Postinfectious glomerulonephritis	(6,15,144)
Pauci-immune crescentic glomerulonephritis	(15,145)
Lupus-like glomerulonephritis	(6,146–148)
Immunotactoid/fibrillary glomerulonephritis	(149,150)
Crescentic glomerulonephritis with foscarnet crystals	(151)
Nonspecified immune complex–mediated glomerulonephritis	(148,152)
Thrombotic microangiopathy	(9,16,153–156)
Amyloidosis	(157,158)
Light chain deposit disease	(158)

In the United States and in many other countries, it is estimated that approximately 25% of HIV-infected individuals are coinfected with hepatitis C virus (142). In the coinfected patients, the morphologic patterns are usually membranoproliferative glomerulonephritis, with or without changes of cryoglobulinemia, or membranous glomerulonephritis and only infrequently combined with HIVAN. Immunotactoid and fibrillary glomerulonephritis are encountered in HIV with or without hepatitis C (149). Postinfectious glomerulonephritis, nonspecific immune complex lesions, and lupus-like glomerulonephritides have been described, the latter in both adults and children (143,146). Some patients with lupus-like nephritis have positive lupus serologies (147), whereas others have a typical full-house immunofluorescence pattern but negative lupus serologies (146). Data from a well-studied patient (159) with three biopsies performed several months apart over 15 months, disclosing lupus-like proliferative glomerulonephritis in two and HIVAN in the third, indicated that the glomerular changes were influenced by viral load. Low viral load was associated with proliferative immune complex glomerulonephritis, while high viral load was associated with HIVAN. The etiology of lupus-like glomerulonephritis may be related to polyclonal B-cell activation and circulating immune complexes, which are common in HIV infection, and deposition in the glomeruli (146,147).

Several reports have described individual HIV-infected patients with anti-GBM disease characterized by crescentic glomerulonephritis (160,161) although some patients with circulating anti-GBM antibodies were described without typical pathologic findings or commensurate clinical course, suggesting that antibody production may be related to B-cell expansion, rather than GBM antigen stimulation in some patients (162).

Glomerulopathies in Children

From the early reports of renal parenchymal involvement in HIV-infected children, it has become apparent that the nature and perhaps the significance of the lesions are different from those in adults. Typical HIVAN accounts for ≤50% of the reported glomerulopathies (19,163,164). Diffuse mesangial hypercellularity, with proteinuria often in the nephrotic range, is almost as common as HIVAN (2,19). Immune complex glomerulonephritis not infrequently accompanies HIVAN or occurs alone (163). Other glomerulopathies include minimal change disease, immune complex–mediated glomerulopathies, as well as lupus-like lesions; these findings may be more common in children than in adults (9). The relationship of diffuse mesangial hypercellularity to HIVAN is uncertain, although a few patients are reported to experience transition to HIVAN.

Pathology

In general, the pathologic findings in these glomerulopathies are, with some exceptions, identical to those seen outside the context of HIV. It should be appreciated that in addition to the expected ultrastructural findings, tubuloreticular structures and, to a lesser degree, the above-mentioned nuclear changes are also present, reflecting HIV infection in patients not treated with HAART. In some settings, such as membranous glomerulonephritis, particularly in association with hepatitis B infection in which there may be mesangial as well as subepithelial deposits with mesangial hypercellularity, the additional finding of tubuloreticular structures certainly first suggests lupus membranous glomerulonephritis. When faced with such a biopsy, the pathologist should recommend serologic tests for both systemic lupus erythematosus and HIV infection, as not all patients are known to be infected at the time of biopsy.

Pathogenesis

In addition to the identification of HIV antigens in circulating and glomerular-bound immune complexes in some patients with IgA nephropathy and circulating immune complexes in lupus-like lesions as discussed above, Kimmel et al. (152) documented HIV antigens complexed to IgA or IgG in four more patients, further suggesting the role of HIV in the pathogenesis of some immune complex–mediated glomerulonephritides.

Thrombotic Microangiopathies

Thrombotic microangiopathies, including hemolytic uremic syndrome (HUS) and thrombotic thrombocytopenic purpura, have been known to occur in HIV-infected patients almost since the initial report of AIDS. The majority of patients have had clinical evidence of thrombotic thrombocytopenic purpura; the renal manifestations typically are of acute renal failure, with varying degrees of proteinuria and hematuria, in the context of microangiopathic hemolytic anemia and thrombocytopenia. HUS associated with

HIV infection may occur in children and adults. The clinical presentation often is of slow onset and lacks diarrhea or features of typical HUS, although may have rapid progression to end-stage renal disease or death (163). Thrombotic microangiopathies may appear at any stage of HIV infection (165). The clinical course is more severe in HIV-infected patients than in non–HIV-infected patients (153). Renal pathologic aspects are the same in thrombotic microangiopathies in the absence of HIV infection (see Chapter 18), except for the presence of tubuloreticular structures and other ultrastructural features of HIV infection. At times, the thrombotic microangiopathic changes can occur simultaneously with HIVAN (79,165). The origin of HIV-associated thrombotic microangiopathies is not known; there is no clear association with *Escherichia coli* O157:H2. Some investigators have suggested the role of HIV injury to endothelium (166) or of HIV infection of megakaryocytes (167).

ACUTE TUBULAR AND INTERSTITIAL LESIONS

Renal tubular and interstitial abnormalities are frequent findings in autopsy and biopsy specimens from HIV-infected patients (23,140) historically found in over half of the autopsied patients with AIDS (168,169). However, in the era of HAART, tubulointerstitial injury has become a more prominent clinically important feature of renal disease in HIV-infected individuals (74,170,171). Kidney disease is increasingly recognized as a significant cause of mortality in this patient population; therefore, guidelines published by the Infectious Diseases Society of America recommend all HIV-positive patients be assessed for kidney disease. If there is greater than 1+ proteinuria or eGFR less than 60 mL/min/1.73 m^2, nephrology referral should be made and a renal biopsy may be indicated. Renal parenchymal disease in HIV-positive patients encompasses acute tubulointerstitial injury, which usually is induced by medications, as in immunocompetent hosts, with HAART agents additionally being a major contributor. Prerenal factors, such as dehydration, fever, sepsis, and drug administration (such as amphotericin), may result in acute renal failure without morphologic abnormalities or may induce ischemic or toxic acute tubular necrosis (37,168,172). Intratubular obstruction due to drug-induced crystals also causes renal failure and rarely papillary necrosis (173–175). Nephrocalcinosis is found in ≤50% of those with AIDS, either at autopsy or by imaging studies (9,176,177). This is usually an incidental finding, but it may be associated with renal insufficiency. Myoglobinuria is associated with medications or HIV-induced polymyositis (169). Other parenchymal abnormalities include renal infarcts related to septic emboli, infarcted tumor following therapy, or direct renal infection.

Clinical Features

The varied types of acute tubular and interstitial lesions in patients with AIDS present as renal functional impairment or electrolyte and acid-base imbalances. Acute tubular necrosis and interstitial nephritis produce acute renal failure, which has been observed in up to 20% of hospitalized HIV-infected patients (178). Patients may have non–nephrotic-range proteinuria. Drug-induced tubular dysfunction, associated with HAART agents, also may produce Fanconi syndrome with acid-base disturbances and increased or decreased concentrations of sodium or potassium in blood and urine (179–181). Intratubular crystal formation, now seen infrequently on renal biopsy, induces hematuria. Renal infarcts produce pain and hematuria, with renal dysfunction if a large enough renal area is involved or if there is an obstructive component. In addition to the structural disorders and their functional consequences delineated here, characteristic fluid, acid-base, and electrolyte disturbances occur in HIV-infected individuals; these manifestations have been described and studied most commonly in patients with AIDS in the era prior to HAART. Dysfunction of endocrine glands, particularly the adrenal, is a not uncommon finding and may be induced by infections including HIV itself, antimicrobial agents, or infiltration by HIV-associated neoplasms (10,58,182,183). The most prevalent electrolyte disturbance is hyponatremia, which may be a consequence of either gastrointestinal fluid loss (hypovolemic) or a syndrome of inappropriate secretion of antidiuretic hormone (euvolemic). Hypo- and hyperkalemia usually result from gastrointestinal fluid and electrolyte loss in the former and drug-induced process due to trimethoprim, dapsone, pentamidine, and ketoconazole among others. Acid-base disturbances can be the result of sepsis, opportunistic infections, or therapeutic agents. Hypoaldosteronism, not uncommon in patients with AIDS, can lead to hyperchloremic metabolic acidosis. Lactic acidosis is becoming more common; in some instances, it has been linked to tenofovir or zidovudine therapy and has a high mortality (58,181).

Pathology

Gross

Kidneys with acute tubulointerstitial lesions are edematous, swollen, and often pale. The foci of infarction are easily appreciated within the renal parenchyma as pale or hemorrhagic areas.

Microscopic

The microscopic changes of acute tubular necrosis and acute interstitial nephritis usually are identical to those in immunocompetent patients with the same lesions (see Chapters 25 and 26), with few exceptions. Tubular necrosis is characterized by degeneration of epithelial cells with loss of proximal cell brush border staining, flattening of the epithelium, foci of denuded tubular basement membranes, cellular debris within lumina, and regeneration with tubular cell mitoses, with variable interstitial edema. In tubular necrosis associated with crystalline precipitation of medications, there are clear crystals often with surrounding macrophages accumulated in tubular lumina more often affecting distal tubules, with necrosis of adjacent epithelium (Fig. 11.20) (175). Tubular necrosis caused by reverse transcriptase inhibitor–induced mitochondrial abnormalities shows proximal tubular cells with atypical enlarged nuclei, variably attenuated cytoplasm, and large mitochondria. By light microscopy, these enlarged mitochondria may be visible as cytoplasmic eosinophilic or blue round structures with hematoxylin and eosin or toluidine blue staining, respectively, and appear angulated with broken and absent

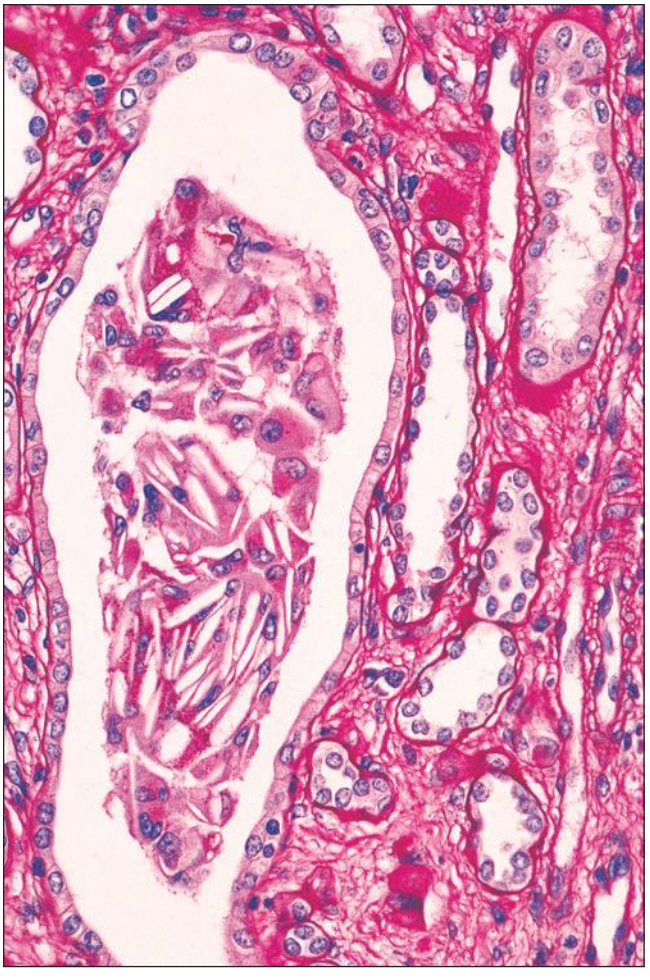

FIGURE 11.20 Intratubular crystals in a patient receiving indinavir therapy. The crystals are within a dilated tubular lumen surrounded and engulfed by macrophages. The distal tubular epithelial cells are flattened. (PAS, ×160.)

cristae on ultrastructural examination (184,185) (Fig. 11.21). Myoglobinuria produces myoglobin (pigmented) casts with associated tubular necrosis. Necrotic tubules may rupture with resulting extratubular Tamm-Horsfall protein or other intraluminal contents eliciting a surrounding interstitial inflammatory response. Rarely, papillary necrosis occurs associated with indinavir stones and interstitial nephritis (173).

Acute interstitial nephritis is characterized by interstitial edema with a mononuclear leukocytic infiltrate that often extends into tubular walls, with concomitant tubular cell necrosis; a neutrophilic infiltrate indicates infection or adjacent infarction. There may be variable numbers of eosinophils or nonnecrotizing granulomata associated with certain drugs or immune reconstitution inflammatory syndrome, which need to be differentiated from infection (186). Rarely, HIV may induce a T- or B-cell lymphocytic infiltrate mimicking interstitial nephritis (187,188). Renal infarcts have foci of nonviable renal parenchyma with surrounding neutrophils, with or without hemorrhage, if the lesion is recent and areas of granulation tissue formation or fibrosis if it is an older infarct.

Natural History

Acute tubular injury and tubulointerstitial nephritides stemming from drug use will often resolve if the offending agent is removed (175,185,189) although are more likely to leave persistent renal dysfunction if there is underlying preexisting or prolonged ongoing renal injury. Once the lesion has progressed to a more chronic process, there will be some residual renal impairment. The immune reconstitution syndrome and HIV-associated lymphoid infiltrates may resolve with steroids (186,188,190). Drugs associated with intratubular stone formation respond well to hydration, and the drug may continue to be administered. Patients with renal infarcts stemming from tumors or sepsis have a poor prognosis, related to the underlying disease process.

Etiology and Pathogenesis

Acute tubular necrosis is a now well-recognized complication of HAART agents, particularly the reverse transcriptase inhibitors. This class of drugs, usually tenofovir but also cidofovir, adefovir, and others, inhibits human mitochondrial DNA polymerase γ, inducing inhibition of de novo mitochondrial DNA synthesis and subsequent mitochondrial DNA depletion. This results in an acquired drug-induced mitochondrial functional deficiency and down-regulation of specific transporters (170,184). Tubular injury due to rhabdomyolysis and myoglobin casts may be responsible for up to 10% of acute kidney injury cases in HIV-infected patients (154). Rhabdomyolysis is associated with HIV infection itself (178) with polymyositis caused by HIV or other viruses (191) or may be drug induced resulting from administration of integrase inhibitors (192,193), nucleoside reverse transcriptase inhibitors via mitochondrial myopathy (194), pentamidine (169), or following the combination of the protease inhibitor, atazanavir, with statins and fluconazole (195,196). Intratubular crystals can precipitate in patients who have been administered indinavir, amphotericin B, acyclovir, atazanavir, or sulfadiazine, particularly in states of dehydration or urine pH above 6, causing acute tubular necrosis by mechanical abrasion or chemical irritation. There is intratubular obstruction and tubular rupture may ensue, leading to focal interstitial nephritis. Acute tubular necrosis also may be related to prerenal mechanisms such as dehydration and appears to have an increased incidence in patients coinfected with hepatitis C (197).

Acute tubulointerstitial nephritis and acute interstitial nephritis are induced by drugs in the vast majority of cases, including those used to treat HIV, other infections, and for noninfectious disorders (179,198) (Table 11.2). There are unusual autoimmune-like disorders in HIV-infected individuals, characterized by benign lymphoid or plasmacytoid infiltrates in several organs including the kidneys, and these disorders may appear as or may be accompanied by acute tubulointerstitial nephritis. The pathogenesis of this diffuse infiltrative lymphocytosis syndrome is uncertain; it may be related to HIV infection directly or to a secondary viral infection (15,188). Immune reconstitution syndrome may have a similar appearance, with or without granulomata (186,209). Epstein-Barr virus also has been implicated in the pathogenesis of acute interstitial nephritis (210).

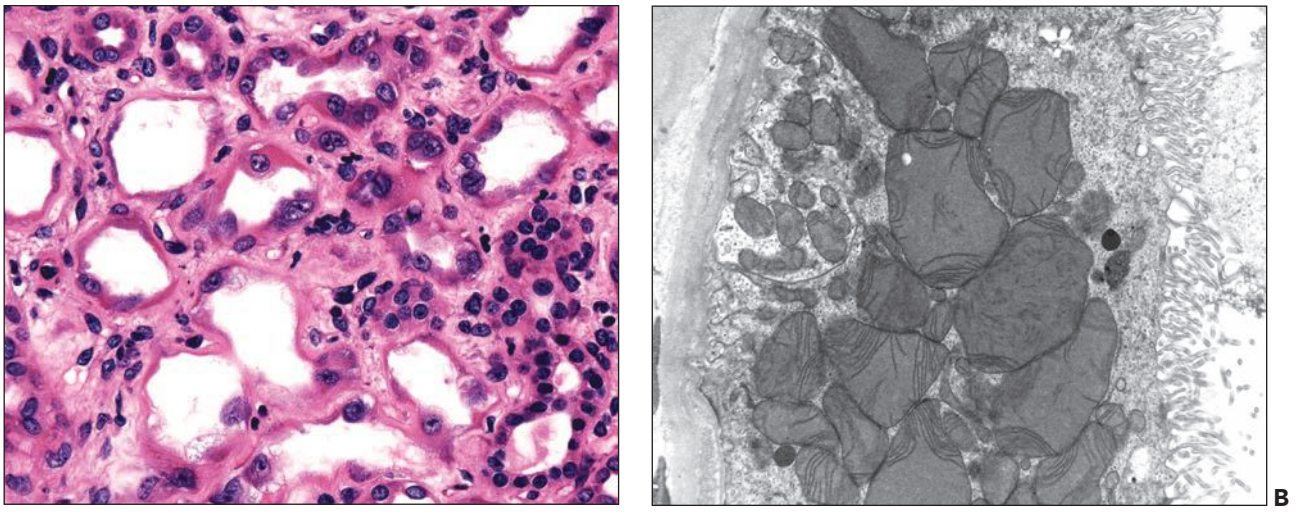

FIGURE 11.21 **Tenofovir-induced mitochondrial injury in proximal tubular epithelium. A:** Tubular cells are necrotic with absent to attenuated and eosinophilic cytoplasm, focally enlarged nuclei, and loss of brush border staining. (H&E, ×160.) **B:** Electron microscopy of a proximal tubule shows markedly enlarged mitochondria with abnormal shapes and reduced numbers of broken distorted cristae. (×10,000.)

CHRONIC TUBULOINTERSTITIAL LESIONS

Progressive kidney disease has emerged as a major cause of mortality in HIV-infected patients (211) with chronic tubulointerstitial injury a prominent clinically important component since the advent of HAART. In an autopsy study of HIV-infected patients with chronic kidney disease, all had associated renal pathology (23). As with acute injury, these lesions may be induced by medications, with HAART agents a major contributor, particularly tenofovir (14,23,25,212). However, with HIV now considered a chronic disease, secondary forms of renal injury such as diabetes and hypertension are increasing as causes of chronic disease in patients with HIV infection (155,213). This may relate to aging of HIV-infected individuals and other underlying renal risk factors. In contrast, there is a decreasing reported incidence of nephrocalcinosis, which has been identified in patients with AIDS either at autopsy or by imaging studies (9,23,176,177) usually as an incidental finding and infrequently associated with renal insufficiency.

TABLE 11.2 **Etiologies of tubulointerstitial lesions in patients with AIDS**

Sources	References
Drug-induced lesions[a]	
Acyclovir	(179,199)
Adefovir	(184,199)
Amphotericin B	(200,201)
Atazanavir	(202)
Cidofovir	(170,199)
Germanium lactate citrate	(203)
Indinavir	(173,175,204)
Interleukin-2	(199)
Pentamidine	(169)
Raltegravir	(192,193)
Ritonavir	(205)
Sulfadiazine	(174,189)
Tenofovir	(170,180,181,185)
Zidovudine	(206)
Myoglobinuria	(178,191,196)
Nephrocalcinosis	(177,207)
Direct renal infection	(3,176)
Hemodynamic factors	
Dehydration	(10,58)
Sepsis	(58,168,208)

[a]In addition to the common medications causing renal failure (see Chapter 25 on interstitial nephritis).

Clinical Features

Chronic tubulointerstitial lesions present as progressive or advanced renal functional impairment, with or without non–nephrotic-range proteinuria. Hypertension is common. As in acute tubulointerstitial injury, Fanconi syndrome or acid-base disorders such as renal tubular acidosis may occur, usually in association with medications such as tenofovir and other reverse transcriptase inhibitors. When chronic interstitial nephritis is associated with intratubular crystal precipitation, patients may develop nephrolithiasis.

Pathology

Gross

Chronic interstitial nephritis is characterized by scarred kidneys with an irregular granular surface.

Microscopic

Chronic interstitial nephritis has features similar to those observed in patients without HIV infection (see Chapter 25). There is interstitial fibrosis with tubular atrophy, with variable numbers of infiltrating mononuclear leukocytes in the interstitium with or without tubular inflammation. Nonnecrotizing granulomata may be present depending on the underlying etiology, such as

certain drugs or intratubular crystal deposition (202). There may be tubular or interstitial calcifications or oxalate deposition, depending on the degree and length of time of renal injury.

Natural History

Chronic tubulointerstitial processes result in some degree of renal functional impairment and may lead to end-stage kidney disease. Removal of an offending drug may result in slowing the progression of the decline in renal function. Interestingly, in patients given tenofovir who have been exposed to the drug for up to 48 months and have acute or progressive renal failure, discontinuation of the drug may still result in restoration of baseline renal function (185). Drugs associated with intratubular stone formation respond well to hydration, and in some cases, the drug may continue to be administered.

Etiology and Pathogenesis

In the current era of HIV infection and treatment, chronic tubulointerstitial injury is related to a broad spectrum of renal disorders, many of which affect the general population. Medications often are responsible for chronic kidney disease, including agents such as tenofovir (212,214), pentamidine (9), indinavir (204), and germanium lactate citrate (203). Due to the associated renal injury and availability of other effective agents, currently indinavir is used less frequently than in the past. Nephrocalcinosis may be a late complication of intrarenal crystal formation. Calcium deposition in the kidney also has been attributed to pentamidine and amphotericin therapy as well as disseminated infection with *Pneumocystis jirovecii* (*carinii*), *Mycobacterium avium* intracellulare, and CMV (168,200,201,207) and possibly due to HIV infection alone.

There are recognized risk factors for the development of progressive chronic kidney injury in patients infected with HIV. These include older age, diabetes, hypertension, lower CD4 counts, exposure to nephrotoxic drugs such as tenofovir or indinavir, and hepatitis C coinfection (212). Progression to end-stage kidney disease is faster and occurs more often in blacks. This is now thought to be related, in part, to APOL1 gene risk variants, which are commonly homozygous or heterozygous in the black population with variable penetrance among different ethnic groups from Africa; these variants appear to confer particular risk for the development of glomerular and vascular disease (215).

INFECTIONS

Historically, direct renal infection with microorganisms other than HIV has been identified in ≤20% of patients with AIDS at the time of autopsy (24,168,216), although it is found in more than half of those who present with acute kidney injury (25). A wide spectrum of microorganisms, encompassing both the common infectious agents seen in immunocompetent hosts and more unusual organisms, make their way into the kidney (Table 11.3). CMV is the most typical offending agent, but accounts for ≤30% of definite or suspected renal infections (176). The kidney may be the site of isolated infection, or it may be part of a systemic process; systemic candidiasis and cryptococcosis affect the kidneys in 5% to 10% of patients (5,24,74,168). Syphilis is increasing in prevalence, and much of this is in the HIV-infected population, in which it can present with glomerular or tubulointerstitial disease (229).

TABLE 11.3 Opportunistic renal infections in patients with AIDS

	References
Bacterial	
Acinetobacter	(176)
Mycobacteria	(168,186,208)
Pseudomonas	(176)
Salmonella	(176)
Fungal	
Aspergillus	(217)
Candida	(218)
Cryptococcus	(218,219)
Histoplasma	(176)
Nocardia	(220)
Zygomycoses	(221,222)
Viral	
Adenovirus	(223)
Cytomegalovirus	(218,224)
Hepatitis B	(137)
Hepatitis C	(142)
Herpes	(16)
Polyoma	(225)
Other	
Leishmania	(226)
Malaria	(227)
Microsporidium	(228)
Pneumocystis	(169)

Clinical Features

The clinical features of renal infection run the gamut from asymptomatic to acute renal failure with or without glomerular disease. The type of organism, extent of infection, and host condition and response all have an impact on the clinical picture. Renal mucormycosis may induce fever and flank pain, acute renal failure, hematuria, or infarction resulting in a mass-like effect when observed with imaging studies (221,222). CMV and *Leishmania* infections may result in hematuria and proteinuria, simulating acute glomerulonephritis (216,224,226). The offending microorganisms may be found in other organs or may be isolated to the kidney in the presence or absence of additional infectious agents elsewhere in the body (219,228). Urine cultures may give negative or positive results, and pyuria is not a constant feature.

Pathology

Gross

The gross pathologic picture varies as much as the clinical presentation. Kidneys may appear normal or have foci of white streaks, areas of hemorrhage, abscesses, or mass-like lesions corresponding to fungus balls. One reported case of *Mucor* infection resulted in an entirely infarcted kidney (222).

Microscopic

On microscopic examination, infectious agents may involve all renal elements, including the interstitium, tubules, glomeruli, and peritubular capillaries. Depending on the organism and host response, the renal picture may range from no

inflammatory reaction to a neutrophilic or mononuclear leukocytic infiltrate to renal infarction. CMV and polyoma virus may evoke acute tubulointerstitial nephritis with mononuclear cells and viral inclusions in epithelial cells, with endothelial cells and leukocytes also targets of CMV infection, or there may be no inflammatory response (Fig. 11.22). Glomerular and peritubular capillary inflammation may occur with CMV, disseminated *P. jirovecii* (*carinii*), and malarial infection (227). Bacterial and fungal infections may involve any portion of the renal parenchyma or be associated with abscess formation (Fig. 11.23). Mycobacterial infections may induce ill-defined granulomata or a more diffuse histiocytic infiltrate.

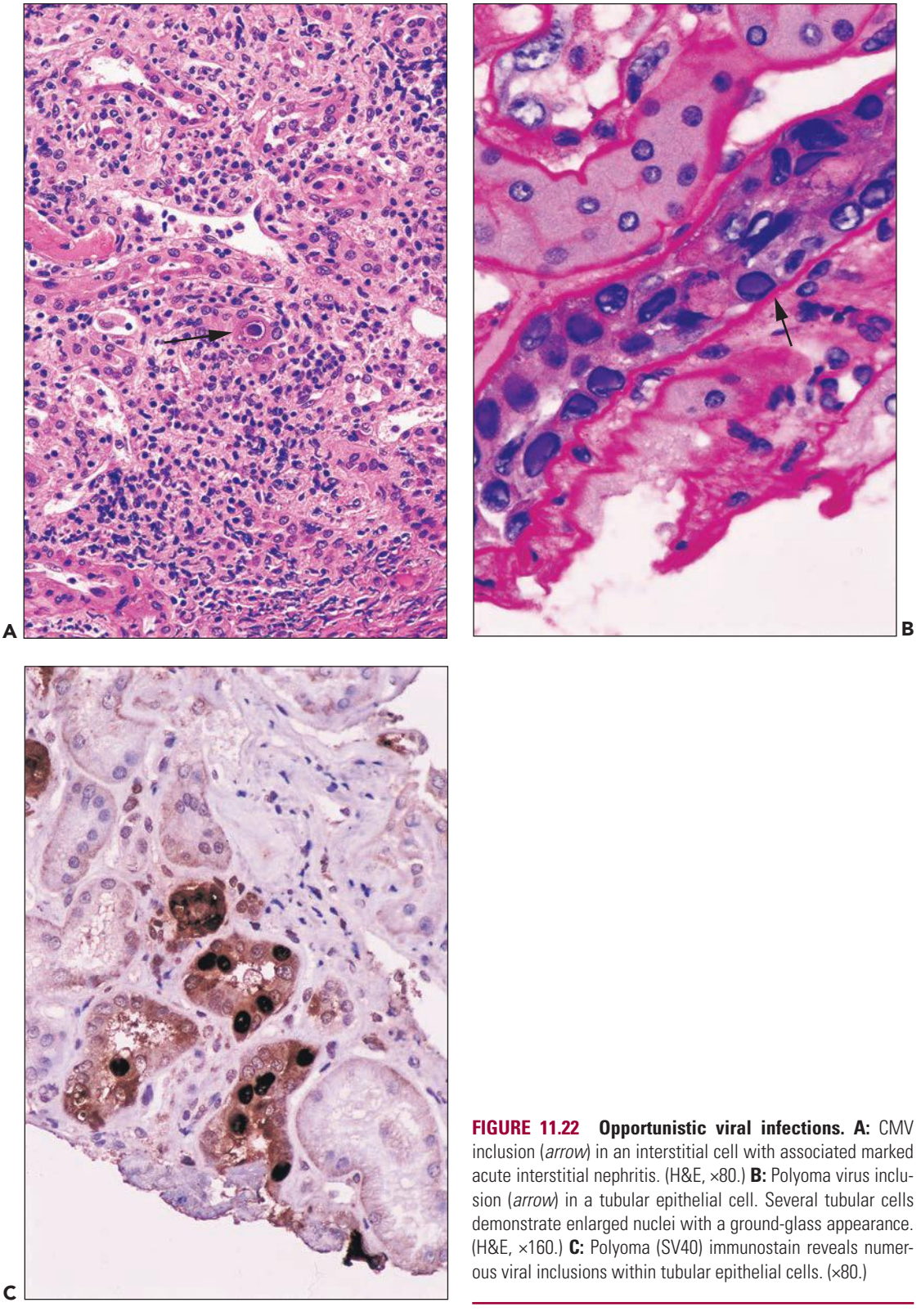

FIGURE 11.22 Opportunistic viral infections. A: CMV inclusion (*arrow*) in an interstitial cell with associated marked acute interstitial nephritis. (H&E, ×80.) **B:** Polyoma virus inclusion (*arrow*) in a tubular epithelial cell. Several tubular cells demonstrate enlarged nuclei with a ground-glass appearance. (H&E, ×160.) **C:** Polyoma (SV40) immunostain reveals numerous viral inclusions within tubular epithelial cells. (×80.)

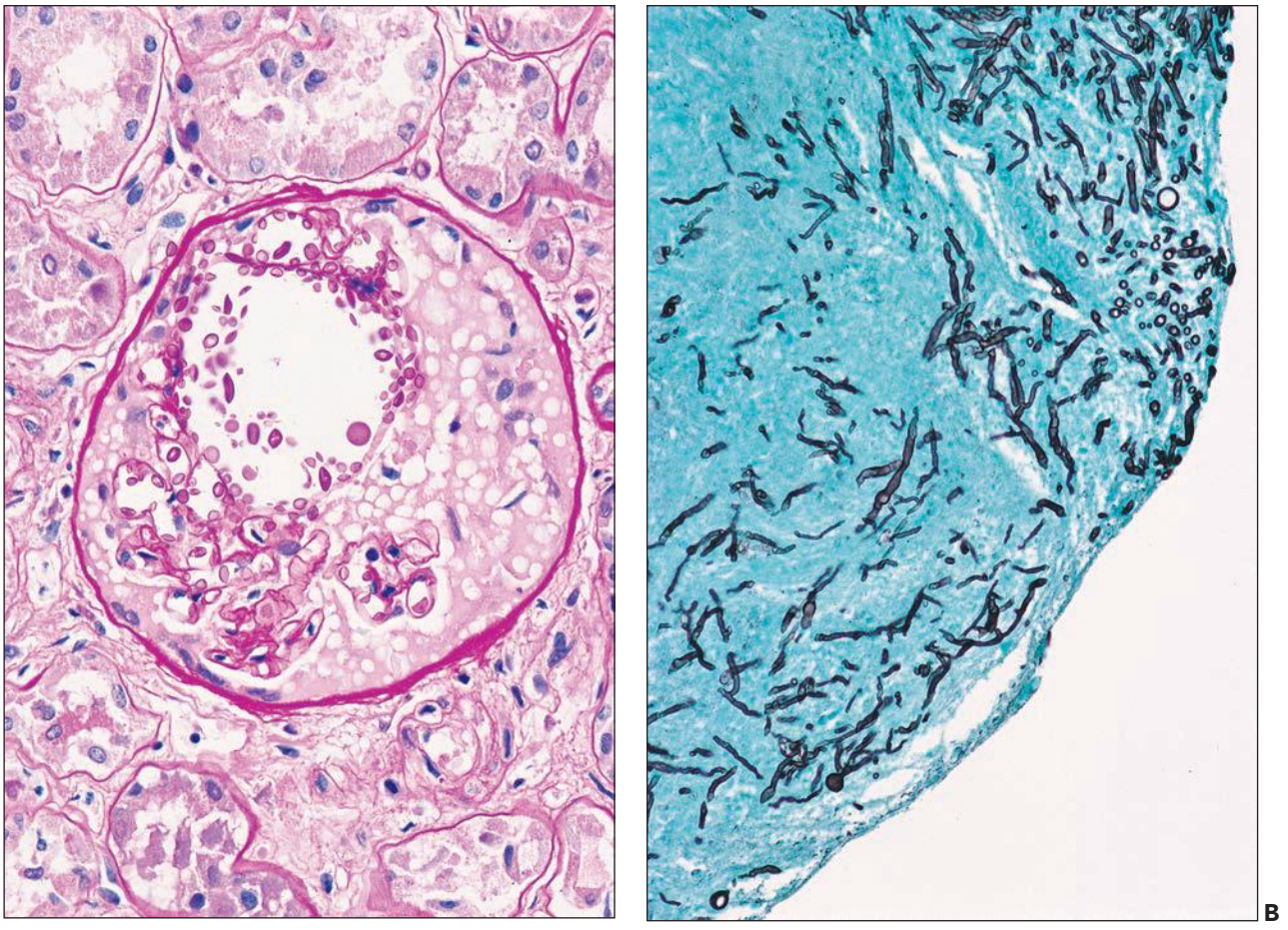

FIGURE 11.23 Opportunistic fungal infections. A: Cryptococcal organisms within glomerular capillaries, several of which are mildly to massively dilated. (PAS, ×160.) **B:** *Aspergillus* species abscess in the renal parenchyma. There are 45-degree branching septate hyphae in necrotic debris. (Gomori methenamine silver, ×80.)

Tubular cell necrosis may be the only morphologic response, as in two reported cases of renal adenovirus infection (223). It may be difficult to differentiate tubulointerstitial nephritis due to infection from that induced by medications. Therefore, in cases of interstitial nephritis, microorganisms should be sought using appropriate special stains, immunochemical stains, or in situ hybridization for viral genome.

Natural History

Disseminated infection involving the kidney is often a preterminal event, as evidenced by the large number of cases identified at autopsy. Isolated renal infection should be treated with the appropriate therapeutic agents; some patients respond, depending upon the severity of infection and overall status of the patient. Isolated fungal infections with or without associated renal infarction may be successfully treated by partial or complete nephrectomy.

Etiology and Pathogenesis

Immunocompromised patients are at increased risk of intrarenal infection, as for infections in other organs. For the more unusual organisms, hematogenous spread likely plays a larger role in this population relative to immunocompetent hosts. Ascending infection also occurs, more often with bacteria and some fungi.

TRANSPLANTATION

With the success of HAART and increased survival of HIV-infected patients, increasing numbers are developing end-stage renal disease of heterogeneous origin. In addition to disorders directly related to HIV infection, its complications and therapy, diseases common to the non–HIV-infected population resulting in progressive renal failure have become more prevalent in this population. Consequently, the former absolute contraindication to transplantation in HIV-infected patients no longer exists. Thus, renal transplantation has become a clinically useful procedure for these individuals (230). It is not the purpose of this chapter to cover in detail transplant pathology in this group (see Chapter 29); transplant rejection appears to be more common in this patient cohort, although interpretation of biopsies is done using the same criteria in the noninfected population (231).

NEOPLASMS

The kidneys are affected by malignant lesions in 4% to 8% of patients with AIDS (15,32,65); they are found in children as well as in adults (232) (Table 11.4). The neoplastic processes include lymphomas and Kaposi sarcoma, which are usually part of disseminated disease and therefore are most often identified at autopsy (19,239). Primary renal cell carcinoma occurs in a much smaller number of cases, and evidence may be found in renal biopsy or nephrectomy specimens (237,241). There has been a single reported case of renal angiosarcoma (241). In the current HAART era, malignancies that are not AIDS defining are of more clinical significance than those that are part of the spectrum of AIDS and may occur more frequently than in patients without HIV infection (242).

Clinical Features

Renal neoplastic processes have a variety of presentations in patients with AIDS. Most frequently, imaging studies, such as computed tomography scanning or ultrasound, are performed for other reasons, and an asymptomatic mass lesion or diffuse renal parenchymal infiltrates are identified. The malignant lesion may result in a palpable mass or induce flank pain, hematuria, and weight loss, as in hosts with normal immune function. Rarely, renal failure may result from diffuse renal infiltration by lymphoma (233–235). Renal cell carcinoma manifests in HIV-infected patients at a younger age and is reported to have a higher prevalence than in the general population (238). Kaposi sarcoma is predominantly seen in those with homosexual or bisexual routes of HIV infection.

Pathology

Gross

Lymphomatous involvement of the kidney appears as a discrete white-gray tumor mass or, if there is diffuse infiltration, as enlarged and somewhat pale kidneys. Renal cell carcinoma has features identical to those in immunocompetent hosts, appearing as a yellowish mass, often with areas of hemorrhage or necrosis. Kaposi sarcoma is a purple-red lesion, as in nonrenal locations.

Microscopic

The types of lymphomas that occur in the context of HIV infection are predominantly B-cell and Burkitt types (Fig. 11.24); there are one case each of renal angiocentric and intravascular lymphoma in the literature (235,236). Lymphomas in HIV-positive patients typically are composed of large immunoblastic lymphoid cells with prominent nucleoli and a B-cell or Burkitt type phenotype on immunochemical stains. Angiocentric lymphomas are of T-cell origin, with cells intermediate in size that invades vascular walls and lumina, while intravascular lymphoma is a high-grade T-cell lesion primarily within the vasculature. Renal cell carcinoma has the usual spectrum of clear and granular cells. Kaposi sarcoma is characterized by spindle cells with numerous small slit spaces and extravasated red blood cells; it may occur as a single lesion or be multifocal. The single case of angiosarcoma had the usual features, with a malignant vascular proliferation in the kidney.

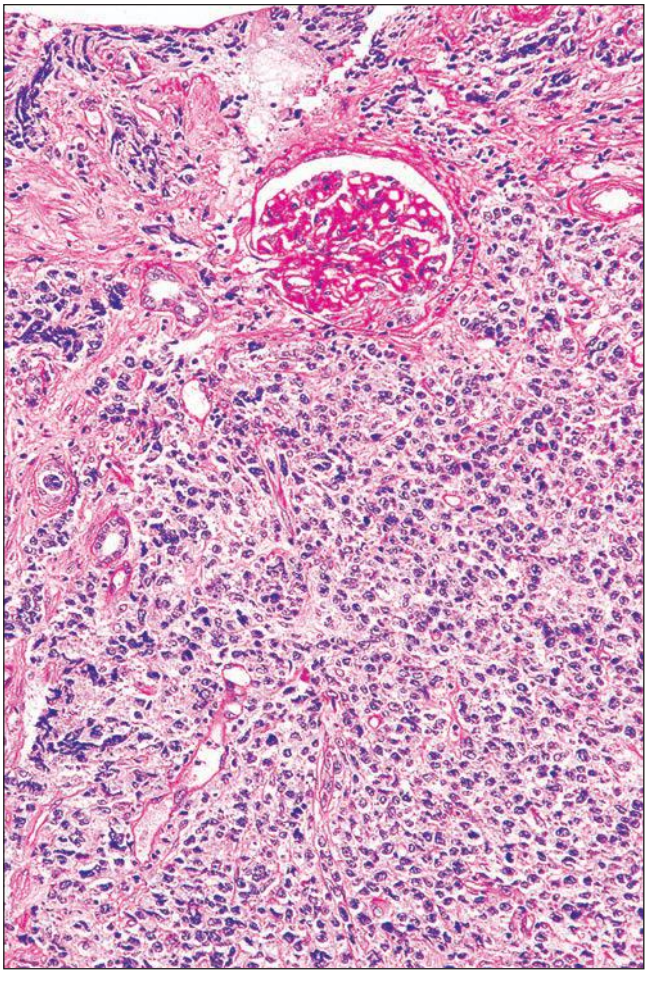

FIGURE 11.24 Large B-cell lymphoma infiltrating the renal parenchyma in an HIV-infected patient. (PAS, ×40.)

TABLE 11.4 Renal malignancies in patients with AIDS

Malignancies	References
Lymphoma	
B-cell, Burkitt-like, angiocentric, intravascular	(233–236)
Renal cell carcinoma	(237,238)
Kaposi sarcoma	(239,240)
Angiosarcoma	(241)

Natural History

Patients with HIV infection and AIDS-defining renal malignancies usually have full-blown AIDS and a poor prognosis. One case of primary renal lymphoma was the initial manifestation of AIDS (233). Therapeutic approaches have varied, and, with the newer antiviral agents, there is no clear optimal treatment course.

Etiology and Pathogenesis

The lack of appropriate immune surveillance allows development of neoplasms in the kidney as in other organs in HIV-infected patients. Viral infection may also play a role,

particularly in Epstein-Barr virus–associated lymphomas and in Kaposi sarcoma, which is associated with human herpes virus 8 (235,240). In non–AIDS-defining malignancies, the usual risk factors play a role, but there is an increased cancer risk in HIV-infected individuals, suggesting an additional role of the above-mentioned factors (242).

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CHAPTER 12

Mark Haas

IgA Nephropathy and IgA Vasculitis (Henoch-Schönlein Purpura) Nephritis

HISTORICAL BACKGROUND

IgA nephropathy first became recognized as a distinct entity in 1968, when Berger and Hinglais (1) reported a cohort of patients with persistent microscopic hematuria, episodes of macroscopic hematuria in some that were often associated with a sore throat, mild to moderate proteinuria without the nephrotic syndrome, and normal renal function in most. Renal biopsies from these patients showed varying histologic features ranging from normal to chronic glomerulonephritis, but most often focal glomerulonephritis, without typical features of acute postinfectious (poststreptococcal) glomerulonephritis. However, immunofluorescence microscopy in each case showed mesangial deposition of IgA, usually with accompanying but less intense staining for IgG and C3, and electron microscopy (EM) confirmed the presence of mesangial immune complex deposits (1,2).

Still, it is almost certain that IgA nephropathy existed long before the techniques of immunofluorescence and EM made its definitive identification possible. For example, in the early 20th century, Volhard and Fahr (3) described an acute form of focal glomerulonephritis occurring at the height of certain infections including tonsillitis. This was characterized by hematuria but not hypertension and only rarely edema and azotemia. These features, which resemble those described by Berger (1,2), appeared to distinguish this form of glomerulonephritis from acute poststreptococcal glomerulonephritis (3). Furthermore, unlike the typical course of poststreptococcal glomerulonephritis, some patients continued to have persistent or episodic hematuria, the latter often exacerbated by recurrent infections (3), and some developed a chronic stage of the disease characterized by proteinuria as well as hematuria. A similar group of patients with "acute focal nephritis" were later described by Ellis (4). In the interval between these early reports and that of Berger and Hinglais (1), a number of investigators described in autopsy and renal biopsy studies lesions of focal glomerulonephritis, most often mesangial proliferative, associated with gross and microscopic hematuria (5–7). It is almost certain that many of the lesions described in these reports were in fact IgA nephropathy.

Subsequent to the initial demonstration by Berger and Hinglais (1) of glomerular IgA deposits in a group of patients with primary glomerulonephritis, similar mesangial deposits of IgA were identified in renal biopsies of patients with Henoch-Schönlein purpura (HSP) nephritis (8). HSP, which had been

initially described over a decade earlier (9,10), is now classified as a form of systemic vasculitis with "IgA-dominant immune deposits affecting small vessels and typically involving the skin, gut, and glomeruli and associated with arthralgias or arthritis" (11), although renal involvement does not occur in all cases. Renal disease in Henoch-Schönlein purpura (Henoch-Schönlein nephritis), and how this may be related to primary IgA nephropathy, are addressed later in this chapter.

The initial portion (and majority) of this chapter focuses on the pathology of IgA nephropathy, including primary and secondary forms but primarily the former, with significant emphasis given to clinicopathologic correlations and potential pitfalls in diagnosis. In this context, the epidemiology, clinical features, treatment, and current understanding of the pathogenesis of primary IgA nephropathy are reviewed in some detail, although references to recent, comprehensive reviews of these latter topics are also provided.

PRIMARY IgA NEPHROPATHY

Epidemiology

IgA nephropathy is recognized as the most common form of primary glomerulonephritis in the world (12–14), although the prevalence of IgA nephropathy among glomerular diseases and its incidence in the general population show considerable variation among geographic regions and among regions with different renal biopsy practices. As shown in Table 12.1, IgA nephropathy accounts for approximately one third of the total renal biopsy diagnoses and nearly one half of all primary

TABLE 12.1 Frequency of primary IgA nephropathy in renal biopsy series

				No. of biopsies		% of biopsies with IgAN	
Reference	Country	Years	Study population	Total	1º Glomerular disease	All biopsies	1º Glomerular disease
Utsunomiya et al. (15)	Japan	1989–1998	C	178		35.4	
Ueda et al. (16)	Japan	1968–1974	A, C	307		27.7	
Koyama et al. (17)	Japan	1985–1993	A, C		1045		47.4[a]
Li and Liu (18)	China	1979–2002	A, C	13,519	9278	31,1	45.3[a]
Sinniah et al. (19)	Singapore	1972–1977	A, C	710		33.7	
Sheu et al. (20)	Taiwan	1983–1992	A		767		25.3[a]
Choi et al. (21)	Korea	1973–1995	A	2097	1732	22.1	26.8
			C	1430	811	10.3	18.2
Briganti et al. (22)	Australia	1985–1997	A, C	2030		19.3	
Clarkson et al. (23)	Australia	1973–1976	A, C	412	278	12.1	18.0[a]
Bailey et al. (24)	New Zealand	1972–1983	A (white)		650		18.5[a]
			A (Polynesian)		153		5.9
Propper et al. (25)	Scotland	1977–1985	A, C	364	232	16.8	26.3
Power et al. (26)	Scotland	1977–1980	A, C	184	119	14.1	21.8[a]
Tiebosch et al. (27)	The Netherlands	1978–1985	A	175	122	16.6	23.8[a]
Gesualdo et al. (28)	Italy	1996–2000	A, C	14,607	6990	16.5	34.5[a]
Stratta et al. (29)	Italy	1970–1979	A		449		15.4
		1980–1994	A		1477		29.4[a]
Simon et al. (30)	France	1976–2002	A, C	1742	898	15.3	29.7[a]
Rivera et al. (31)	Spain	1994–2001	A	8439		13.4	
			C	939		11.6	
Johnston et al. (32)	United Kingdom	1978–1985	A, C	6441	3309	9.3	18.1
Sissons et al. (33)	England	1970–1974	A, C	630		4.0	
Polenakovic et al. (34)	Macedonia	1975–2001	A	1304	716	6.5	11.8
Seedat et al. (35)	South Africa	1981–1986	A, C (black)		252		0.8
			A,C (Indian)		75		13.3
Bahiense-Oliveira et al. (36)	Brazil	1979–1999	A		943		11.6
Galla et al. (37)	United States	1978–1982	C	296		10.8	
		1982–1983	A, C	223		9.4	
Smith and Tung (38)	United States	1975–1985	A, C	708		7.3	
Jennette et al. (39)	United States	pre-1985	A, C	1723		6.2	
Haas (40)	United States	1980–1994	A, C	6067		4.6	
Nair and Walker (41)	United States	2001–2005	A	4504	1228	6.9	25.4
	United States	2001–2005	A (ages 20–39)	1082	416	14.2	37.0[a]
Alexander et al. (42)	Canada	Pre-1977	A, C	250		4.8	

[a]Most common primary glomerular disease in the study.
A, adults; C, children; IgAN, IgA nephropathy, 1º, primary.

TABLE 12.2 Incidence of primary IgA nephropathy

Reference	Country (region)	Study period	New IgAN cases/10^6 persons/year
Utsunomiya et al. (15)	Japan (Yonago)	1983–1998	45
Briganti et al. (22)	Australia (Victoria)	1985–1997	43
Frimat et al. (43)	France (Nancy)	1988–1991	40
Simon et al. (30)	France (N. Brittany)	1976–1985	28
		1986–1995	28
		1996–2002	26
Alamartine and Berthoux (44)	France (Rhone-Alpes)	1987–1988	27
Rambausek et al. (45)	Germany (Heidelberg)	1973–1986	24
Tiebosch et al. (27)	The Netherlands (three sites)	1978–1985	19
Stratta et al. (29)	Italy (Torino)	1990–1994	15
Wyatt et al. (46)	United States (Kentucky)	1985–1994	10
		1975–1984	6
Bailey et al. (24)	New Zealand (White)	1972–1983	6
	New Zealand (Polynesian)	1972–1983	2

glomerular diseases diagnosed by renal biopsy in certain Asian countries, including Japan, Mainland China, and Singapore (15–21). In most European and Australian studies, IgA nephropathy accounts for 10% to 20% of renal biopsy diagnoses and 20% to 30% of primary glomerular diseases (22–34), although in the United States and Canada, these percentages are generally lower (37–40,42). Still, IgA nephropathy has been found to be the most common primary glomerular disease in the United States among adults aged 20 to 39, accounting for 14% of renal biopsy diagnoses in this age group (41).

Geographic differences in the frequency of diagnosis of IgA nephropathy are also reflected in studies determining the incidence of IgA nephropathy as new cases per 1,000,000 population per year in different regions of the world (Table 12.2). While all of the factors underlying these geographic differences are not known, two factors appear to play significant roles: renal biopsy practices in different countries and race. In some Asian countries, most notably Japan, there are well-established screening programs to detect urinary abnormalities in children and young adults, with renal biopsies presently being performed in those individuals with persistent microscopic hematuria and/or persistent mild proteinuria (15). In a recently published study, 48% of Japanese children initially identified through the urinary screening program who subsequently underwent a renal biopsy had IgA nephropathy (15). The opposite end of the renal biopsy practice spectrum is represented by many if not most centers in the United States and Canada, as well as in New Zealand and some centers in the United Kingdom (24,26,33), where renal biopsies are often not performed in individuals (particularly adults) with microscopic hematuria and mild proteinuria (less than 0.5 or 1.0 g/d or less than 2+ on dipstick) unless there is accompanying renal insufficiency and/or hypertension (47). Geddes et al. (48) recently reported that only 5.8% of Canadian patients with biopsy-proven IgA nephropathy had proteinuria of less than 0.5 g/d, as compared with greater than 20% of IgA nephropathy patients from Scotland, Finland, and Australia. The increase in the apparent frequency of IgA nephropathy among primary glomerulonephritides in Torino, Italy, from 15.4% during the 1970s to 34.5% from 1990 to 1994 has been attributed to a change in renal biopsy practices and a resulting increase in isolated urinary abnormalities as the indication for renal biopsy (from 4% to 30%) (29).

Race also appears to be an important determinant in the frequency of IgA nephropathy. Several studies in the United States, summarized in Table 12.3, have reported a considerably lower incidence of IgA nephropathy in African Americans as compared with that in Caucasians (37–40), although one study from Shelby County (Memphis), Tennessee, found similar, relatively low (less than 6 cases per million per year) incidences in Caucasian and African American children (49). Notably, IgA nephropathy also appears to be uncommon in African blacks. In a study from Natal, South Africa (35), it was found that IgA nephropathy comprised less than 1% of primary glomerular

TABLE 12.3 Frequency of IgA nephropathy in different races in the U.S. renal biopsy series

References	Years	Region of the United States	Fraction (%) of total biopsies with IgA nephropathy				
			White	Black	Hispanic	Asian	Native American
Haas (40)	1980–1994	Midwest	178/3264 (5.5%)	15/1373 (1.1%)	26/280 (9.3%)	16/133 (12.0%)	
Smith and Tung (38)	1975–1985	Southwest	15/334 (4.5%)	1/62 (1.6%)	19/268 (7.1%)		12/44 (27.3%)
Jennette et al. (39)	pre-1985	Southeast	100/1292 (7.7%)	6/461 (1.3%)			
Galla et al. (37)	1978–1983	South	51/298 (17.1%)	3/221 (1.4%)			

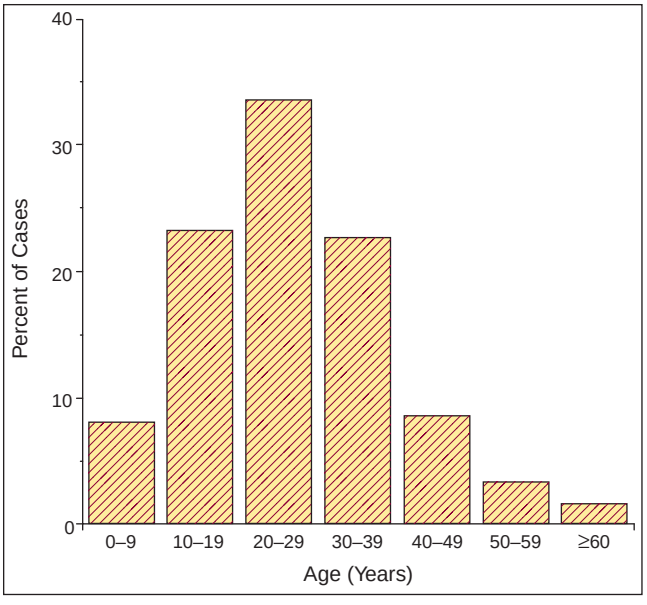

FIGURE 12.1 Age distribution of patients with primary IgA nephropathy. Data represent a total of 1172 cases from four separate studies (17,21,23,33).

diseases in blacks, as compared with 13% of primary glomerular diseases in Indians (see Table 12.1). Among biopsies processed at the University of Chicago from 1980 to 1994, we also found a higher frequency of IgA nephropathy in specimens from Asian Americans than from Caucasians (see Table 12.3), although the frequency in the former group was only 12%, well below that reported in studies from Japan and China (see Table 12.1), consistent with the concept that race and differences in renal biopsy practice are both major contributors to the geographic variability seen in the incidence of IgA nephropathy. A high incidence of IgA nephropathy has also been reported in Native Americans from New Mexico (38), although its incidence among the Polynesian population of New Zealand is substantially lower than among New Zealanders of European descent (24) (see Tables 12.1 and 12.3).

Clinical Presentation and Laboratory Findings

IgA nephropathy can occur in individuals of virtually any age, from young children to the elderly (40), but occurs most commonly between the ages of 10 and 40 years (Fig. 12.1). Most studies show a male predominance, with an overall average male:female ratio of approximately 2:1 (50). However, this ratio tends to be higher in the predominantly Caucasian populations of Western Europe, Australia, and North America than in Japan (15,17,22,23,25,30,40,48,51), and in Hong Kong, a slight female predominance has been reported (52,53).

The two major clinical presentations of primary IgA nephropathy are *asymptomatic urinary abnormalities* and *macroscopic hematuria*, the former being most common in adults and the latter in children (Table 12.4). When macroscopic hematuria is a presenting symptom, this frequently occurs at the time of or 1 to 2 days following an infectious illness, most commonly pharyngitis or tonsillitis but occasionally gastroenteritis, pneumonia, or urinary tract infection (23,50,54). This presentation thus differs from that of acute poststreptococcal glomerulonephritis in which macroscopic hematuria is typically observed 1 to 2 weeks after an episode of pharyngitis or tonsillitis and 3 to 6 weeks after a skin infection (55), although rare cases of IgA nephropathy presenting several weeks following a streptococcal pharyngitis have been reported (56). Recurrent macroscopic hematuria is not uncommon over the course of the disease. This is often associated with infections and may occur in patients who did not initially present with macroscopic hematuria. Unilateral or bilateral abdominal pain, in some instances related to intestinal vasculitis, may be present and can be severe, giving the false impression that the accompanying hematuria is secondary to passage of a renal stone (54,57). Hypertension is noted in approximately 25% of patients at presentation, with this fraction increasing with increasing age, and develops in an additional 25% of patients over time. When hypertension is present at presentation in children and young adults, it is often accompanied by proteinuria and renal insufficiency (50). Table 12.5, which is taken from an exhaustive review of the literature published by Ibels and Gyory in 1994 (50), summarizes clinical features at presentation from 82 series of patients with IgA nephropathy.

The majority of patients with IgA nephropathy present with some degree of proteinuria, although this is often mild and nephrotic syndrome is relatively uncommon in most series (see Tables 12.4 and 12.5). In the original series of Berger (2), in which only 4 of 55 patients were hypertensive and only 3 had renal insufficiency, most patients had only mild proteinuria (less than 1 g/d) and none had nephrotic syndrome. Likewise, in children, who most often present with macroscopic and/or microscopic hematuria with normal renal function, fewer than 50% have proteinuria of greater than 1 g/1.73 m^2/24 h or

TABLE 12.4 Presenting clinical syndromes in children and adults with IgA nephropathy

Main clinical syndrome	Age <15 yr (109 patients) %	Age 15–64 yr (1023 patients) %	Age ≥65 yr (108 patients) %
Asymptomatic urinary abnormalities	26.6	**46.9**	**31.5**
Macroscopic hematuria	**50.5**	15.1	5.6
Nephrotic syndrome	9.2	11.8	15.7
Nephritic syndrome	11.9	3.1	5.6
Chronic renal failure	0.9	12.9	13.9
Acute renal failure	0.9	6.7	27.8
Hypertension	0	3.4	0

Modified from Rivera F, Lopez-Gomez JM, Perez-Garcia R. Clinicopathologic correlations of renal pathology in Spain. *Kidney Int* 2004;66:898–904.

TABLE 12.5 Clinical and laboratory features at presentation or biopsy in patients with IgA nephropathy

	Total numbers	Mean	Range
Sex (M/F)	7239/3347 patients	2.16	1.1–10.3
Mean age (years)	82 series	30.4	19–42
Family history of nephritis (IgA or other)	129/1146 patients	11.3%	3%–20%
Duration of symptoms (months)	2765 patients	50	19–105
Infection-related exacerbations	874/2150 patients	40.7%	10%–69%
Loin or abdominal pain	270/861 patients	31.4%	7%–37%
Macroscopic hematuria	3218/7541 patients	42.7%	5%–87%
Microscopic hematuria	4754/5432 patients	87.5%	53%–100%
Proteinuria >1 g/d	2082/4448 patients	46.8%	18%–81%
Proteinuria >3 g/d	736/6807 patients	10.8%	0%–38%
Elevated serum creatinine	1000/4842 patients	20.7%	5%–38%
Hypertension[a]	2159/8551 patients	25.2%	7%–52%

[a]An additional 772/3074 (25.1%) patients developed hypertension during follow-up.

Modified from Ibels LS, Gyory AZ. IgA nephropathy: analysis of the natural history, important factors in the progression of renal disease, and a review of the literature. *Medicine* 1994;73:79–102.

greater than 1+ on dipstick and fewer than 10% have proteinuria in the nephrotic range (≥3.5 g/1.73 m^2/24 h) (15,31,58–60). Proteinuria of greater than 1 g/d or greater than 1+ by dipstick at the time of renal biopsy is also uncommon in most Japanese series (e.g., (17,61,62)), most likely reflecting the considerable fraction of IgA nephropathy patients identified through that country's urinary screening program. By contrast, in most North American studies as well as in other studies focusing on patients with significant (but not severe) glomerular alterations on renal biopsy, the majority of patients have proteinuria of greater than 1 g/d (40,51,63–65), and in two large series from the United States, 47% and 48%, respectively, of patients with primary IgA nephropathy had proteinuria of ≥2 g/d (40,51). As is discussed below, a small number of patients will present with an overlap of IgA nephropathy and minimal change disease or perhaps more correctly minimal change disease with incidental mesangial IgA deposits. Identification of these patients is important as their proteinuria is steroid responsive and most have an excellent prognosis (66–69).

The frequency of renal insufficiency at the time of initial presentation or diagnosis likewise varies between different studies. This frequency is greater in adults than in children and in North American series compared with those from Asia and Europe. In our series from Chicago (40) and that of Radford et al. (51) from the Mayo Clinic, in which nearly 50% of patients had proteinuria of 2 g or more at the approximate time of renal biopsy, the majority of patients had initial serum creatinine levels greater than 1.2 mg/dL, and the mean serum creatinine among 220 patients in our series was 2.2 ± 1.9 (SD) mg/dL. By contrast, in the German study of Bogenschutz et al. (70) in which only 88 (39%) of 226 patients had proteinuria of greater than 1 g/d at the time of biopsy, only 34% of patients had an initial serum creatinine greater than 1.2 mg/dL, and in the Japanese series of Koyama (17) in which 97 of 322 (30%) patients presented with greater than 1+ proteinuria by dipstick, only 23% of patients had an initial serum creatinine greater than 1.3 mg/dL. IgA nephropathy rarely presents with acute renal failure in children or young adults, although this occurs more often in the elderly (see Table 12.4), perhaps due in part to the frequent presence of an underlying chronic renal disease (e.g., due to essential hypertension) in this population. Severe, crescentic forms of IgA nephropathy may present with acute renal failure (71), similarly to other forms of crescentic glomerulonephritis. Reversible acute renal failure, which may be severe and even require dialysis, can occasionally occur in association with episodes of macroscopic hematuria resulting from IgA nephropathy. The glomerular histopathologic lesions in such cases are often relatively mild (72–76). This acute renal failure is felt to result from injury to tubular epithelium and/or tubular obstruction by red blood cell casts (Fig. 12.2). Interestingly, patients with IgA nephropathy who are receiving anticoagulant drugs may be more susceptible to this form of acute renal failure (77).

Serum IgA levels tend to be higher in patients with IgA nephropathy than in healthy subjects, with significant elevations in up to 50% of patients (23,78,79). However, the elevation in serum IgA levels is not a consistent enough finding for this to be

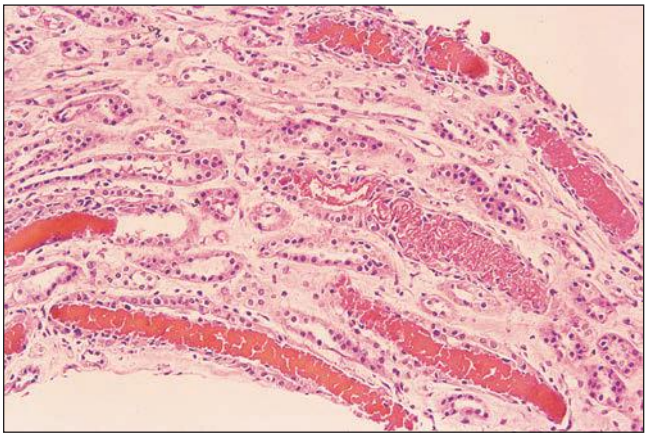

FIGURE 12.2 IgA nephropathy presenting with acute renal failure. Photomicrograph of the medulla shows collecting tubules packed with red blood cells, apparently producing urinary obstruction. (Hematoxylin-eosin [H&E] stain, magnification ×200.)

useful as a diagnostic marker for IgA nephropathy (49,78,79). Serum IgA levels also have no prognostic significance as a marker for disease severity or progression (80–82). Serum levels of IgA-fibronectin aggregates were initially reported to be elevated in 93% of patients with IgA nephropathy or Henoch-Schönlein nephritis, as compared with fewer than 20% of patients with other glomerular diseases (83). However, in a subsequent study with a greater number of patients involving a larger number of patients with IgA nephropathy or Henoch-Schönlein nephritis, only 38% of serum samples from these patients had elevated levels of IgA-fibronectin aggregates, although 48% of patients had an elevated level on at least one occasion (79). Serum levels of IgA-fibronectin aggregates clearly cannot be used as an alternative to a renal biopsy for the diagnosis of IgA nephropathy.

Serum levels of total complement, C3, and C4 are within the normal range or are elevated (mainly C4) in the vast majority of patients with IgA nephropathy and are only rarely decreased (23,81). The normal levels of C3 in IgA nephropathy contrast with those of acute postinfectious glomerulonephritis, in which C3 levels are often depressed (84). Still, there is serologic evidence of complement activation in IgA nephropathy, in the form of activated forms of C3 (85–87). Monoclonal antibodies developed against neoantigens expressed on C3 breakdown products (C3b, iC3b, C3d, and C3dg) that are formed following C3 activation have been detected in 30% to 50% of plasma samples from patients with IgA nephropathy (85,86). In one study, such evidence of C3 activation was found in 75% of adult and 57% of pediatric IgA nephropathy patients when serial plasma samples were analyzed (85). Mean plasma C3a levels have also been reported to be significantly higher in patients with IgA nephropathy than in healthy individuals or those with non–immune-mediated renal diseases (87). The significance of this apparent C3 activation on the course of IgA nephropathy remains unclear. While studies from one laboratory have shown a correlation between high plasma levels of activated C3 (as detected by one of the monoclonal antibodies noted above), but not those of C3a, and deterioration of renal function (86,87), another laboratory found no association between levels of neoantigen from the same C3 breakdown products (albeit detected using a different monoclonal antibody) and the degree of proteinuria or the presence of chronic renal insufficiency (85). Elevated urinary levels of interleukin-6 (IL-6), a cytokine secreted by both mesangial and tubular epithelial cells, or an elevated ratio of the urinary concentration of IL-6 to that of epidermal growth factor (EGF) has also been reported to correlate with clinical and histologic progression of IgA nephropathy (88,89).

Correlation of Clinical Parameters With Clinical Outcomes

A considerable number of clinical parameters and laboratory findings have been reported to correlate with clinical outcomes in patients with IgA nephropathy. These range from results of highly specialized assays performed only in a limited number of laboratories, such as those discussed in the previous paragraph, to routine parameters measured in most or nearly all patients suspected of having kidney disease. In IgA nephropathy, as in a number of other glomerular diseases, three of the following parameters are most consistently and reproducibly found to be correlated with disease progression: glomerular filtration rate (GFR) or serum creatinine level at the time of presentation or renal biopsy, severity of proteinuria, and presence or absence of hypertension. As shown in Table 12.6, which is taken from a review by D'Amico (96) and summarizes results from 23 studies from four continents examining actuarial renal survival in relatively large cohorts of nonselected adults with biopsy-proven IgA nephropathy, reduced GFR (or elevated serum creatinine), severe proteinuria (defined in different studies as greater than 1, ≥2, ≥3 g/d, or nephrotic range), and hypertension were found to be independent predictors of progression to end-stage renal disease (ESRD) by multivariate analysis in nearly all studies in which such analysis was performed. In the majority of these studies, the multivariate analysis included histopathologic parameters (which will be discussed later) as well as multiple clinical parameters, some but not all of which are listed in Table 12.6. In a number of studies, including a German study of 239 patients (70) and a study of 148 patients from the Mayo Clinic (50), serum creatinine at the time of the renal biopsy was found to be a strongest independent predictor of renal survival. By contrast, Bartosik et al. (63) found that among 298 patients from Toronto, the mean arterial pressure and severity of proteinuria over time were the most important prognostic indicators of deterioration of renal function. Furthermore, time-averaged proteinuria during follow-up is of greater predictive value than proteinuria at the time of renal biopsy with respect to rates of disease progression (110), perhaps, at least in part, because factors other than active glomerular injury contribute to proteinuria.

As shown in Table 12.6, a number of additional demographic and clinical features have been found to correlate with an increased risk of progression to ESRD in some but not all studies, often by univariate but not multivariate analysis. These include male sex, older age at presentation or diagnosis, and the absence of any history of macroscopic hematuria, although notably in studies from the Mayo Clinic, younger age at diagnosis and female sex were found to be independent risk factors for disease progression (51). It is of interest that the absence of macroscopic hematuria has been found to be correlated with shortened renal survival, at least by univariate analysis, in the majority of studies in which this has been examined. Active crescentic lesions on renal biopsy have been linked to episodes of macroscopic hematuria in IgA nephropathy (111); however, overall the presence of macroscopic hematuria tends to be more frequently associated with mild histologic lesions. In our study of over 200 patients (mostly adults) with IgA nephropathy, 17 of 38 (45%) patients with normal glomerular histology had macroscopic hematuria, as compared with 35 of 104 (34%) patients with moderate histologic lesions and 15 of 68 (22%) patients with the most severe histologic lesions in terms of activity and chronicity (40). We have more recently found similar results in children with IgA nephropathy: 22 of 27 (81%) whose renal biopsy showed normal glomerular histology had at least one episode of macroscopic hematuria prior to biopsy, as compared with 14 of 25 (56%) children with diffuse proliferative glomerulonephritis and 0 of 4 with advanced chronic glomerulonephritis.

One factor that has not been shown to correlate with clinical outcome is race, at least among patients from the same geographic region. Lau et al. (112) recently reported that clinical features at presentation and 5-year renal survival among Caucasian and African American children with IgA nephropathy from Tennessee were not significantly different except for a higher incidence of macroscopic hematuria among Caucasians. In IgA nephropathy patients (mostly adults) from Chicago, race and ethnicity (white, black, Hispanic, Asian) were not significant prognostic indicators of renal survival by univariate analysis, although the numbers of Hispanic and Asian patients were small in this study (40).

TABLE 12.6 **Statistical analysis of the predictive value, as risk factors for ESRF, of some clinical features in 23 studies selected from the literature**

						Hematuria		Severe proteinuria		Arterial hypertension	
Authors	**Country**	**No. of patients**	**Age**	**Sex**	**Reduced GFR**	**Absence of macroscopic hematuria**	**Marked erythrocyturia (cell count)**	**At presentation**	**During follow-up**	**At presentation**	**During follow-up**
Droz et al. (80)	France	244	●■	●■	—	●□	—	●■	—	●■	—
Nicholls et al. (90) and Packham et al. (91)	Australia	845	●	●	●	○	●	●	—	●	—
D'Amico et al. (92,93)	Italy	292	●■	○	●■	●□	—	●■	—	●■	—
Beukhof et al. (94)	The Netherlands	75	○	—	●■	●■	●□	●■	—	●■	—
Rekola et al. (95)	Sweden	155	●□	○■	●□	○	—	●■	—	●■	—
Bogenschutz et al. (70)	Germany	239	●□	○	●■	●□	—	●□	—	●□	—
Alamartine et al. (97)	France	282	○	○	○	○	—	●■	—	●■	—
Ibels and Gyory (50)	Australia	121	●□	—	●■	●□	—	●■	—	●□	—
Johnston et al. (32)	United Kingdom	253	●□	○	●■	○	—	●■	—	●□	—
Katafuchi et al. (98)	Japan	225	●□	○	●■	○	○	●■	—	○	—
Yagame et al. (99)	Japan	206	○ ●	○ ●	●■	○	—	●■	—	●□	—
Radford et al. (51) Donadio et al. (100)	United States	148	○ ■[a]	○ ■[b]	●■	—	—	●□	●■	●□	○□
Haas (40)	United States	109	—	○	●	●	—	●	—	●	—
Kobayashi et al. (101)	Japan	366	○	○	●■	○	—	●□	●■	●■	—
Koyama et al. (102)	Japan	335	—	—	●■	—	—	●■	—	○	—
Frimat et al. (103)	France	210	○	○■	●■	●■	—	●■	—	●■	—
Vleming et al. (104)	The Netherlands	83	○	○	●■	●□	●□	●■	—	●■	—
Rychlik et al. (105)	Germany and Czech Republic	177	—	—	●■	●■	—	●■	—	●■	—
Daniel et al. (106)	France	194	—	—	●□	●■	●■	●■	—	●■	—
Syrjanen et al. (107)	Finland	223	●□	○	○□	○	—	●■	—	●■	—
Li et al. (108)	Hong Kong	168	—	—	●■	—	—	●■	—	●■	—
Rauta et al. (109)[c]	Finland	259	—	●□	●□	●□	—	●□	—	●■	●■
Bartosik et al. (63)[d]	Canada	298	○	○	○	—	—	●■	●■	○	●■

[a]Youngest at higher risk.
[b]Female at higher risk.
[c]Multivariate analysis refers to the subgroup of patients with normal renal function at diagnosis.
[d]Slope of CrCl over time, instead of renal survival, was used as end point for the statistical analysis.
ESRF, end-stage renal failure; GFR, glomerular filtration rate.
At the univariate analysis, ●, significant; ○, not significant.
At the multivariate analysis, ■ significant; □, not significant.
From D'Amico G. Natural history of idiopathic IgA nephropathy and factors predictive of disease outcome. *Semin Nephrol* 2004;24:179.

Pathologic Findings

Gross Pathology

The kidneys of most patients with IgA nephropathy are likely to appear grossly normal in the absence of changes related to chronic glomerulonephritis with associated tubulointerstitial scarring and/or to hypertensive vascular disease. A case of diffuse proliferative and crescentic IgA nephropathy has been reported in a pig-tailed macaque that was euthanized 1 year after experimental coinfection with simian immunodeficiency virus and *Mycobacterium bovis*; both of the animal's kidneys were found to be swollen and enlarged (113), suggesting that similar gross changes in the kidneys may occur in cases of human IgA nephropathy that show similarly severe histologic changes.

Light Microscopy and Histopathologic Classification

In Berger's original series of patients with IgA nephropathy, the majority of renal biopsies showed focal glomerulonephritis, although a significant number showed chronic glomerulonephritis and approximately 10% were histologically normal (2). Subsequent studies have confirmed that while focal or diffuse mesangial proliferative glomerulonephritis are the most common histologic lesions seen on renal biopsies from patients with IgA nephropathy, there is a wide degree of histologic variability in this disease, ranging from no detectable histologic lesion to diffuse proliferative and crescentic glomerulonephritis, much as is the case with lupus nephritis (17,40,50,80,97,114–118).

Because of the highly diverse histologic presentation of IgA nephropathy, a number of histologic classification systems have been devised and tested for their value in predicting clinical outcomes, most often actuarial renal survival. These classification systems are of two basic types: semiquantitative and single grade. Semiquantitative scoring systems, such as those employed by Alamartine et al. (97), Kobayashi et al. (61), and Radford et al. (51), assign a semiquantitative grade (e.g., 0, 1, 2, or 3 corresponding to absent, mild, moderate, or severe) to each of a number of parameters comprising the glomerular, tubular, interstitial, and vascular compartments and generate a sum score for each compartment as well as a total histologic score by adding the sum scores for each compartment. The number of individual scores in such systems generally ranges from 10 to 20. Semiquantitative scoring systems have the clear advantage of identifying specific morphologic changes (or combinations of these) that are best correlated with clinical outcome and/or with each other. However, despite generally good correlations between total histologic scores and renal failure rates (51,61,97), semiquantitative scoring systems are felt by many pathologists to be too time consuming to be used routinely in busy renal biopsy practices. Still, abbreviated versions of these, focusing on histologic changes in a single compartment (e.g., tubulointerstitial changes) or only on chronic changes within each compartment, have been used at some centers and found to show good correlation with clinical outcomes (52,106).

Single-grade systems combine various glomerular and tubulointerstitial features, in most instances with emphasis on the former, into a relatively small number (most often five) of histologic grades (40,114–116,119). Of these, the three most widely used are those of Lee et al. (114), Haas (40), and modifications of different versions of the World Health Organization (WHO) and closely related International Society of Nephrology/Renal Pathology Society (ISN/RPS) classification for lupus nephritis (see Chapter 14). The classification of Lee et al. (114) was based on the previously published classification system of Meadow et al. (120) for HSP IgA vasculitis nephritis (see section on IgA vasculitis later in this chapter), whereas that of Haas (40) borrowed features of the Lee et al. and WHO lupus nephritis classifications, as well as from findings of D'Amico et al. (92) with respect to the influences of multiple individual histologic parameters on renal survival in a large cohort of Italian IgA nephropathy patients. Both of the latter classification systems have been independently verified to be clinically relevant (63,103,106,116,118), although it has not been shown that the system alone is superior either to a semiquantitative tubulointerstitial score (106) or to a model based on the mean arterial pressure and urinary protein excretion averaged over time during 2 to 3 years of observation (63) in predicting clinical progression of IgA nephropathy. Another potential shortcoming of both the Lee et al. (114) and Haas (40) classifications is that both can be vague with respect to terminology, limiting their reproducibility. For example, the Lee et al. (114) schema does not clearly distinguish between mesangial sclerosis and segmental glomerulosclerosis (121), while that of Haas (40) does not distinguish between mesangial and endocapillary hypercellularity. Furthermore, while both of these classifications have five individual histologic subclasses, the majority of cases of IgA nephropathy fall within just one or two of these subclasses (63,121,122), limiting their overall clinical utility.

The Oxford Classification and Its Clinical Applicability

Documentation of the clinical relevance of the histologic classifications of Lee et al. (114) and of Haas (40), as well as of other classifications (52,116–119), has been based on retrospective studies, most often at single centers, using the development of ESRD as their primary end point. However, rates of progression to ESRD from the time of diagnosis (biopsy) are largely related to irreversible damage already present at the time of biopsy, as well as compensatory mechanisms (e.g., glomerular hyperfiltration) that result from this underlying nephron loss. This is borne out by the finding that the strongest and most consistent histologic predictors of the development of ESRD in IgA nephropathy are tubular atrophy/interstitial fibrosis (TA/IF) and, to a somewhat lesser extent, glomerular sclerosis (93,96). By contrast, time-averaged proteinuria, the strongest clinical correlate of the rate of decline of renal function in IgA nephropathy (110,121), reflects in large part active glomerular injury. Time-averaged proteinuria during follow-up is of greater predictive value than proteinuria at a single time point (e.g., the time of biopsy) with respect to rates of disease progression (110), perhaps, at least in part, because factors other than active glomerular injury contribute to proteinuria at any given time point. Still, there are different elements of active glomerular injury (e.g., mesangial proliferation, endocapillary proliferation, glomerular necrosis, and crescent formation) that may have rather different implications with respect to prognosis and/or potential response to immunosuppressive therapy and may affect clinical parameters such as proteinuria very differently. As such, there remains a potentially important role for histologic assessment in guiding the clinician's approach to the patient with IgA nephropathy, provided the right histologic parameters are evaluated.

With this in mind, an international committee comprising of pathologists and nephrologists from four continents first convened in 2004 for the purpose of developing a new, evidenced-based, international consensus histologic classification for IgA nephropathy. A number of features distinguished

the approach of this group from that used in the development of prior histologic classifications of IgA nephropathy (123,124):

1. The pathologists scored different histologic parameters from biopsies of 265 closely monitored patients with active (i.e., with proteinuria, without advanced chronic renal insufficiency) IgA nephropathy. The parameters for this scoring were agreed upon and criteria for different lesions (e.g., mesangial hypercellularity) defined at a meeting of the participating pathologists, and subsequently each biopsy was scored by a minimum of three pathologists and by four or five in 83% of cases.
2. The parameters scored by the pathologists included a comprehensive list of glomerular, tubulointerstitial, and vascular findings with no preconceived determination as to the relative importance of any of these. The inclusion of individual histologic parameters in the final classification was determined by three factors: reproducibility among the pathologists, independence from other parameters, and value as a predictor of clinical outcome.
3. The 265 cases included biopsies from 206 adults and 59 children and were from 17 different centers based in eight countries and four continents. Thus, the aim was to develop a classification that would be applicable worldwide. The participating nephrologists determined a minimum set of clinical data that had to be available for all patients included in the study. This included follow-up for a minimum of 3 years (and/or until an end point of ESRD or ≥50% decline in estimated GFR [eGFR]) with a sufficient number of determinations of eGFR during this interval to allow for determination of the slope of eGFR versus time, as a measure of the rate of renal functional decline.

The scoring of the slides and the analysis of the pathologic and clinical data took approximately 4 years, with consensus working meetings of the full group of participating pathologists and nephrologists held at Oxford University in 2005 and at the conclusion of the study in 2008 (hence the name Oxford Classification). Three noninterdependent histologic parameters were found to be significant predictors of both the rate of renal functional decline and survival from ESRD or ≥50% decline in eGFR by univariate analysis, as well as an independent predictor of one or both of these outcomes in a multivariate analysis including initial eGFR, mean arterial pressure, and proteinuria (123): mesangial hypercellularity in ≤50% versus greater than 50% of glomeruli, presence or absence of segmental sclerosis in one or more glomeruli, and TA/IF in ≤25% versus greater than 25% of the renal cortical tissue present. Furthermore, the presence of TA/IF in greater than 50% of the cortex was associated with significantly worse outcomes (both the rate of eGFR decline and ESRD or ≥50% decline in eGFR) than TA/IF in 26% to 50%. One additional histologic parameter—endocapillary hypercellularity in ≥1 glomerulus—was not significantly correlated with the above outcomes by multivariate analysis but was strongly correlated with response to immunosuppressive therapy. Among patients whose biopsies showed endocapillary hypercellularity, those who were treated with immunosuppressive agent(s) had a significantly lower rate of eGFR decline than those who were not (123). Notably, a number of other morphologic parameters, including crescents and vascular lesions, were not found to be significant predictors of clinical outcomes or response to therapy. However, it should be emphasized that patients who progressed

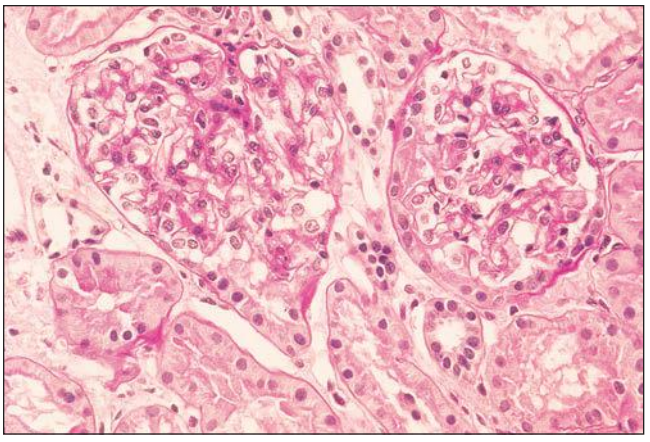

FIGURE 12.3 IgA nephropathy with minimal histologic lesion (Oxford Classification score M0 E0 S0 T0). The glomeruli are normocellular and histologically unremarkable. There is minimal TA, IF, or interstitial inflammation. (Periodic acid-Schiff [PAS] stain, ×400.)

to ESRD within 12 months of biopsy and those with an initial eGFR of less than 30 mL/min/1.73 m^2 were excluded from the Oxford cohort (123); this would have excluded substantial fractions of those patients with very advanced chronic disease and rapidly progressive disease with large numbers of crescents.

Thus, the outcome of this large international study was the recommendation that the primary classification of biopsies with IgA nephropathy include four histologic parameters, M, E, S, and T (illustrated in Figs. 12.3 through 12.16):

- M0 or M1, indicating mesangial hypercellularity (≥4 cells in one or more mesangial areas) in ≤50% versus >50% of glomeruli
- E0 or E1, indicating endocapillary hypercellularity in zero versus one or more glomeruli
- S0 or S1, indicating segmental sclerosis in zero versus one or more glomeruli
- T0, T1, or T2, indicating TA/IF in ≤25%, 26% to 50%, or >50% of renal cortex, respectively

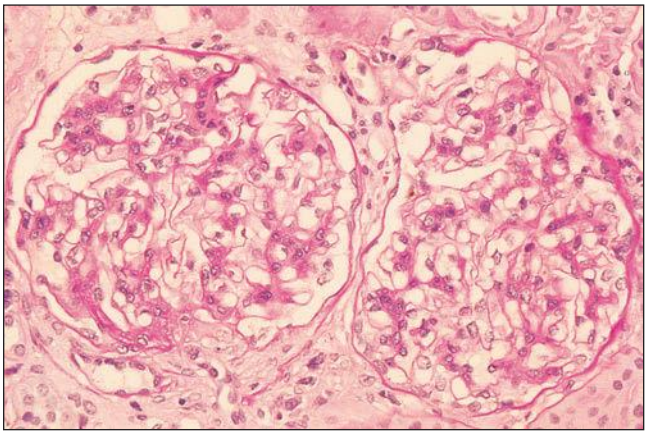

FIGURE 12.4 IgA nephropathy with mesangial proliferation (M1 E0 S0 T0). The glomeruli show a mild increase in mesangial matrix, and the glomerulus at left, which was representative of the majority of the glomeruli on this biopsy, shows a segmental increase in mesangial cellularity. (PAS, ×400.)

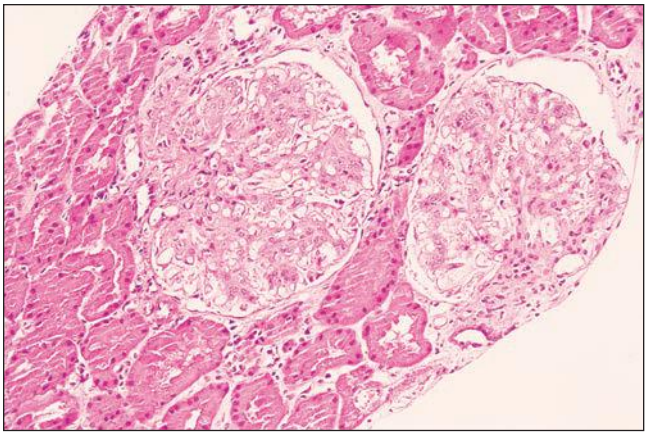

FIGURE 12.5 IgA nephropathy with diffuse mesangial proliferative glomerulonephritis (M1 E0 S0 T0). There is a diffuse increase in mesangial matrix and cellularity, without endocapillary proliferation, segmental glomerulosclerosis, crescent formation, or TA/IF. (PAS, ×200.)

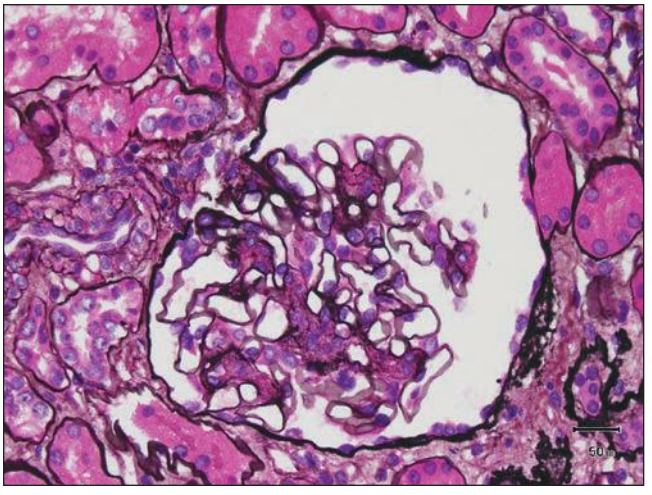

FIGURE 12.7 IgA nephropathy with mesangial proliferation (M1 E0 S0 T0). Note that expanded mesangial areas do not stain black with the methenamine silver stain, this staining is typical of immune complex deposits rather than mesangial matrix. EM (see Fig. 12.22) confirmed the presence of extensive mesangial deposits. (Jones methenamine silver stain, ×400.)

Studies examining clinicopathologic correlations in IgA nephropathy using the Oxford (MEST) Classification as well as other morphologic parameters are reviewed in detail later in this chapter (see Prognosis and Clinicopathologic Correlations).

Immunohistologic Findings

Glomeruli

In the original series of patients with IgA nephropathy described by Berger and Hinglais (1,2), it was noted that the glomeruli showed deposits of IgA by immunofluorescence in the intercapillary (mesangial) areas. Berger (2) noted that in only 5 of 55 cases were the deposits large enough to be clearly evident by light microscopy, although on retrospective analysis of silver-stained sections he was able to find small mesangial deposits in a larger number of cases. The mesangial IgA deposits were accompanied by C3 and in all but 2 of 55 cases by IgG (2).

Following these original reports, the immunohistology of IgA nephropathy has been examined in multiple case series together comprising many hundreds of patients. It is now well accepted that the diagnosis of IgA nephropathy depends on the demonstration, by immunofluorescence or immunohistochemistry, of glomerular staining that is IgA dominant or IgA codominant, involving the mesangium with or without staining of peripheral capillary walls, in a patient without evidence of systemic lupus erythematosus (SLE) or Henoch-Schönlein

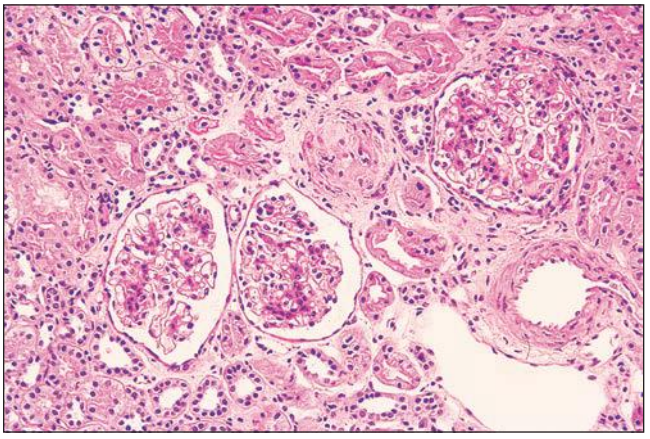

FIGURE 12.6 IgA nephropathy with diffuse mesangial proliferative glomerulonephritis (M1 E0 S0 T0). There is a diffuse increase in mesangial matrix and cellularity, without endocapillary proliferation or segmental glomerulosclerosis. There is mild chronic change, more than in Figure 12.5, but the degree of TA/IF is less than 25%. (PAS, ×200.)

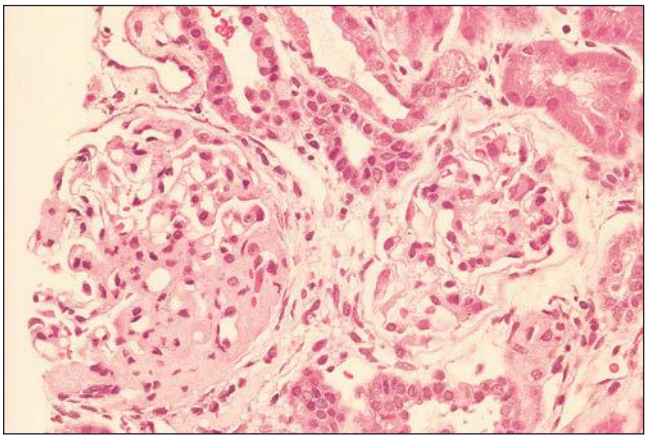

FIGURE 12.8 IgA nephropathy resembling focal segmental glomerulosclerosis (M0 E0 S1 T0). The glomerulus at left shows perihilar segmental sclerosis with associated hyalinosis as well as an increase in mesangial matrix; however, neither glomerulus shows mesangial or endocapillary hypercellularity. A small number of red blood cells are seen within a tubular lumen above the segmentally sclerotic glomerulus. (H&E, ×400.)

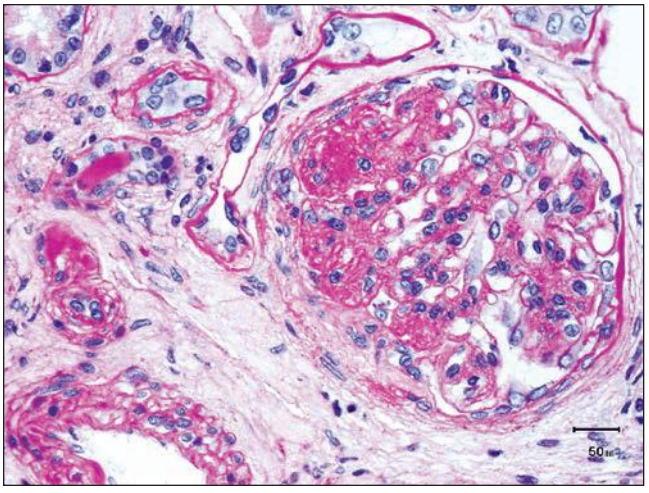

FIGURE 12.9 IgA nephropathy with mesangial hypercellularity and segmental glomerulosclerosis (M1 E0 S1 T0). The glomerulus shows an increase in mesangial cellularity and matrix, as well as segmental sclerosis with capsular adhesion. While a small number of double contours of the glomerular basement membrane are present, there is no definite endocapillary proliferation. (PAS, ×400.)

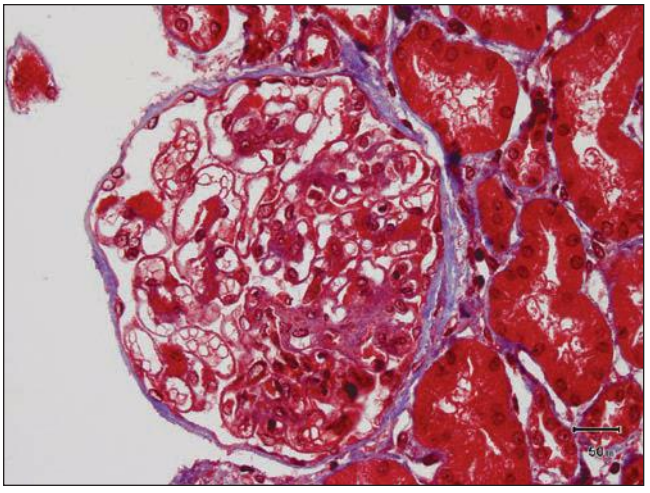

FIGURE 12.11 IgA nephropathy with endocapillary proliferation (M0 E1 S0 T0). There is segmental endocapillary proliferation (4 to 6 o'clock) but no mesangial hypercellularity. There are, however, mesangial immune complex deposits that stain red on this trichrome stain. (Masson trichrome stain, ×400.)

purpura (125,126). As noted in Table 12.7, which summarizes results of 13 studies comprising over 2200 patients, over 40% of cases of IgA nephropathy contain mesangial deposits of IgG and over 50% contain mesangial deposits of IgM, although in each case, the overall intensity of staining for IgA was at least as great as that for either of the other immunoglobulins. IgA deposited in the glomeruli of patients with IgA nephropathy is predominantly of the IgA1 subclass. In different studies, IgA2 has been reported to be present (in lesser amount than IgA1) in between 0% and 53% of biopsies, although in the majority of studies, the presence of glomerular IgA2 is uncommon (128,133–140). Most studies indicate that the IgA present in the glomerular deposits is polymeric, based on the absence of secretory component and the presence of J chain within the deposits (134,135,138,141), as will be discussed in more detail below in the section dealing with the pathogenesis of IgA nephropathy.

With respect to complement components, C3 is detected in glomeruli in greater than 90% of cases of primary IgA nephropathy (see Table 12.7), as are the C3 breakdown products C3c and C3d (125,131,142). Early components

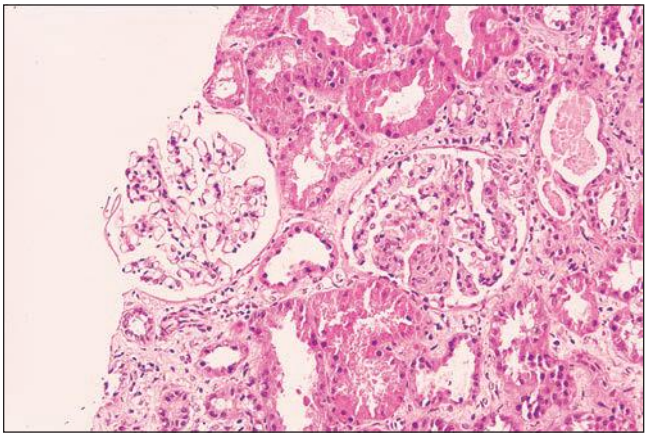

FIGURE 12.10 IgA nephropathy with focal endocapillary proliferation (M0 E1 S0 T0). The glomerulus at left is unremarkable; however, that at right shows segmental endocapillary hypercellularity, as well as a small cellular crescent between 1 and 2 o'clock. TA/IF is present, but overall, this was less than the 25% cutoff for T1 according to the Oxford Classification. (H&E, ×200.)

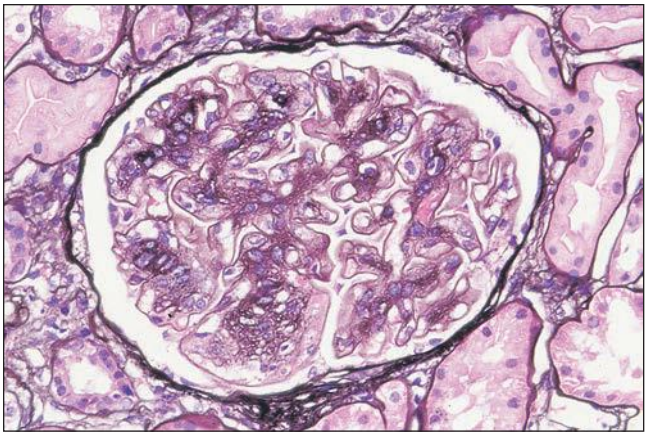

FIGURE 12.12 Mesangial and endocapillary proliferative IgA nephropathy (M1 E1 S0 T0) resembling membranoproliferative glomerulonephritis. There is an increase in silver-positive mesangial matrix, hyperlobulation, and mesangial and endocapillary hypercellularity. Several double contours of the glomerular basement membrane are apparent. (Jones methenamine silver, ×400.)

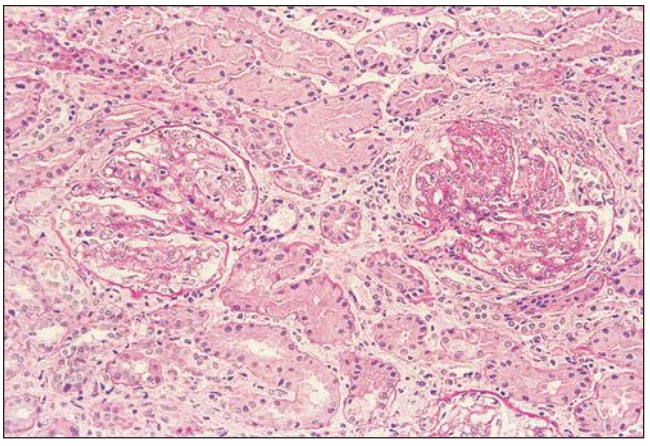

FIGURE 12.13 IgA nephropathy with diffuse mesangial and endocapillary hypercellularity; the glomerulus at right shows a segmental fibrocellular crescent with segmental sclerosis of the tuft adjacent to the crescent (M1 E1 S1 T0). There is less than 25% TA/IF. (PAS, ×200.)

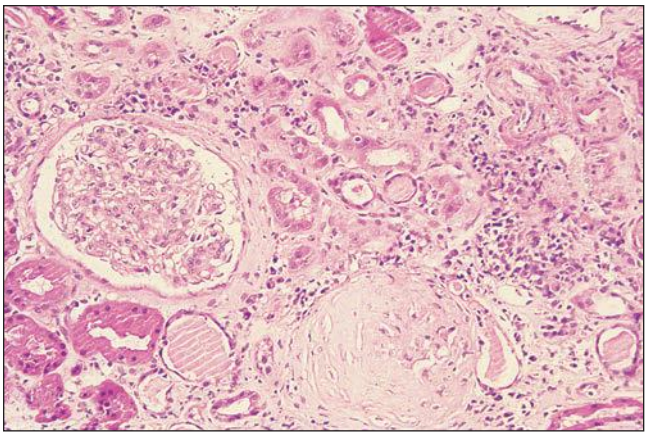

FIGURE 12.15 Advanced chronic IgA nephropathy with residual mesangial hypercellularity (M1 E0 S0 T2). There is TA/IF, with a nonspecific mononuclear cell inflammatory infiltrate in the sclerotic interstitium. Arterioles present (upper right) show hypertensive changes. One of the two glomeruli shown is globally sclerotic, while the other shows mild and segmental mesangial hypercellularity. (H&E, ×200.)

of the classical complement pathway, namely, C1q and C4 (53,129,131,132,142), are absent in most cases of IgA nephropathy, although C4 has been reported in up to 30% of cases, more often those with deposits containing multiple immunoglobulins rather than IgA alone (143). However, in many if not most cases, this C4 deposition probably indicates activity of the lectin pathway of complement activation rather than that of the classical pathway (144). In the lectin pathway, C4 becomes activated independently of C1 following the binding of mannose-binding lectin to carbohydrate ligands (145). Properdin, a component of the alternative pathway, has been reported to be present in nearly all cases in some studies (132,143), although in less than 50% in others (129). Terminal components of complement C5, C6, and C9 as well as neoantigens of the C5b-9 membrane attack complex (MAC) have also been detected by immunofluorescence in glomeruli of patients with IgA nephropathy, and dual immunostaining studies have shown colocalization of MAC neoantigens and IgA (but interestingly not IgG or IgM) at identical sites in the mesangium and peripheral capillary walls (131).

Lai et al. (53,148) have studied in some detail the light chain composition of glomerular IgA deposits in patients with IgA nephropathy from Hong Kong. They found that 29 of 45 (64%) biopsies showed predominant staining for lambda light chains by immunofluorescence, while only 1 of

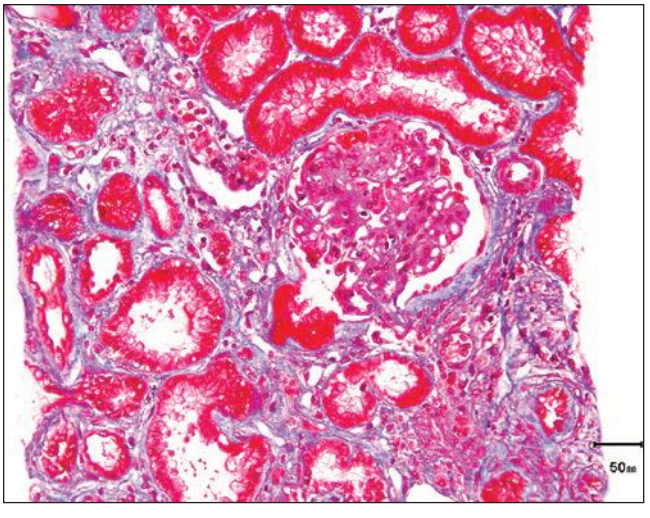

FIGURE 12.14 IgA nephropathy with mesangial hypercellularity, segmental glomerulosclerosis, and TA/IF (M1 E0 S1 T1). The glomerulus present shows segmental mesangial hypercellularity and segmental sclerosis. There is moderate TA/IF, overall estimated to involve greater than 25% of the renal cortical tissue present. (Masson trichrome stain, ×400.)

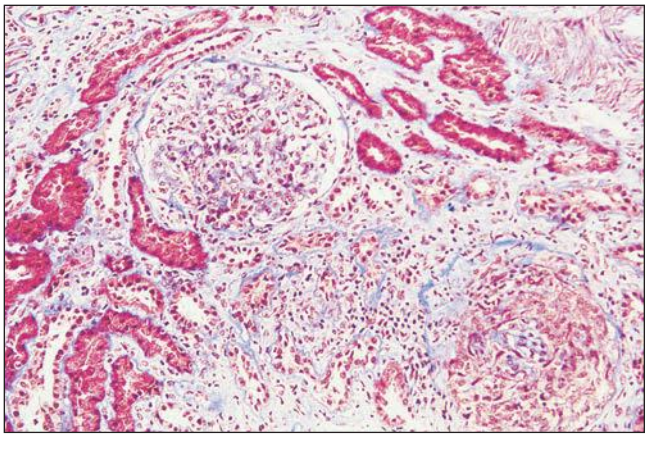

FIGURE 12.16 Severe chronic and active IgA nephropathy (M1 E1 S0 T2). As shown by the Masson trichrome stain, there are severe TA and IF, overall involving more than 50% of the cortical tissue present. There is also a persistent active glomerulonephritis with mesangial and endocapillary hypercellularity, and one glomerulus with a circumferential, largely cellular crescent (lower right). (Masson trichrome stain, ×200.)

TABLE 12.7 Glomerular immunofluorescence/immunohistochemical findings in primary IgA nephropathy

Reference	No. of biopsies	Percent of biopsies positive for: IgA	IgG	IgM	C3	C1q	Kappa	Lambda
Haas (40)[a]	813	100	26	54	95	6	87	97
Sinniah et al. (19)	239	100	50	21	83	2		
Lai et al. (53)	237	100	63	38		3		
Yoshimura et al. (127)	232	100	85	87	98	45		
Jennette (125)	180	100	62	84	98	10	97	100
Vangelista et al. (128)	142	100	15	51	100	8		
Ibels and Gyory (50)	121	100	25	47	90			
Okada et al. (129)	111	100	50	52	92	12		
Woodroffe et al. (126)	78	100	22	43	82	14		
Smith (130)	28	100	18	89			68	100
Sissons et al. (33)	25	100	74	42	100	0		
Rauterberg et al. (131)	23	100	86	61	100	9		
McCoy et al. (132)	20	100	70	65	85	0		
Average (weighted)	**2249**	**100**	**43.0**	**54.0**	**93.3**	**10.4**	**88.2**	**97.6**

[a]Includes 279 cases from The University of Chicago Hospitals, 274 cases from Johns Hopkins Hospital, and 260 cases from the Cedars-Sinai Medical Center.

45 biopsies (2%) showed kappa predominance; the remaining 15 (33%) cases showed equivalent staining for kappa and lambda. Seventeen (38%) of the biopsies showed staining for lambda in the absence of kappa (148). Smith (130) has noted similar findings in Native Americans and, to a lesser degree, Caucasians, from the Southwestern United States. Others, however, have found exclusively lambda staining less frequently, if at all. In 813 cases of primary IgA nephropathy, we have examined at three separate institutions, 11% showed glomerular staining for lambda alone, 1% for kappa alone, 86% for both kappa and lambda, and 2% for neither kappa nor lambda. Jennette (125) found glomerular staining for lambda alone in only 3% of cases, although the intensity of lambda staining exceeded that for kappa in an additional 64%. Suzuki et al. (139) found staining for both kappa and lambda in each of 191 cases examined, although they too commented that the intensity of staining for lambda was usually equal to or stronger than that for kappa.

Mesangial deposits of fibrinogen are also seen in the majority of cases of IgA nephropathy (129,131,132). By immunofluorescence, this mesangial fibrinogen staining has a granular appearance, in contrast to the nonspecific pseudolinear staining that is often observed with direct immunofluorescence staining for fibrinogen, the latter mainly in glomerular capillary loops (Fig. 12.17). Fibrinogen staining is also encountered in active crescentic and necrotizing lesions; in these instances, the distribution of the staining corresponds to that of the crescent or area of necrosis, and the staining has a blotchy or globular rather than a granular pattern.

The prototypical pattern of glomerular IgA deposits in IgA nephropathy, as originally described by Berger (2), is that of global and diffuse staining limited to mesangial areas (Fig. 12.18). The intensity of IgA staining is quite variable but is always at least equal to, and in the great majority of cases is greater than, that for any other immunoglobulin (i.e., IgG, IgM) present. In occasional cases, most often with relatively low-intensity IgA staining, this mesangial staining may be more segmental (Fig. 12.19). In a significant subset of cases, no more than 40% in most studies (127,128,131,132,150) but as high as 70% in one (149), deposits of IgA are seen segmentally in peripheral glomerular capillary walls in addition to globally in the mesangium (Fig. 12.20). In most biopsies showing peripheral capillary IgA staining (not including nonspecific pseudolinear staining that may be seen in some cases), EM confirms the presence of subendothelial, subepithelial, and/or intramembranous deposits (127). The potential prognostic implications of such peripheral capillary deposits are discussed below (see Prognosis and Clinicopathologic Correlations).

Extraglomerular Deposits

Specific staining of extraglomerular structures within the kidney is uncommon in IgA nephropathy, although tubular casts and, in cases where there is moderate to heavy proteinuria, protein

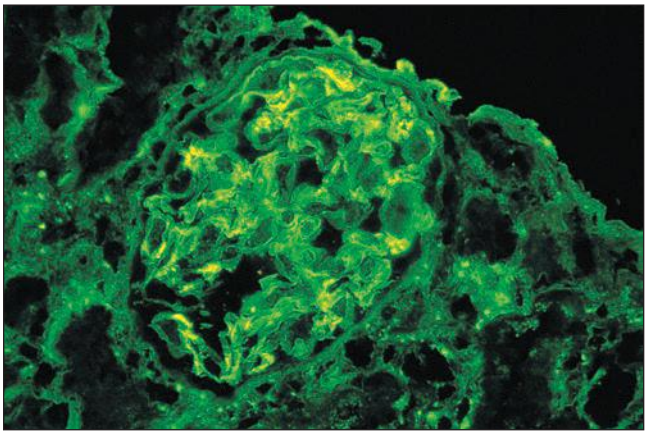

FIGURE 12.17 Glomerular fibrinogen deposition in IgA nephropathy. Immunofluorescence shows fairly global, predominantly granular mesangial staining for fibrinogen, with weaker pseudolinear staining in glomerular capillary walls. (Fluorescein isothiocyanate–conjugated [FITC] anti-human fibrinogen, ×400.)

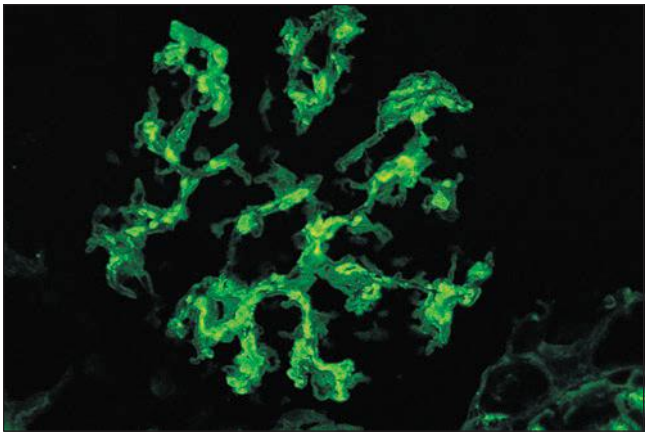

FIGURE 12.18 IgA nephropathy. Immunofluorescence shows global, granular to globular staining for IgA limited to the mesangium. (FITC anti-human IgA, ×400.)

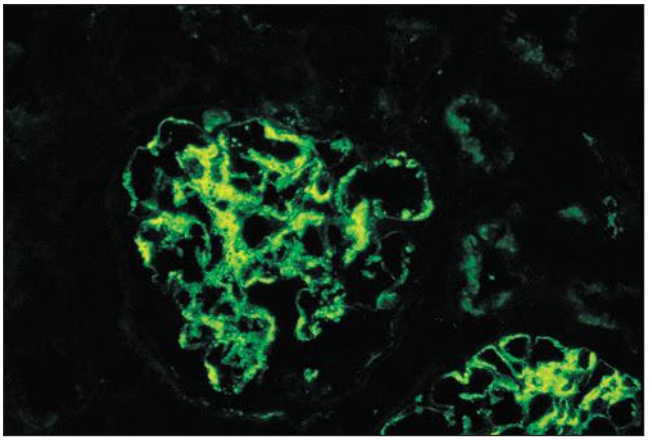

FIGURE 12.20 IgA nephropathy. There is granular staining for IgA in the mesangium and in some peripheral glomerular capillary walls. (FITC anti-human IgA, ×400.)

resorption droplets within tubular epithelial cells typically stain for IgA and serve as convenient internal controls for IgA immunofluorescence. IgA staining within arterioles and/or small interlobular arteries has been reported in approximately 5% of renal biopsies showing IgA nephropathy (128,151); however, the deposits typically stop abruptly at the glomerular hilum. Although the vascular deposits of IgA are granular and usually accompanied by deposits of C3, their presence does not correlate with specific histopathologic changes in the vessels or with a greater incidence of hypertension or renal insufficiency (151).

Granular deposits of IgA in blood vessels of the superficial dermis of normal-appearing skin have been reported in a high fraction (up to 89% in one study (152)) of patients with IgA nephropathy, without systemic manifestations of HSP (152–155). These vascular IgA deposits are accompanied by C3 and fibrin in most cases, by IgM in the majority, and less often by IgG and C1q (151,152). C1q was seen, albeit most often weakly, in approximately 50% of IgA-positive skin biopsies examined by Thompson et al. (152) but in none of 45 skin biopsies reported by Baart de la Faille-Kuyper et al. (153). The latter group also found that among 262 patients with various nephropathies undergoing a biopsy of normal-appearing skin, 35 of 45 patients with vascular IgA deposits on the skin biopsy also had renal biopsy findings (including mesangial IgA deposits) indicative of IgA nephropathy (24 cases) or Henoch-Schönlein nephritis (11 cases), a level of specificity suggesting a potential diagnostic utility for skin biopsy in cases of suspected IgA nephropathy where a renal biopsy could not be safely performed. A similar conclusion was reached by Lee et al. (154), who found IgA in dermal vessels in 7 of 11 (64%) patients with IgA nephropathy as compared with 19 of 161 (12%) patients with SLE and other immune-mediated disorders. However, this level of specificity was not found by Hirbec et al. (155), who reported dermal IgA staining in 50% of patients with IgA nephropathy and 30% of patients with other immune complex–mediated glomerular diseases, or by Thompson et al. (152), who found cutaneous vascular deposits of IgA in 4 of 5 patients with immune complex–mediated glomerular diseases, 6 of 15 patients with non–immune-mediated renal diseases, and 5 of 7 healthy individuals.

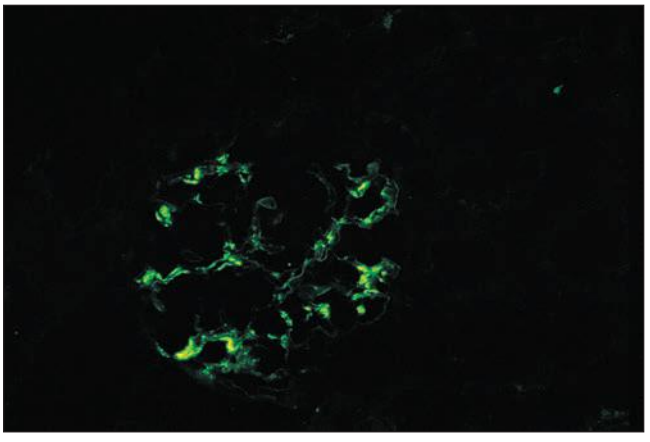

FIGURE 12.19 IgA nephropathy. Mesangial staining for IgA is much less intense than that in Figure 12.18 and not completely global. This biopsy was from a young adult male with a history of gross hematuria during an upper respiratory infection, persistent microscopic hematuria, very mild proteinuria, and normal renal function. Glomeruli were histologically unremarkable. Immunofluorescence showed only the modest mesangial staining for IgA and C3. Small mesangial electron-dense deposits were seen by EM, with no other deposits and no abnormalities of the glomerular basement membranes. He was diagnosed with mild IgA nephropathy (Oxford Classification M0 E0 S0 T0). (FITC anti-human IgA, ×400.)

Electron Microscopic Findings

The diagnosis of IgA nephropathy is typically made on the basis of the immunofluorescence and light microscopic findings, together with the clinical data, and it is only in rare cases that EM is needed for an actual diagnosis of IgA nephropathy (156). An example of the latter might involve a patient with a positive antinuclear antibody (ANA), a mesangial proliferative glomerulonephritis, and immunofluorescence showing moderate to strong mesangial staining for IgA, IgG, IgM, and C3, with weak staining for C1q. In this case, EM may be helpful in distinguishing between IgA nephropathy and mesangial (class II)

TABLE 12.8 Ultrastructural location of glomerular immune complex deposits in primary IgA nephropathy and IgA vasculitis (Henoch-Schönlein purpura) nephritis

	Percentage of cases	
Location of deposits	IgA nephropathy (*n* = 756)	IgAV nephritis (*n* = 68)
None	0.5	0
Mesangial only	68.8	39.7
Mesangial + subendothelial (SEn)	14.0	26.5
Mesangial + subepithelial (SEp)	5.7	7.4
Mesangial + intramembranous (IM)	2.1	1.5
Mesangial + SEn + SEp	4.4	17.6
Mesangial + SEn + SEp + IM	2.4	2.9
Mesangial + SEn + IM	1.3	2.9
Mesangial + SEp + IM	0.7	1.5

lupus nephritis (see Differential Diagnosis, below). Still, there are a number of fairly characteristic ultrastructural features of IgA nephropathy, and some studies suggest that certain EM features may have prognostic significance.

Table 12.8 shows the locations of electron-dense, immune complex deposits within glomeruli in 756 cases of IgA nephropathy examined by EM. In our experience, failure to detect deposits by EM is very rare in IgA nephropathy (0.5% of cases). This has also been the case in most other studies (58,115,119,127,146,157), although in some studies, the absence of deposits by EM has been reported in up to 25% of cases (50,114,147). Virtually all cases of IgA nephropathy show mesangial deposits within expanded mesangial regions. The most typical location of mesangial deposits is in the paramesangium (i.e., the interface of the glomerular basement membrane with the mesangial matrix), such as shown in Figure 12.21. Deposits located deeper in the mesangial matrix, such as are seen in Figure 12.22, have been postulated by some investigators to indicate more chronic lesions (158). Very large mesangial deposits, described as hemispherical (159), may be present and cause prominent bulging of the mesangium, resembling a capillary with a large subendothelial deposit (Fig. 12.23). Mesangial deposits in IgA nephropathy typically show uniform electron density without specific substructure, although occasionally deposits may show areas of electron lucency, microvesicular change, or even membrane-like structures indicative of partial resorption (Fig. 12.24) (160). Collagen fibrils have been noted within the expanded mesangial matrix in some relatively advanced cases (158).

In our experience, deposits involving the glomerular capillary wall (i.e., subendothelial, subepithelial, and/or intramembranous) in addition to the mesangium are seen in approximately 30% of cases of IgA nephropathy. These findings are similar to those reported in most other series, which found peripheral capillary wall deposits in between 20% and 40% of cases (127,146,161), although the frequency of such deposits in some series is only 10% to 20% (50,162). Subendothelial deposits are seen more commonly than subepithelial deposits in our series and that of Lee et al. (146), although the opposite was observed by Yoshimura et al. (127). When subendothelial deposits are present in IgA nephropathy, they are often quite segmental and appear to extend from paramesangial deposits (Fig. 12.25). Occasionally, there are subendothelial deposits associated with duplication of the glomerular basement membrane (Fig. 12.26), although when present, this tends to be

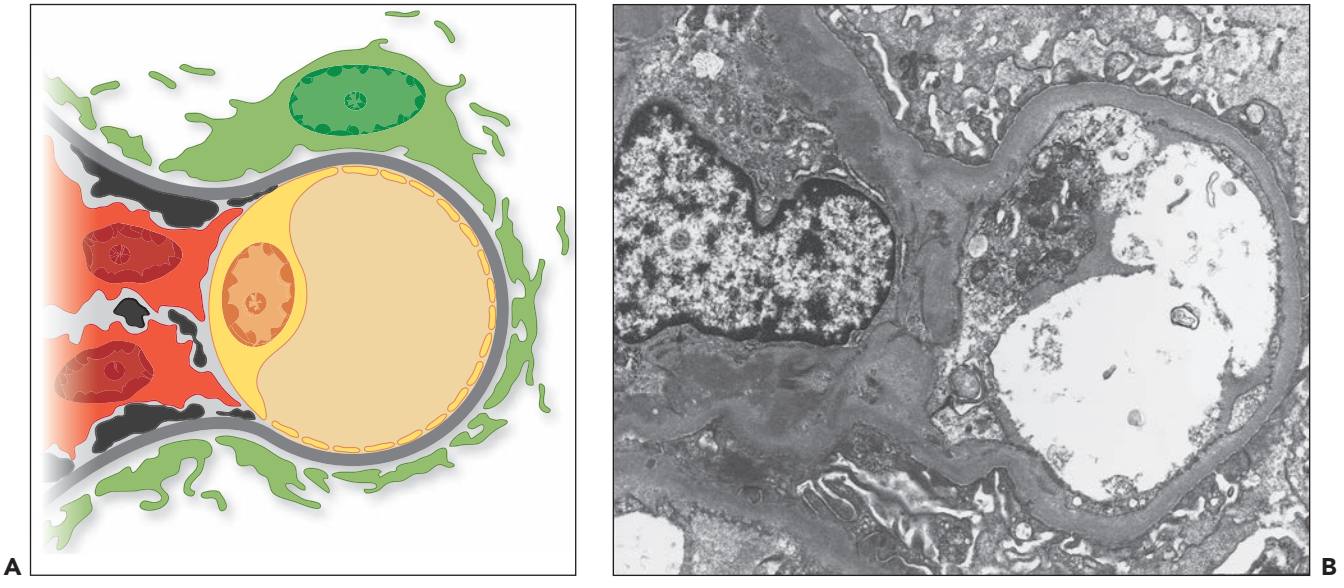

FIGURE 12.21 IgA nephropathy. A: Drawing of a glomerular capillary and adjacent mesangium showing mesangial immune deposits (*black*), especially immediately beneath the paramesangial basement membrane. **B:** Electron micrograph showing paramesangial electron-dense deposits within a mildly expanded mesangium. A small subendothelial deposit is also present (lower right portion of the capillary loop). Glomerular basement membranes are unremarkable, and the majority of podocyte foot processes appear intact. (Uranyl acetate and lead citrate stain, original magnification ×6300.)

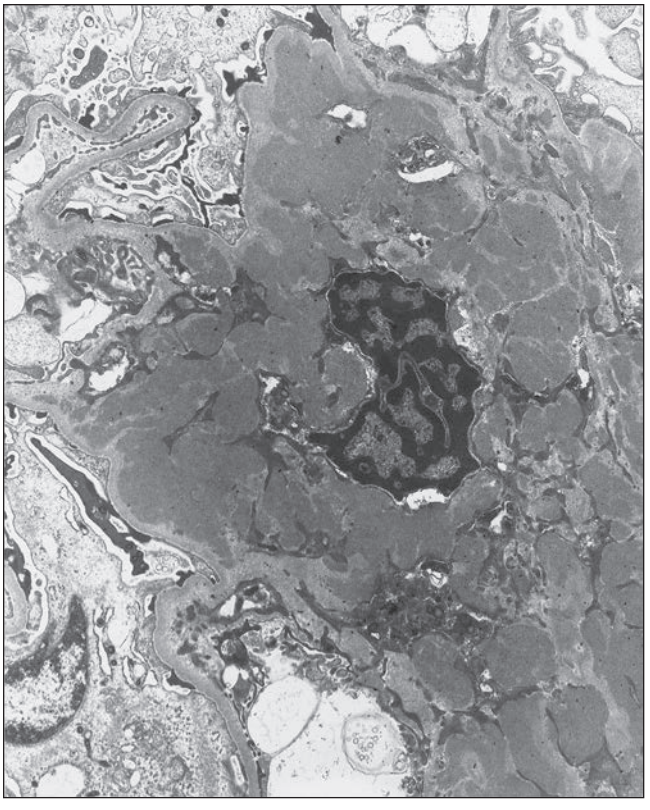

FIGURE 12.22 IgA nephropathy. A large amount of mesangial electron-dense deposit is present within the expanded mesangium. No subendothelial or subepithelial deposits are present, however. Light microscopy of this biopsy is shown in Figure 12.7. (Uranyl acetate and lead citrate, original magnification ×3800.)

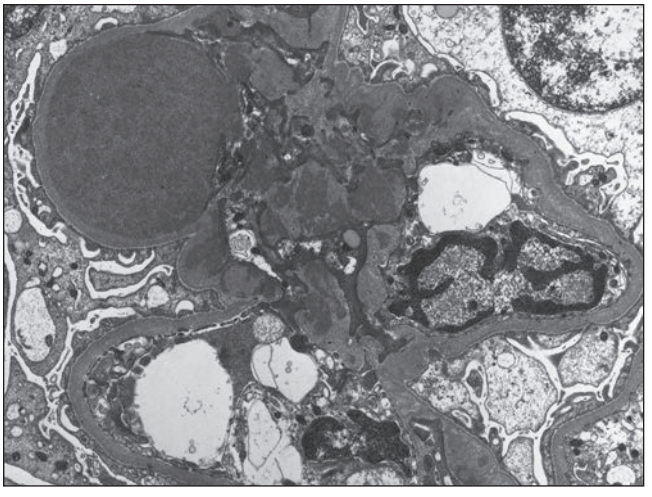

FIGURE 12.23 IgA nephropathy. There are prominent mesangial electron-dense deposits, including a large deposit (upper left) with associated bulging of the mesangium into the urinary space. Podocyte foot processes show a significant degree of effacement. (Uranyl acetate and lead citrate, original magnification ×5000.)

more segmental than in type I membranoproliferative glomerulonephritis (MPGN). Infrequently, there are large subendothelial deposits resembling those seen in lupus nephritis (Fig. 12.27). The presence of large, hump-like subepithelial deposits suggests the possibility of an IgA-dominant postinfectious glomerulonephritis rather than IgA nephropathy, as discussed below (see Differential Diagnosis).

Electron-dense deposits have been noted in preglomerular arterioles in some cases of IgA nephropathy and rarely in the basement membrane of the Bowman capsule (163,164). However, deposits in peritubular capillaries, small arteries, or tubular basement membranes are not seen.

Structural abnormalities of the glomerular basement membranes are relatively common in IgA nephropathy and may be so pronounced that they suggest the possibility of Alport syndrome. The most common abnormality is thinning of the peripheral capillary basement membranes and in particular the lamina densa, which may be widespread or localized (159,165–167). Berthoux et al. (165) found glomerular basement membrane thinning (mean thickness 208 vs. 365 nm in normal controls and 344 nm in cases of IgA nephropathy without thinning) in 23 (39%) of 59 biopsies examined from patients with IgA nephropathy and notably in 14 (67%) of 21 biopsies from females with IgA nephropathy. Others have noted a significantly lower mean glomerular basement membrane thickness in patients with IgA nephropathy than in normal controls (269 vs. 339 nm; Ref. (168)). A significant association between glomerular basement membrane thinning and hematuria was noted by some investigators (159,165) but not by others (166,168). Segmental splitting of the glomerular basement membrane, resembling that seen in Alport syndrome or in cases of severe glomerular hyperfiltration (169), is also not an uncommon finding in IgA nephropathy (159,164,166,167,170). This change may be associated with the presence of subendothelial or intramembranous immune complex deposits but may also be seen in cases in which deposits are limited to the mesangium, as in Figure 12.28, which also shows thinning of the glomerular basement membrane. Other less common alterations of the glomerular basement membranes that may be seen segmentally in IgA nephropathy include widening, lysis of the lamina densa, and rarely frank disruption (159,166,167).

Differential Diagnosis

The diagnosis of IgA nephropathy is usually straightforward, as there are relatively few glomerular diseases in which dominant or codominant IgA deposits occur (Table 12.9). HSP nephritis, which will be reviewed in detail later in this chapter, cannot be distinguished from IgA nephropathy on a renal biopsy, and this distinction must be made on clinical grounds. Lupus nephritis may in some cases show glomerular IgA staining by immunofluorescence that is as or more intense than staining for IgG and IgM. In most instances, however, these cases can be readily distinguished from IgA nephropathy clinically and serologically. Rare cases have been reported in which a patient who developed SLE had a renal biopsy showing a mesangial proliferative or membranous lesion with predominant IgA deposits months to several years prior to developing clinical and serologic manifestations of SLE (171). However, such cases of latent lupus nephritis typically show C1q deposits by immunofluorescence and tubuloreticular inclusions by EM (172), whereas these findings are quite uncommon in IgA nephropathy. Cases of C1q nephropathy (173,174) and

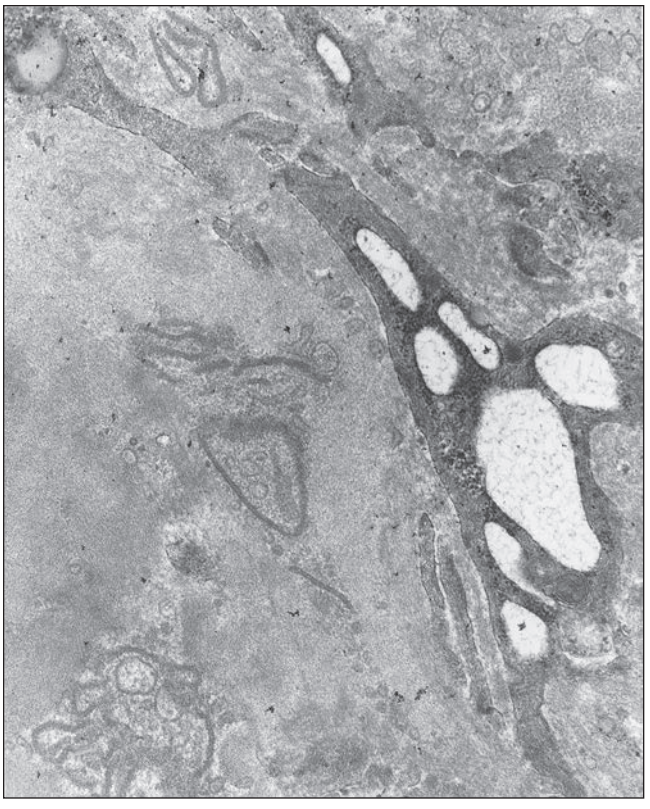

FIGURE 12.24 Chronic IgA nephropathy. This electron micrograph shows several largely resorbed mesangial deposits. The deposits contain electron-lucent areas, as well as microvesicular and membrane-like structures. (Uranyl acetate and lead citrate, original magnification ×17,000.)

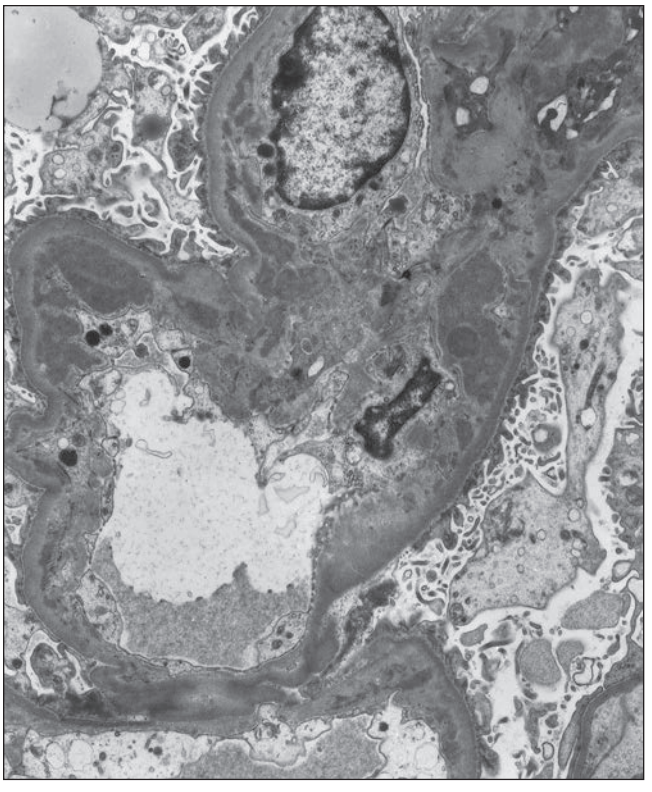

FIGURE 12.25 IgA nephropathy. There are mesangial electron-dense deposits that extend into the adjacent glomerular capillary as subendothelial deposits. (Uranyl acetate and lead citrate, original magnification ×3800.)

human immunodeficiency virus (HIV)-associated lupus-like glomerulonephritis (175,176) may also exhibit strong glomerular IgA staining, but like lupus nephritis also show prominent C1q staining.

IgA-dominant postinfectious glomerulonephritis has been reported to occur following infections with staphylococci, including *Staphylococcus aureus*, methicillin-resistant *S. aureus* (MRSA), and *S. epidermidis* (177–181), and less commonly after nonstaphylococcal infections (182). A number of these lesions have been reported in patients with underlying diabetic nephropathy (178,180,182). The light microscopic appearance of these cases ranges from diffuse proliferative and exudative glomerulonephritis typical of acute postinfectious glomerulonephritis to mild mesangial proliferative glomerulonephritis, the latter possibly representing a resolving lesion. In the acute phase, these lesions are clearly identifiable as postinfectious not only histologically but also by the presence of coarse granular IgA deposits by immunofluorescence (Fig. 12.29) and large, hump-shaped subepithelial deposits by EM (178,180). Patients with acute poststaphylococcal glomerulonephritis, like those acute poststreptococcal lesions but unlike most patients with IgA nephropathy, are also frequently hypocomplementemic (178). In the resolving phase, the differentiation of these lesions from IgA nephropathy may be very difficult if not impossible, especially as unlike the IgG deposits in poststreptococcal glomerulonephritis, the IgA deposits in the poststaphylococcal lesions appear to persist beyond the acute phase of the disease. While not a definitive finding, the presence on EM of multiple partially or largely resorbed subepithelial deposits, particularly in the mesangial "notch" or "waist" region (Fig. 12.30), suggests a resolving postinfectious lesion (180,183,184).

Autopsy studies as well as studies of donor kidney biopsies have demonstrated incidental mesangial IgA deposits in a significant fraction of cases, ranging from 4% in an autopsy study from Singapore (185) to 16% in a recent Japanese study of perioperative renal transplant biopsies involving mainly living donors with no overt signs or symptoms of renal disease (186). While a retrospective analysis of these latter cases showed mild microscopic hematuria as well as mild mesangial hypercellularity and glomerular macrophage infiltration in a subset of kidneys with mesangial IgA (and more often those with both IgA and C3) (186), it remains questionable as to whether even the latter cases truly represent an extremely mild form of IgA nephropathy. Regardless, perhaps the greatest consequence of incidental mesangial IgA deposits from the standpoint of the renal pathologist involves interpretation of renal biopsies with such deposits and a superimposed glomerular disease. Minimal change disease with mesangial IgA deposits, presenting as steroid-responsive nephrotic syndrome, has already been noted (65–68), and likewise, cases of idiopathic membranous nephropathy with mesangial IgA deposits have been reported (187–189). These latter biopsies, of which an example is shown in Figure 12.31, show changes of membranous nephropathy

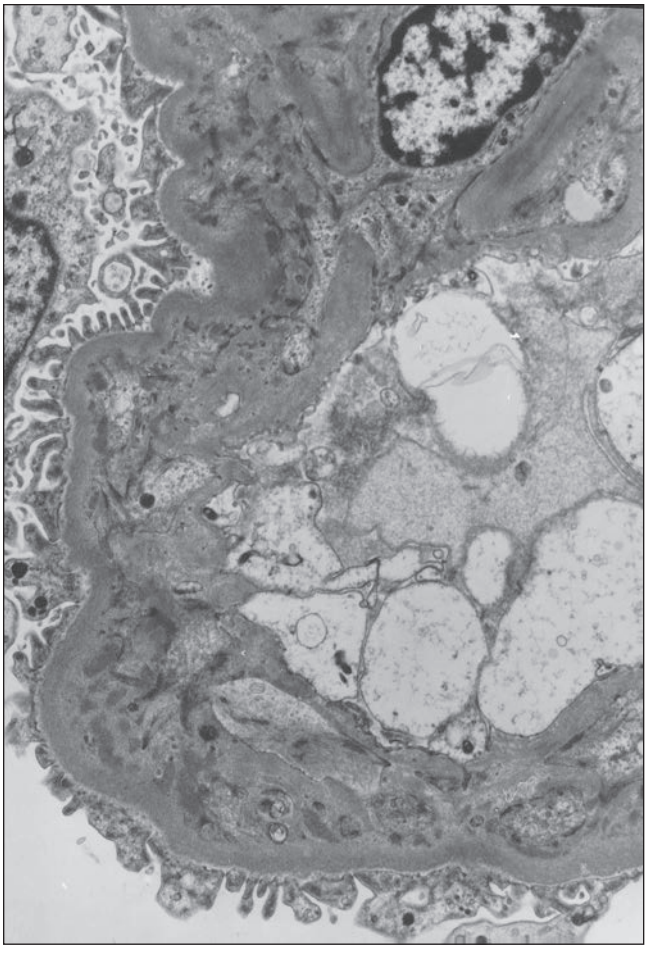

FIGURE 12.26 IgA nephropathy. Subendothelial electron-dense deposits associated with duplication of the glomerular basement membrane. (Uranyl acetate and lead citrate, original magnification ×5000.)

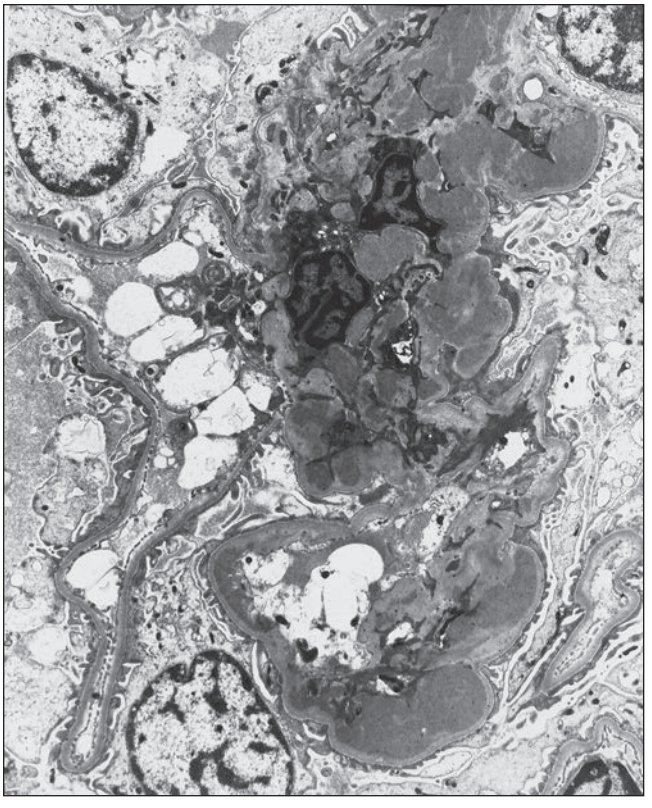

FIGURE 12.27 IgA nephropathy. There is a large amount of mesangial electron-dense deposit and a segmental, large subendothelial deposit resembling a "wire loop" of lupus nephritis. (Uranyl acetate and lead citrate, original magnification ×3000.)

with variable thickening of glomerular capillary loops histologically, often with basement membrane "spikes" evident on silver stains, granular immunostaining for IgG along glomerular capillary loops, and numerous subepithelial deposits by EM. In addition, there is an increase in mesangial matrix and an increase in mesangial cellularity, often mild and segmental, as well as mesangial deposits by EM corresponding to the mesangial immunostaining for IgA (187–189).

More important from a clinical management standpoint are cases of ANCA-associated necrotizing and crescentic glomerulonephritis (ANCA-GN) with mesangial IgA (190–194). The high rate of responsiveness of such lesions to immunosuppressive therapy (e.g., corticosteroids plus cyclophosphamide) render it important that they be recognized and distinguished from necrotizing and crescentic forms of IgA nephropathy that generally have a poorer response to therapy (19,195,196). Serologically, indirect immunofluorescence assays for ANCA are positive in approximately 15% of cases of IgA nephropathy and a higher fraction of cases of IgA nephropathy with crescents; nearly all of these positives are P-ANCA without associated seropositivity for antimyeloperoxidase or anti–proteinase 3 (197). Histologically, cases of ANCA-GN with mesangial IgA show mild or absent mesangial or endocapillary hypercellularity, both in glomeruli with crescents (Fig. 12.32) and in those without, although this is often most evident in the latter glomeruli. By contrast, mesangial and/or mesangial plus endocapillary hypercellularity is prominent in cases of IgA nephropathy with crescents and/or necrotizing glomerular lesions (Figs. 12.13, 12.33, and 12.34) (190).

Pathogenesis of Primary IgA Nephropathy

In considering the pathogenesis of primary IgA nephropathy, four sets of questions need to be addressed:

1. What are the properties of the IgA that is deposited in the glomeruli (and more specifically, the mesangium), and are there properties of this IgA that are unique to patients with IgA nephropathy?
2. What is/are the source(s) of the mesangial IgA?
3. What are the mechanisms involved in mesangial IgA deposition, and do specific properties of the IgA and/or the mesangium in patients with IgA nephropathy promote this deposition?
4. What are the events involved in the glomerular response to IgA deposition that lead to glomerulonephritis, and what role(s) do specific properties of the IgA and/or mesangium in patients with IgA nephropathy play in promoting these events?

Consideration of these issues best begins with a brief review of the structure, subclasses, and synthesis of IgA in humans.

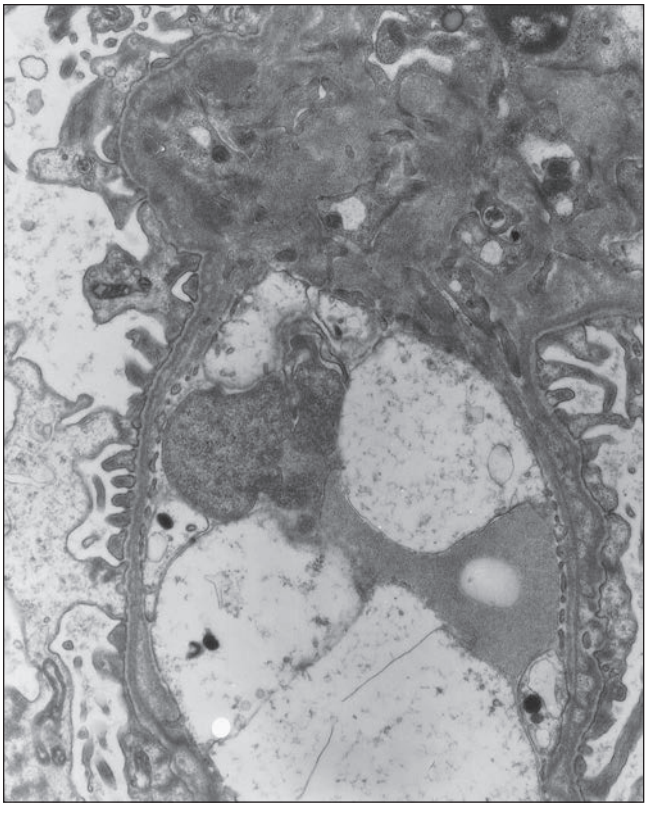

FIGURE 12.28 Glomerular basement membrane structural abnormalities in IgA nephropathy. This glomerular capillary shows both thinning (left) and splitting (right) of the GBM. Foot processes are effaced overlying the area of GBM splitting. Paramesangial electron-dense deposits are present. (Uranyl acetate and lead citrate, original magnification ×8000.)

TABLE 12.9 Major differential diagnosis of dominant/codominant mesangial IgA deposits

IgA nephropathy
Primary
Secondary (e.g., liver disease)
Familial
IgA vasculitis (Henoch-Schönlein purpura) nephritis
Lupus nephritis
C1q nephropathy
HIV-associated lupus-like GN
IgA-dominant postinfectious (poststaphylococcal) GN
Mixed lesions
ANCA-associated GN + mesangial IgA
Minimal change disease + mesangial IgA
Membranous nephropathy + mesangial IgA
Incidental (latent) mesangial IgA deposits

Structure and Production of Human IgA

There are two subclasses of human IgA, IgA1 and IgA2, and both can exist as monomers (mIgA) or polymers (pIgA), the latter mainly dimers. IgA dimers contain the 21 kDa linking protein known as the J chain (198). The main structural difference between these subclasses is the presence in IgA1 of an 18-amino-acid hinge region located between the CH1 and CH2 portions of the molecule (199,200). This hinge region is composed of proline, serine, and threonine residues and carries *O*-linked carbohydrate side chains that have been documented to be present on two of the serine and three of the threonine residues (201) (Fig. 12.35). These *O*-glycans consist of a core *N*-acetylgalactosamine (GalNAc) that in most instances is linked to galactose and/or sialic acid (198,200). It is worth noting here that unlike humans, nonprimate mammals including rodents have only a single type of IgA that lacks a hinge region and is therefore structurally closer to human IgA2 than IgA1. As will become evident below, this limits the usefulness of rodent models in our understanding of the pathogenesis of IgA nephropathy and, in particular, the glomerular deposition of IgA.

There are two main sites of IgA production. Most IgA is produced at mucosal sites; the great majority of this becomes contained within mucosal secretions and very little enters the systemic circulation. The transepithelial transport of IgA from submucosal plasma cells into the lumen is accomplished via the polymeric immunoglobulin receptor (pIgR), which is expressed on the basolateral membrane and binds J chain–containing immunoglobulins (IgA and IgM). After binding, the receptor-immunoglobulin complex is internalized and the immunoglobulin is ultimately secreted into the lumen, still retaining a portion of the pIgR known as the secretory component. As the J chain is essential for this transepithelial transport of IgA, essentially all mucosally derived IgA, including both IgA1 and IgA2, is pIgA (200,202). The remainder of human IgA is produced mainly in the bone marrow and secreted into the blood. The great majority of this marrow-derived IgA is monomeric IgA1 (mIgA1) (198).

Properties of Circulating and Mesangial IgA in Patients With IgA Nephropathy

Total serum IgA concentration is elevated in one third to one half of the adults with IgA nephropathy and a somewhat higher percentage of children (54,203). However, high

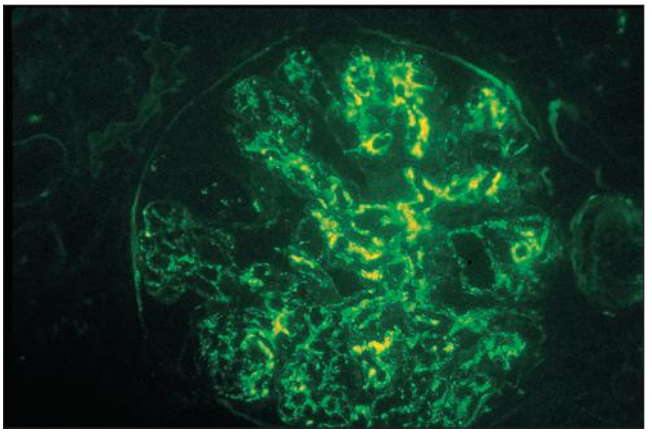

FIGURE 12.29 IgA-dominant postinfectious glomerulonephritis. Immunofluorescence for IgA shows staining in the mesangium and peripheral glomerular capillary walls, with a "starry sky" pattern and segmental distinct deposits corresponding to subepithelial "humps." (FITC anti-human IgA, ×400.)

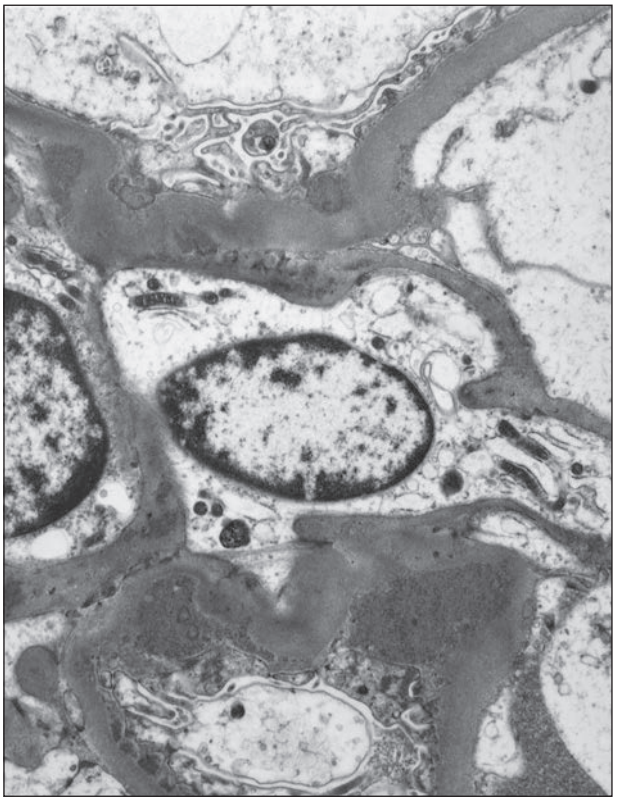

FIGURE 12.30 IgA-dominant postinfectious glomerulonephritis (resolving phase). Electron micrograph shows subepithelial deposits in the "notch" region underlying the mesangium (lower portion of figure) and occasional mesangial deposits. (Uranyl acetate and lead citrate, original magnification ×5000.)

concentrations of serum IgA do not necessarily lead to mesangial IgA deposition, as evidenced by the lack of such deposits in most patients with IgA multiple myeloma (204,205). Indeed, the IgA in the serum of patients with IgA nephropathy shows a number of atypical features. First, the increase

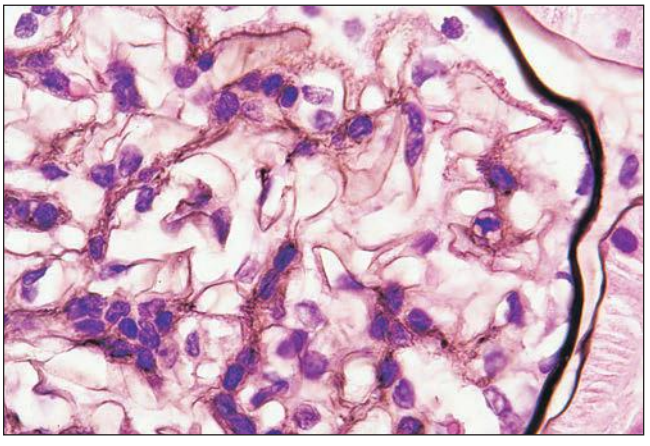

FIGURE 12.31 Superimposed membranous and IgA nephropathies. Methenamine silver stain shows glomerular basement membrane "spikes" typical of membranous nephropathy (best seen between 12 and 2 o'clock), with segmental mesangial hypercellularity (*lower left*). (Jones methenamine silver stain, ×1000.)

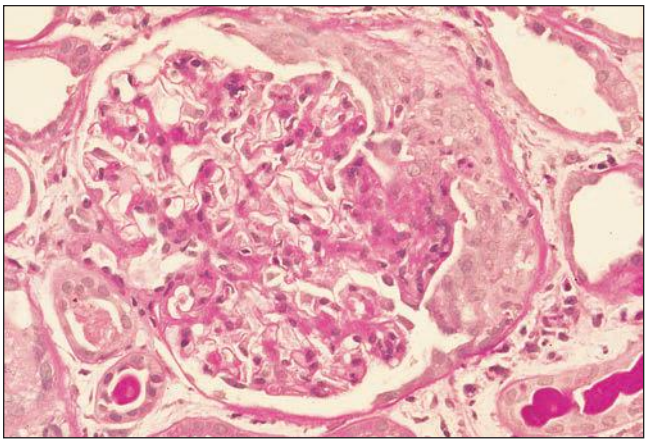

FIGURE 12.32 ANCA-associated crescentic glomerulonephritis with mesangial IgA. Portions of the glomerular tuft not directly adjacent to the hilum or to the crescent are not hypercellular. (PAS, ×400.)

in serum IgA, when present, is accounted for by an increase in pIgA1, with levels of mIgA1 and of IgA2 being within the normal range (200,206). Second, there is an elevated ratio of lambda to kappa light chains in this pIgA1, particularly in patients with active disease (207,208). Third, there is altered *O*-glycosylation (galactosylation and sialylation) in the hinge region of this IgA1, as demonstrated both by altered lectin binding and mass spectroscopy, with no abnormalities of the *N*-linked sugars noted (209,210).

These features of serum IgA in patients with IgA nephropathy correlate well with those of IgA deposited in the mesangium. As noted earlier, the glomerular deposits of IgA in these patients consist predominantly of IgA1 (128,133–140), and much of this is polymeric based on the

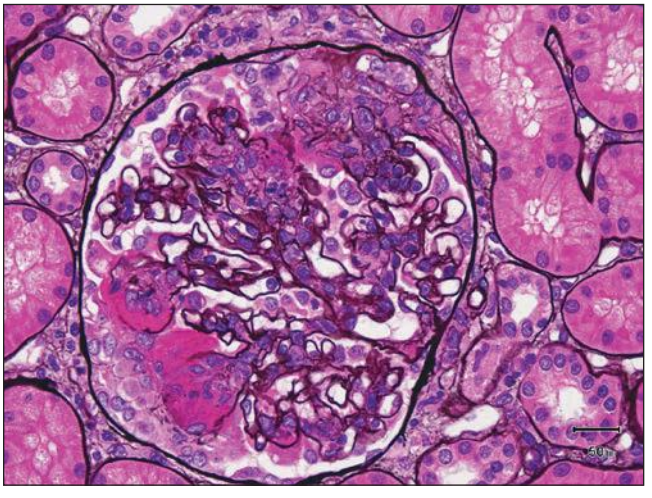

FIGURE 12.33 IgA nephropathy with fibrinoid necrosis and crescent formation. The methenamine silver stain shows fibroid necrosis with associated disruption of the glomerular basement membrane and associated early crescent formation, most evident in lower left quadrant of this glomerulus. In contrast to the case with ANCA-associated crescentic glomerulonephritis (see Fig. 12.32), the glomerular tuft shows segmental mesangial and endocapillary hypercellularity. (Jones methenamine silver, ×400.)

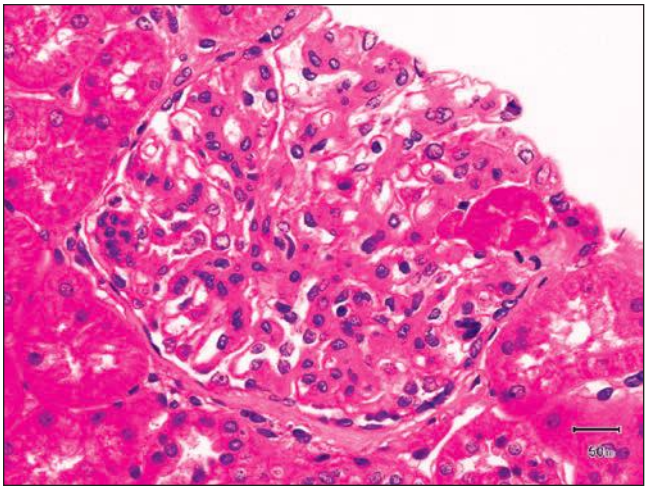

FIGURE 12.34 IgA nephropathy with segmental fibrinoid necrosis. In addition to the segmental necrotizing lesion, this glomerulus also shows mesangial hypercellularity and matrix expansion. (H&E, ×400.)

presence of J chain (134,135,138,141) (see Immunohistologic Findings). The intensity of immunostaining for lambda light chains also exceeds that for kappa in the majority of cases of IgA nephropathy (130,139,148,211). Furthermore, when the *O*-glycosylation of IgA1 eluted from kidneys (nephrectomy or autopsy specimens, or combined from a large number of biopsy specimens) with IgA nephropathy was studied using lectin binding and mass spectrometry, there was decreased galactosylation and sialylation in the hinge region that was even more pronounced than that seen in serum IgA1 from IgA nephropathy patients (212,213). These findings suggest that the most abnormally *O*-glycosylated pIgA1 molecules are those most likely to be deposited in the glomeruli, and indeed, fractions of IgA1 from IgA nephropathy patients enriched in molecules with underglycosylated hinge regions correspond to those fractions showing the greatest degree of glomerular accumulation in the perfused rat kidneys (214).

The abnormal *O*-glycosylation of IgA1 is posttranslational, as the primary structure of the hinge region of IgA1 is normal in patients with IgA nephropathy (199). There is also no evidence that this abnormal glycosylation is due to post–secretory degradation of the *O*-linked glycans (209). Evidence for a functional defect in core 1, β1,3-galactosyltransferase 1 (C1GALT1), the enzyme that catalyzes addition of galactose to *O*-linked GalNac, was reported in peripheral blood B cells from patients with IgA nephropathy (200), and a recent study of Serino et al. (215) identified a possible molecular mechanism underling the reduced C1GALT1 activity. These investigators identified a microRNA (miR-148b) within human peripheral blood mononuclear cells (PBMCs) that acts to reduce levels of C1GALT1 mRNA and protein within these cells. Furthermore, Serino et al. (215) showed that PBMCs from patients with IgA nephropathy had significantly higher levels of miR-148b than PBMCs from health control subjects, whereas cells from patients with HSP nephritis, membranoproliferative GN type I, and focal segmental glomerulosclerosis (FSGS) did not. Transfecting cells from patients with IgA nephropathy with an inhibitor (a mutated form) of miR-148b restored expression of C1GALT1 mRNA and protein to normal levels. Furthermore, transfecting an IgA1-producing B-cell line with a molecular mimic of miR418b increased production of galactose-deficient IgA1, whereas transfection with the inhibitor reduced production of galactose-deficient IgA (215). While the basis for the increased levels of miR-148b remains unknown, these findings open a potential new avenue for the treatment of IgA nephropathy (215,216).

Source(s) of the IgA Within Glomerular Deposits

Because the IgA deposited in the glomeruli of patients with IgA nephropathy is mainly pIgA1 and under normal conditions mucosal IgA is almost exclusively polymeric while bone marrow–derived IgA is nearly all monomeric, and noting the common association between infections involving mucosal surfaces and the onset of symptoms in IgA nephropathy, a number of investigators hypothesized that the mesangial IgA in patients with IgA nephropathy is mucosally derived (217–219). Furthermore, a number of studies have demonstrated increased serum levels of IgA antibodies directed against food and other mucosal-associated antigens (220–222). However, more recent evidence strongly suggests that abnormalities in IgA immune responses to mucosal antigens, including a loss of oral tolerance to these antigens and a shift in production of pIgA1 from plasma cells associated with mucosal tissues to those in the

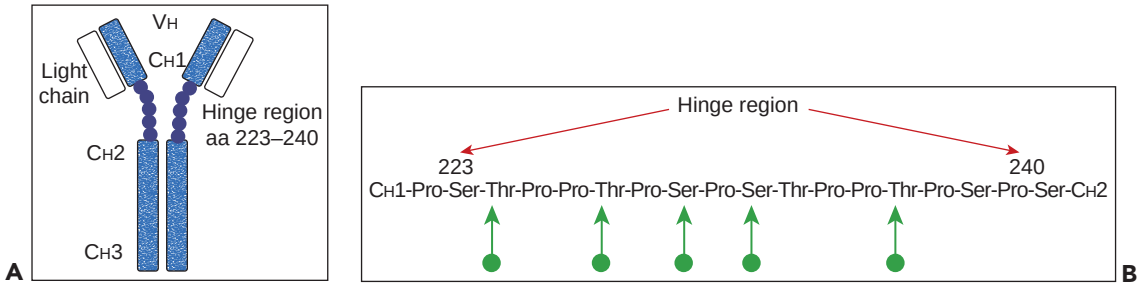

FIGURE 12.35 *O*-glycosylation of the hinge region of IgA1. A: Structure of monomeric IgA1. There are two α1 heavy chains and two κ or λ light chains. The heavy chains contain three constant region domains (CH1, CH2, and CH3) and a variable (VH) region; the 18-amino-acid hinge region is located between the CH1 and CH2 domains. **B:** Amino acid sequence of the hinge region, indicating those serine and threonine residues that have been shown to be *O*-glycosylated. (Modified from Barratt J, Feehally J, Smith AC. Pathogenesis of IgA nephropathy. *Semin Nephrol* 2004;24:197–217.)

bone marrow, most likely underlie the presence of circulating, abnormally glycosylated pIgA1 that ultimately becomes deposited in the glomeruli (200,206,223–227). A major portion of this evidence can be summarized as follows:

1. Patients with IgA nephropathy have increased numbers of plasma cells containing pIgA and IgA1 in the bone marrow, and bone marrow cultures from these patients produce increased amounts of pIgA1 (as well as mIgA1) compared with age- and sex-matched controls (225–227).
2. By contrast, numbers of mucosal-associated plasma cells producing pIgA are not elevated, and in some instances have been found to be decreased, in patients with IgA nephropathy (228,229), and levels of IgA and of IgA1 are not increased in the saliva of patients with IgA nephropathy who have elevated serum IgA and IgA1 levels (206).
3. Patients with IgA nephropathy, unlike healthy controls, respond to intranasal antigen challenge with influenza virus with increased levels of IgA antibodies in the circulation (230), providing an explanation (in the form of abnormal handling of mucosal antigens and breakdown of oral tolerance) other than spillage of mucosal IgA into the circulation for the presence of IgA antibodies against food and other mucosal environmental antigens in the serum of patients with IgA nephropathy (220–222).

It remains unclear why the abnormal production of IgA1 by the bone marrow of patients with IgA nephropathy involves pIgA1, which is more characteristic of mucosal secretions, as well as mIgA1. Perhaps, the apparent dysregulation of the "mucosa-bone marrow axis" of IgA production associated with IgA nephropathy somehow also involves J chain expression, although this is speculation.

Mesangial Deposition of IgA in IgA Nephropathy

The mesangial deposits of IgA in IgA nephropathy could potentially result from deposition of circulating immune complexes, binding of IgA to specific antigen(s) planted in the mesangium, and/or binding of IgA (or more specifically, abnormally glycosylated pIgA1) to specific receptors expressed on mesangial cells in the absence of antigen.

IgA nephropathy is commonly described as an immune complex–mediated glomerular disease. It was initially hypothesized that the IgA deposited in the mesangium is derived from circulating immune complexes (219,231–233). Support for this hypothesis comes from observations in both humans and experimental models. In humans, episodes of macroscopic hematuria and other clinical and histologic features of active glomerulonephritis in some patients (mainly children) with IgA nephropathy have been found to be associated with an increase in circulating IgA immune complexes (219,232,234), although such evidence of active disease has also been found to be associated with increases in serum pIgA not in the form of immune complexes (235). The frequent recurrence of mesangial IgA deposits in renal allografts of recipients whose original disease was IgA nephropathy (236) (also see Renal Transplantation in Patients With IgA Nephropathy, below) is also consistent with a scenario of mesangial deposition of circulating immune complexes, although nephritogenic aggregates of abnormal IgA not configured as immune complexes with bound antigen could also explain the recurrence. The frequent presence of IgA deposits in dermal blood vessels of patients with IgA nephropathy has also been taken as evidence for this scenario, although as noted previously (see Immunohistologic Findings) such deposits are not specific for IgA nephropathy and may be seen in a number of different renal diseases and even in normal individuals (152,155). In a mouse model, intravenous injection of pIgA-containing immune complexes produced a mesangial pattern of IgA and C3 immunostaining with focal glomerulonephritis and associated hematuria (237).

In patients with IgA nephropathy without circulating IgA immune complexes, it has been hypothesized that such complexes form in situ, perhaps with antigens planted in the mesangium (231). A number of potential antigens have been proposed to be involved in the pathogenesis of IgA nephropathy, including food antigens (gliadin, casein, ovalbumin, bovine serum albumin, and others) (220–222,238,239), viral antigens (cytomegalovirus, hepatitis B surface antigen) (240–242), and bacterial antigens (e.g., *Haemophilus parainfluenzae*, *S. aureus* cell envelope antigen) (243–245). While findings with food and viral antigens have generally not proven to be consistent or highly reproducible (231,246–250), those with bacterial antigens may be somewhat more promising. For example, Koyama et al. (244) reported colocalization of *S. aureus* cell envelope antigen ("possible adhesion") and IgA by immunofluorescence in 79 of 116 (68%) renal biopsy specimens from patients with IgA nephropathy and 6 of 10 specimens from patients with HSP nephritis but in none of 76 specimens lacking glomerular immune complex deposits. This antigen was found, however, in 3 of 10 biopsy specimens with lupus nephritis (244). Recently, Schmitt et al. (251) demonstrated tissue deposits of IgA-binding regions (IgA-BR) of staphylococcal M proteins in the majority of renal biopsy specimens from patients with both IgA nephropathy and HSP nephritis, although there was no correlation between the presence of IgA-BR and clinical or histopathologic findings.

Finally, abnormally glycosylated IgA1 is itself an antigen, forming immune complexes with IgG or other IgA1 molecules (252,253). Tomana et al. (252) demonstrated IgG (mainly IgG2) and IgA1 antibodies directed against IgA1 hinge region *O*-glycans and circulating immune complexes composed of IgG anti-GalNAc antibodies and abnormally glycosylated pIgA1 in sera of patients with IgA nephropathy. Such antibodies were also found in smaller amounts in sera of normal subjects and patients with non-IgA mesangial proliferative glomerulonephritis, although the size of immune complexes formed from the association of abnormally glycosylated IgA1 and antibodies directed against it are larger in patients with IgA nephropathy (and HSP with nephritis) than in normal subjects (253). Whether immune complexes containing these antibodies are present in glomeruli of patients with IgA nephropathy remains to be determined, although serum levels of IgG antibodies specific for galactose-deficient IgA1 were found to correlate with levels of proteinuria in patients with IgA nephropathy, suggesting that the immune complexes formed are likely to be pathogenically relevant (253). Still, while it was reported that there is a positive correlation between serum IgA and IgG2 levels in patients with IgA nephropathy, this same study demonstrated that the mesangial IgG present in patients with IgA nephropathy is almost exclusively IgG1 and IgG3, with IgG2 identified in only 1 of 11 biopsies examined (254).

Abnormally glycosylated pIgA1, and/or immune complexes containing abnormally glycosylated pIgA1, may bind directly to receptors expressed on mesangial cell plasma membranes, and pIgA1 bound to mesangial receptors may also serve as a planted antigen for in situ immune complex formation with circulating anti-IgA1 antibodies. A number of putative mesangial cell IgA receptors have been proposed, including the Fc receptor for IgA (Fc alpha receptor or CD89) (255,256), the Fc alpha/mu receptor (257), a novel form of mesangial Fc alpha receptor (258), and an asialoglycoprotein receptor similar to or unique from the hepatic form (259). CD89 exists in both membrane-bound and soluble isoforms. Binding of pIgA to the membrane-bound form of CD89 on myeloid cells may result in the formation of circulating complexes prone to mesangial deposition (260,261), whereas binding to the smaller soluble isoform, shed from myeloid cells, has been suggested as having a possible protective effect against progressive disease (261,262). However, the presence of these receptor proteins on human mesangial cells and/or in mesangial IgA deposits have not been confirmed in all studies (261,263–265).

Another candidate IgA receptor that has been documented to be present on human mesangial cells at both mRNA and protein levels is transferrin receptor (TfR or CD71), which actually exists in two forms, TfR1 and TfR2 (261,266,267). In patients with IgA nephropathy, mesangial TfR expression is enhanced and colocalized with IgA deposits (266,268). Furthermore, pIgA1 but not mIgA1 or IgA2 was found to bind to mesangial cell TfR, and abnormally glycosylated IgA1 from patients with IgA nephropathy bound more efficiently than did IgA1 from healthy individuals (267). TfR expression on cultured human mesangial cells is up-regulated by pIgA1 binding, more so by pIgA1 from patients with IgA nephropathy than from controls. Furthermore, it was found that pIgA1 stimulated proliferation of these mesangial cells and that this proliferation was inhibited by a monoclonal antibody against TfR or by the presence of soluble ectodomains of TfR1 or TfR2 (269). Together, these findings suggest a potentially important role for mesangial cell TfR as a binding site for abnormally glycosylated IgA1 in patients with IgA nephropathy.

The Glomerular Response to Bound IgA

The development of glomerulonephritis following IgA deposition appears to primarily involve two mechanisms: (a) activation and proliferation of mesangial cells in response to IgA binding to receptors on these cells and subsequent cross-linking of the receptors and (b) activation of complement.

Binding of pIgA1 from patients with IgA nephropathy, and to a somewhat lesser extent pIgA1 from normal controls, to cultured human mesangial cells in vitro has been reported to stimulate proliferation of these cells, production of proinflammatory cytokines such as interleukin (IL)-1, IL-6, and platelet aggregating factor, secretion of fibronectin, expression of mRNAs for collagen types I and IV, and expression of RNA for the profibrotic transforming growth factor (TGF)-β as well as TGF-β secretion (270–272). Expression of $\alpha_v\beta_3$ integrins on cultured human mesangial cells has also been found to be up-regulated by exposure to pIgA and was greatly potentiated when the IgA was desialylated and degalactosylated (273).

Additional studies (274) indicate that while some IgA-containing immune complexes stimulate proliferation of mesangial cells in vitro, others inhibit such proliferation. Stimulation of mesangial cell proliferation was seen only with IgA1 in complexes, and those complexes with the highest content of galactose-deficient IgA1 produced the greatest degree of stimulation (274). Furthermore, uncomplexed, desialylated and degalactosylated IgA was found to decrease proliferation and increase apoptosis of cultured mesangial cells, the latter perhaps through enhanced nitric oxide release and p53 activation (275). These effects could potentially modulate mesangial proliferation in IgA nephropathy, and/or together with enhanced TGF-β release and matrix protein synthesis could favor progression toward sclerosis (275). Clearly, much additional work is needed to characterize the events that determine proliferation, progression, and potential resolution of glomerulonephritis, which form the basis of the great variability in histologic and clinical expression of IgA nephropathy.

Activation and Role of Complement

As noted above (see Table 12.7), glomerular deposits of IgA in IgA nephropathy are usually accompanied by C3, but only rarely by C1q, findings consistent with observations that IgA does not activate the classical pathway of complement (276). In those cases of IgA nephropathy in which mesangial C1q was detected, it was accompanied by IgM and tended to occur in patients with significant proteinuria, suggesting possible nonspecific trapping rather than true activation of the classical pathway (277). Human IgA does activate complement by the alternative pathway (276,278) and by the more recently described mannose (or mannan)-binding lectin (MBL) pathway (144,145,279,280), and both of these pathways are likely to become activated in and contribute to glomerular injury in IgA nephropathy (281). Furthermore, activation of both of these pathways by IgA involves polymeric rather than monomeric IgA (278,279), and aberrantly glycosylated GalNAc- and Gal-exposing IgA glycoforms from patients with IgA nephropathy were found to be more effective in activating complement than IgA from control subjects (282).

Evidence for the potential importance of complement in producing glomerular injury comes from a number of different animal models of IgA nephropathy, in which depletion of complement using cobra venom factor prevented the development of hematuria and proteinuria (283,284). In human IgA nephropathy, a study using confocal microscopy showed that in mild lesions, the majority of glomerular immune complex deposits consisted of IgA and C3 coated by a layer of IgA alone, whereas more severe lesions were associated with the presence of large C3 deposits and/or deposits of IgA and C3 without the outer coat of IgA, suggesting that free access of complement to cell and/or matrix receptors could trigger an inflammatory response (285). As noted earlier, immunofluorescence studies have shown colocalization of components and neoantigens of the C5b-9 MAC with IgA in glomeruli of patients with IgA nephropathy, with more intense staining for MAC (but not IgA) seen with more active glomerular lesions (131). However, cases of IgA nephropathy with hematuria, proteinuria, mesangial hypercellularity, and even in one case, small crescents have been reported in patients with C9 deficiency and absence of glomerular deposition of C9 and MAC neoantigen, suggesting that formation of the MAC is not essential for the development of symptomatic IgA nephropathy (286,287).

Genetic Factors and the Role of the Renin-Angiotensin System

This section will briefly review potential roles of certain genes in predisposing individuals to developing IgA nephropathy and in promoting progression of renal disease in affected individuals. For a more detailed and exhaustive treatment of this subject, the reader is referred to specific review articles (253,288,289). Genetic and other aspects of familial IgA nephropathy are discussed later in this chapter.

Human Leukocyte Antigens

Initial studies in cohorts of French IgA nephropathy patients showed an association between IgA nephropathy and the human leukocyte antigens (HLA) Bw35 antigen (290,291), a finding supported by reports of HLA-identical siblings sharing this antigen (292,293). A number of Japanese studies reported an association between IgA nephropathy and HLA DR4 (294–296). However, each of the above studies involved relatively small numbers of patients from a very limited geographic region, and Bw35, DR4, nor any HLA DQ alleles have been consistently found to be associated with the development of IgA nephropathy (297,298).

One study of French patients reported an association between HLA DQB1*0301 and unfavorable outcomes in IgA nephropathy (299), although this was not confirmed by others (298). Two separate HLA DQA alleles were found to have a significant association with progression of IgA nephropathy in cohorts of Chinese patients, DQA 2U with worse outcomes and DQA*201 with better outcomes (300), although these findings need to be confirmed in other cohorts of patients.

A more recent genome-wide association study (GWAS) (301) identified several loci influencing susceptibility to IgA nephropathy, three of which were localized to the major histocompatibility complex (MHC) locus on chromosome 6p21. The strongest genetic effect was observed for the MHC-II locus containing the HLA-DQB1, DQA1, and DRB1 genes (301). As discussed in a recent review (253), certain haplotypes within these loci, which encode genes associated with antigen presentation and processing, were found to reduce the odds of developing IgA nephropathy by over 50% (301).

T-Cell Receptor Genes

As increased production of IL-2 and other T-cell–derived cytokines have been reported in patients with IgA nephropathy (289,302), a number of researchers have examined potential associations between T-cell receptor (TCR) genes and disease progression in IgA nephropathy. In one such study, patients with the TCR Cβ allele were found to exhibit more rapid disease progression and greater levels of proteinuria after a follow-up interval of approximately 4 years (303), although the reproducibility of this finding in other patient populations remains to be tested.

Regulators of Complement Factor H

Complement factor H (CFH) and related gene products modulate the alternative pathway of complement by binding C3a and C5a convertases, and mutations in CFH can lead to uncontrolled activation of the alternative complement pathway and development of dense deposit disease, C3 glomerulopathy and membranoproliferative GN, type I (304,305). The GWAS noted above found that carriers of a common deletion encompassing the CFH-related genes CFHR1 and CFHR3 had an approximately 30% lower risk of developing IgA nephropathy than individuals without this deletion, and rare persons with two copies of the deletion had a nearly 60% lower risk for developing the disease (301). As CFHR1 and CFHR3 appear to compete with CFH for binding to C3b (306), reductions in the levels of these gene products may enhance the inhibitory action of CFH on the complement cascade and reduce the glomerular inflammatory response to bound, abnormally glycosylated IgA1 (253).

Angiotensin-Converting Enzyme and Other Renin-Angiotensin System Gene Polymorphisms

There are three human angiotensin-converting enzyme (ACE) genotypes, II, ID, and DD, differing by the insertion (I) or deletion (D) of a fragment of DNA in intron 16 of the ACE gene (307). The DD genotype is associated with higher serum and tissue ACE levels, leading to increased angiotensin and decreased bradykinin concentrations (290,307). A number of studies from North America, Europe, and Asia have examined potential associations of ACE genotypes with the development and progression of IgA nephropathy. In most (308–314) but not all (315,316) of these studies, the DD genotype was associated with clinical and/or histologic (i.e., increased chronic histopathologic changes) evidence of disease progression, and in some studies, this genotype was an independent predictor of clinical progression in a multivariate analysis. In one study (317), the ACE DD genotype was significantly associated with disease progression only in patients with one (MM) of three possible genotypes of the angiotensinogen gene, suggesting a possible interaction between two components of the renin-angiotensin system (RAS). By contrast, none of these studies found an association between ACE genotype and the development of IgA nephropathy.

Expression of genes encoding a number of components of the RAS, including renin, angiotensinogen, ACE, and angiotensin II receptors (AT1 and AT2), were found to be higher in renal cortex from patients with IgA nephropathy than from control patients with renal malignancies, both in glomerular and tubulointerstitial compartments (318). IgA nephropathy patients with the 4G/4G genotype of the plasminogen activator inhibitor-1 (PAI-1) gene, the product of which appears to promote glomerular sclerosis and interstitial fibrosis (319), were found to have a higher mean level of proteinuria, a lower mean creatinine clearance, and more severe histologic changes than patients with the other PAI-1 genotypes (4G/5G, 5G/5G), although mean serum PAI-1 levels were not significantly different among cohorts of patients with the different genotypes (316). Patients with IgA nephropathy also showed overexpression of genes associated with fibrosis (TGF-β1, collagen type IV, α-smooth muscle actin [SMA]), particularly in the tubulointerstitial compartment. Furthermore, in patients with IgA nephropathy, glomerular levels of renin, angiotensinogen, and ACE expression were all positively correlated with levels of TGF-β1 expression, and tubulointerstitial levels of both angiotensinogen and ACE expression were positively correlated with those of α-SMA expression (318). These findings may in part explain the reported effectiveness of angiotensin-converting enzyme inhibitor (ACEi) therapy in slowing the progression of IgA nephropathy (see Treatment of Primary IgA Nephropathy, below).

Prognosis and Clinicopathologic Correlations

In Berger's original cohort of IgA nephropathy patients (2), progression to ESRD was rare, and throughout the 1970s and 1980s, IgA nephropathy was generally felt to be a benign

disease, supported by studies from Europe, Asia, and Australia indicating actuarial 10-year renal survival rates from the time of diagnosis or renal biopsy of greater than 80% (17,32,50, 70,80,90,92,94,95,97,99,108). Over the past 15 to 20 years, however, it has become evident that IgA nephropathy is not as benign as once thought. Several studies from North America (40,51,63) and one from Japan (98) have documented 10-year renal survival rates in the range of 60% to 75%, and it has become clear that renal survival rates in IgA nephropathy may vary greatly depending on regional renal biopsy practices (40,96). It is now generally felt that most patients with IgA nephropathy develop a progressive decline in renal function, though at a highly variable rate, and 15% to 40% of patients will eventually develop ESRD (47). Considering this and that IgA nephropathy is the most common form of primary glomerulonephritis worldwide (Refs. (12–14); also see Table 12.1), it is not surprising that IgA nephropathy is now documented to account for at least 1% to 3% of cases of ESRD in North America and Europe and a somewhat higher percentage in Asia and Australia (320,321).

The highly variable clinical course of IgA nephropathy is related in significant part to the marked variability in its histopathologic presentation. Clinicopathologic correlations in IgA nephropathy have been extensively studied. Many of those studies performed prior to the development of the Oxford Classification and parameters that have been found to be significantly associated with rates of renal survival and/or decline in renal function are summarized in Table 12.10.

The strongest pathologic predictor of clinical outcome in IgA nephropathy is the extent of TA and IF. In nearly all studies in which this has been examined, tubulointerstitial scarring is an independent predictor of progression to ESRD in a multivariate analysis including various pathologic and (in some studies) clinical parameters. However, this is not surprising in that TA/IF represents in large part a measure of chronic renal injury already present at the time of the biopsy, and as such a measure of how close the kidney is to being an end-stage organ. A key element in the development of the Oxford Classification, introduced earlier in this chapter, is that its morphologic components (mesangial hypercellularity, endocapillary proliferation, and segmental glomerulosclerosis as well as TA/IF) were determined on the basis or being predictive of the rate of decline of renal function or of a response to immunosuppressive therapy, in addition to the development of ESRD (123).

Findings in the Original Oxford Study Cohort

Tables 12.11 and 12.12 show the rates of renal functional decline (slope of eGFR vs. time) of patients from the original Oxford study cohort according to different combinations of these four parameters. Notably, while mesangial hypercellularity (M1) and segmental glomerulosclerosis (S1) individually result in only a modest rate of renal functional decline, the combination of these lesions (or of endocapillary hypercellularity [E1] and segmental glomerulosclerosis) results in a pronounced rate of renal functional deterioration (see Table 12.11). Similarly, the presence of moderate or severe TA/IF (T1 or T2) greatly accentuates the impact of both mesangial hypercellularity and endocapillary hypercellularity on this deterioration (see Table 12.12).

A somewhat surprising finding of this study is that TA/IF, a lesion generally felt to represent irreversible chronic change, was highly predictive of the rate of decline in renal function, even in a multivariate analysis including proteinuria. Still, there is evidence from repeat renal biopsies in patients with IgA nephropathy that immunosuppressive therapy may result in a reduction in TA/IF, especially when this is accompanied by interstitial inflammation and edema (65). Recent findings in renal allograft biopsies (322,323) further support the notion that TA/IF with accompanying mononuclear cell inflammation may often represent an active lesion, capable of producing progressive damage to the kidney and potentially amenable to immunosuppressive therapy.

The Oxford Classification is based entirely on light microscopic findings and does not consider immunofluorescence or electron microscopic findings as potential prognostic factors.

Coppo et al. (324) compared the applicability of the Oxford Classification to predict renal outcomes in children, as compared with adults, in the original Oxford study cohort. As noted above, this cohort consisted of 59 children in addition to 206 adults. They found that while children had more mesangial and endocapillary hypercellularity and less segmental glomerulosclerosis and TA/IF than adults, the predictive value of these four lesions on the rate of decline of renal function was not significantly impacted by patient age. In addition, the predictive value of the M, E, and S scores was not different in the 59 children and 206 adults; the T score was not included in the latter analysis, presumably because too few of the pediatric biopsies had T > 0 (324).

Validation Studies of the Oxford Classification

Validation is an essential step in the process of adoption of any medical prognostic model (121). Since the publication of the Oxford Classification in 2009, there have been several published studies recapitulating the process of relating the M, E, S, and T scores to clinical outcome, thus evaluating the performance of the threshold values of these parameters. In considering these studies, it should be noted that a predictive model derived in one cohort may not perform as well in independent cohorts because of erroneous conclusions in the derivation of the initial model, substantial differences in the validation cohort, or both (121). The results of a number of these validation studies are summarized in Table 12.13.

One of the first studies to provide a true statistical validation of the Oxford Classification included 187 patients (143 adults and 44 children) from four North American centers (325). Subjects included in this study met the same inclusion and exclusion criteria as those in the Oxford cohort, demonstrating a similar spectrum of both clinical and pathologic characteristics. The reproducibility of the pathologic scoring system derived in the Oxford cohort was also tested in this study, and for most elements of the scoring system, the interobserver reliability scores were as good or superior to those documented in the original Oxford study (123,124). Three of the four pathologic variables identified in the Oxford derivation cohort also predicted a faster rate of renal functional decline in the North American validation data set, including segmental glomerulosclerosis, endocapillary proliferation, and TA/IF (Oxford S, E, and T scores) (325), thus supporting the generalizability of the original data (123). The impact of endocapillary proliferation on renal functional decline was significantly less in patients who received immunosuppression than in those who did not, consistent with findings in the original Oxford study

TABLE 12.10 **Statistical analysis of the predictive value, as risk factors for ESRF, of some histologic features in 22 studies selected from the literature**

Authors	Country	No. of patients	Classes of severity according to Lee, Haas, or other classification	Semiquantitative evaluation of elementary lesions						
				Glomerular, tubulointerstitial, vascular, or total score	Global glomerular sclerosis	Segmental glomerular sclerosis	Crescents	Tubulointerstitial damage	Vascular damage	Peripheral capillary deposits by IF or EM
Droz et al. (78)	France	244	—	●TO	●	●	●	●	—	—
Nicholls et al. (90); Packham et al. (91)	Australia	640	●OT	—	●	●	●	●	●	—
D'Amico et al. (92,93)	Italy	292	—	—	●■	●■	●□	●■	●□	●■
Beukhof et al. (94)	The Netherlands	75	—		●□	○□	○□	●□	○□	—
Rekola et al. (95)	Sweden	155	●OT■OT	●TO	●	—	—	●	—	●
Bogenschutz et al. (70)	Germany	239	—	●GL +TI	●□	●□	—	●■	○	—
Alamartine et al. (97)	France	282	—	●TO	●	—	○	●	●	—
Ibels and Gyory (50)	Australia	121	—	—	●■	●■	●□	●■	—	●□
Johnston et al. (32)	United Kingdom	253	—	—	—	●□	—	—	—	○
Katafuchi et al. (98)	Japan	225	—	—	●□	●□	●■	●■	●□	○
Yagame et al. (99)	Japan	206	●OT ■OT		—	●□	—	—	—	○
Radford et al. (51) Donadio et al. (100)	United States	148		■GL■TO	●□	—	—	●□	●□	—
Haas (40)	United States	109	●HA							
Kobayashi et al. (101)	Japan	366		●TO■TO	●□	●□	○	●■	●□	○
Koyama et al. (102)	Japan	335	●OT□OT	—	—	—	—	—	—	—
Frimat et al. (103)	France	210	●LE	—	—	—	—	—	—	—
Vleming et al. (104)	The Netherlands	83	●OT■OT	—	—	—	—	—	—	—
Rychlik et al. (105)	Germany and Czech Republic	177			●■	—	●■	—	—	●□
Daniel et al. (106)	France	194	●HA□HA	●TI+VA■nTI	—	—	●■	●■	●■	—
Li et al. (108)	Hong Kong	168	●OT■OT	●GL ■GL	—	—	—	—	—	—
Rauta et al. (109)[b]	Finland	259		●TO■GL	—	—	○	●□	●■	—
Bartosik et al. (63)	Canada	132	●LE□LE							

[a]Significant only at the analysis based on slope of GFR.

[b]Multivariate analysis refers to the subgroup of patients with normal renal function at diagnosis.

ESRF, end-stage renal failure; LE, Lee; HA, Haas; OT, other; GL, glomerular; TI, tubulointerstitial; VA, vascular; TO, total; IF, immunofluorescence; EM, electron microscopy.

At the univariate analysis, ●, significant; ○, not significant.

At the multivariate analysis, ■, significant; □, not significant.

From D'Amico G. Natural history of idiopathic IgA nephropathy and factors predictive of disease outcome. *Semin Nephrol* 2004;24:179.

TABLE 12.11 Impact of glomerular lesions on deterioration of renal function

Proliferative lesion	Segmental glomerulosclerosis	No. of patients	Slope of eGFR (mean ± SD) mL/min/1.73 m²/y
None (M0, E0)	No (S0)	13	0.7 ± 2.5
	Yes (S1)	22	–1.5 ± 2.7
Mesangial hypercellularity (M1, E0)	No (S0)	31	–2.2 ± 4.3
	Yes (S1)	88	–4.7 ± 7.6
Endocapillary hypercellularity (M0 or M1, E1)	No (S0)	21	1.2 ± 1.2
	Yes (S1)	90	–4.9 ± 10.0

Data are from the original Oxford patient cohort.

Modified from Cattran DC, Coppo R, Cook HT, et al. The Oxford Classification of IgA nephropathy: rationale, clinicopathological correlations, and classification. *Kidney Int* 2009;76:534–545.

cohort. Performance of the Oxford scoring was also validated by demonstrating a parallel relationship across quintiles of risk comparing the observed to predicted rate of renal functional decline in both cohorts. Importantly, the validity of these predictive variables was reinforced by the fact that the analyses were performed on a population differing both in geographic origin as well as era of care. The entire validation population was derived from North America, and the patients were treated approximately 5 years after those of the original Oxford cohort.

The main difference between the findings in the North American validation (325) and original Oxford studies (323) was a lack of predictive value of the mesangial hypercellularity score (M score) on clinical outcomes in the former study. While variability in scoring of this somewhat subjective variable between pathologists in either or both studies could possibly account for this difference, another possible explanation could be the greater use of antihypertensive treatment and inhibitors of the RAS in the North American validation cohort, possibly reflecting the different era of care.

Shi et al. (327), in a study of 410 IgA nephropathy patients from a single center in China, found that mesangial hypercellularity (M1), segmental glomerulosclerosis (S1), endocapillary hypercellularity (E1), and TA/IF (T1 and, to a significantly greater extent, T2) were all significant predictors of the development of ESRD by univariate analysis, with S and T scores also being independent predictors of renal survival in a multivariate analysis that included clinical as well as morphologic parameters. As in the original Oxford cohort, E1 was not an independent predictor of the development of ESRD, but patients with E1 lesions did show benefit from immunosuppressive therapy. In addition, while mesangial hypercellularity (M1) was not an independent predictor of ESRD, this lesion as well as TA/IF were independent predictors of lack of response of proteinuria to RAS blockade alone (327).

El Karoui et al. (326) evaluated the performance of the MEST score in a retrospective study of 128 adult patients from Paris that overall had more advanced disease than the Oxford cohort. They found that by univariate analysis, mesangial hypercellularity, endocapillary proliferation, segmental glomerulosclerosis, and TA/IF were all significantly associated with an increased risk of poor outcome, the latter defined as a doubling of serum creatinine (SCr) or ESRD. However, by multivariate analysis including clinical (eGFR, proteinuria, and mean arterial pressure at the time of biopsy) as well as histologic parameters, only mesangial hypercellularity and eGFR at biopsy were significantly associated with a bad outcome, and only TA/IF and eGFR were significantly associated with the rate of decline of eGFR.

In the cohort of El Karoui et al. (326), FSGS-type lesions, including segmental glomerulosclerosis as defined in the Oxford cohort (124), as well as lesions of cellular and collapsing FSGS as defined according to the Columbia classification for FSGS

TABLE 12.12 Impact of glomerular lesions and tubular atrophy/interstitial fibrosis on deterioration of renal function

Glomerular lesion	Tubular atrophy/ interstitial fibrosis	No. of patients	Slope of eGFR (mean + SD) mL/min/1.73 m²/y
None (M0, E0)	≤25% of cortex (T0)	30	–0.6 ± 3.0
	>25% of cortex (T1 or T2)	5	–1.0 ± 1.2
Mesangial hypercellularity (M1, E0)	≤25% of cortex (T0)	89	–2.7 ± 5.5
	>25% of cortex (T1 or T2)	30	–7.9 ± 9.1
Endocapillary hypercellularity (M0 or M1, E1)	≤25% of cortex (T0)	88	–3.0 ± 1.9
	>25% of cortex (T1 or T2)	23	–6.9 ± 1.2

Data are from the original Oxford patient cohort.

Modified from Cattran DC, Coppo R, Cook HT, et al. The Oxford Classification of IgA nephropathy: rationale, clinicopathological correlations, and classification. *Kidney Int* 2009;76:534–545.

TABLE 12.13 Summary of Studies Correlating Oxford Classification Parameters (M, E, S, T) with clinical outcomes

			Parameters predictive of outcome	
References	**No. of patients**	**End point**	**Univariate analysis**	**Multivariate analysis[a]**
Cattran et al. (123)[b]	265 (206 Ad, 59 Ch)	Rate of eGFR decline	M, S, T	S, T
	265 (206 Ad, 59 Ch)	ESRD or ≥50% decline in eGFR	M, S, T	M,T
Herzenberg et al. (325)	187 (143 Ad, 44 Ch)	Rate of eGFR decline	Not done	E, S, T
El Karoui et al. (326)	128 Ad	ESRD or doubling of SCr	M, E, S, T	M
	128 Ad	Rate of eGFR decline	Not done	T
Shi et al. (327)	410	ESRD	M, S, T	S, T
Kang et al. (328)	197 Ad	ESRD or ≥50% decline in GFR	T	T
Alamartine et al. (329)	183 Ad	ESRD or doubling of SCr	E, S, T	None[e]
Katafuchi et al. (330)	702 (Ad and Ch)	ESRD	Not done	S, T
Zeng et al. (331)	1026 Ad	Rate of eGFR decline	M, S, T	M, T
	1026 Ad	ESRD or ≥50% decline in eGFR	M, S, T	M, T
Halling et al. (332)	99 Ch	ESRD or >50% decline in GFR	M, E, T	M[c,f], E[d,f], T[c,f]
Shima et al. (333)	161 Ch	eGFR < 60 mL/min/1.73 m^2	M, T	M, T
Le et al. (334)	218 Ch	ESRD or >50% decline in GFR	S, T	T

Studies summarized are those with a minimum of 99 patients (Ad, adults; Ch, children). Histologic parameters evaluated include mesangial hypercellularity (M1 vs. M0), segmental glomerulosclerosis (S1 vs. S0), endocapillary hypercellularity (E1 vs. E0), and tubular atrophy/interstitial fibrosis (T ≥ 1 vs. T0) according to criteria defined in the Oxford Classification (324). See text for additional details of these studies, including correlations of histologic parameters with responses to therapy.

[a]Including M, E, S, and T scores, clinical and demographic parameters including initial or time-averaged proteinuria, eGFR at biopsy, blood pressure, age, and gender, and in some studies other histologic parameters such as crescents and vascular lesions.

[b]Original Oxford cohort.

[c]Significant by one of two models used.

[d]Significant by each of two models used.

[e]Of all clinical and morphologic parameters included, only eGFR at biopsy was a significant predictor of the study outcome.

[f]Each of these three parameters, as well as crescents and global glomerulosclerosis, was significant by one of two models used.

(335), were seen in the great majority of biopsies; cellular FSGS lesions were differentiated from endocapillary proliferation by the presence of a overlying layer of swollen and often vacuolated epithelial cells (326). These investigators examined whether the type of FSGS lesions present affected clinical outcomes in their cohort of IgA nephropathy patients. They hypothesized that some segmental sclerosis lesions may reflect primary podocytopathy, as opposed to simply postinflammatory scarring or injury relating to hyperfiltration and nephron loss (336). By univariate analysis, cellular and collapsing lesions were significantly correlated with a bad outcome, while perihilar, tip, and FSGS (NOS) variants were not. By multivariate analysis, none of these FSGS patterns were significantly associated with adverse outcome as defined above, although collapsing, cellular, and FSGS (NOS) lesions were significant predictors of a faster rate of renal functional decline (326).

Kang et al. (328) studied 197 Korean patients whose renal biopsies were retrospectively classified according to the Oxford Classification. Using ESRD or a 50% reduction in eGFR as an end point, these investigators found that only the T score significantly correlated with the likelihood of reaching the end point by univariate and multivariate analyses. However, patients with biopsies showing mesangial hypercellularity (M1) and segmental glomerulosclerosis (S1) had significantly more proteinuria and were each significantly more likely to receive inhibitors of the RAS and immunosuppressive agents than patients whose biopsies did not show these lesions (328).

In a retrospective study of 183 patients, including some with very mild and very advanced disease, Alamartine et al. (329) found that segmental glomerulosclerosis, endocapillary hypercellularity, and TA/IF (but not mesangial hypercellularity) were predictive of a doubling of serum creatinine or development of ESRD by univariate analysis, although by multivariate analysis including proteinuria, blood pressure, and eGFR at biopsy, only the latter parameter was predictive of these adverse outcomes. It is notable that in this latter study and that of Kang et al. (328), mesangial hypercellularity was seen in 21% and 26% of biopsies, respectively, compared with 81% in the original Oxford cohort, and endocapillary hypercellularity in 14% and 11%, respectively, compared to 42% in the Oxford cohort (123).

In a large Japanese study, Katafuchi et al. (330) studied 702 patients with IgA nephropathy, patient ages ranged from 8 to 82 years. Four hundred and sixteen patients met the entry criteria of the original Oxford study (eGFR ≥30 mL/min/1.73 m^2, urine protein/creatinine ratio [Upr/Ucr] ≥0.5), 254 patients had eGFR ≥30 mL/min/1.73 m^2 but Upr/Ucr < 0.5 (97% with M0 score), and 32 patients had eGFR < 30 mL/min/1.73 m^2 (88% with T2, 78% with crescents). Follow-up was 62 months with eight patients developing ESRD within 12 months. By multivariate analysis that included M, E, S, T, and clinical parameters, S1 and T1/T2 lesions were associated with ESRD. M1 showed a tendency for high risk of ESRD compared with M0, while E1 showed no significant association

with the development of ESRD. Crescents were also associated with the development of ESRD in the entire cohort and in the patients who did not meet the Oxford study inclusion criteria but not in those who did meet these criteria.

Zeng et al. (331) performed a multicenter evaluation of the Oxford Classification in 1026 adult patients with IgA nephropathy recruited from 18 centers in China. Outcomes variables included time to a 50% reduction in eGFR or ESRD (the combined event), the rate of eGFR decline, and proteinuria at follow-up. Compared to the Oxford cohort, there were no significant differences in eGFR at the time of biopsy, but time-averaged proteinuria was lower in the Chinese cohort. The use of immunosuppressive therapy was similar to that in the Oxford cohort, and 89% received angiotensin II blockade. During a median follow-up of 53 months, 15.5% of the patients (159 cases) reached the combined event, a proportion that was lower than in the Oxford study. By univariate analysis, M1, S1, and T1/T2 were associated significantly with a combined event, while E1 and crescents were not associated with either the rate of eGFR decline or renal survival from a combined event. By multivariate analysis, M1 and T1/T2 alone were associated with the rate of eGFR decline or renal survival from a combined event. TA/IF of 25% to 50% (T1) and greater than 50% (T2) versus were associated with a 3.7-fold and 15.1-fold higher risk of the combined event, respectively, compared with less than 25% (T0), indicating T score as the most powerful predictor of renal survival in IgA nephropathy independent of clinical features.

Three validation studies of the Oxford Classification have been performed in study populations consisting entirely of children. Halling et al. (332) found that mesangial and endocapillary hypercellularity (M1 and S1, respectively) as well as TA/IF ($T \geq 1$), but not segmental glomerulosclerosis, were significant predictors of a poor outcome (ESRD or a greater than 50% decline in measured GFR) by univariate analysis and by multivariate analysis including additional histologic parameters and proteinuria at 1-year follow-up (but interestingly, not in an analysis including proteinuria at the time of biopsy). Notably, Halling et al. (332) also found that global glomerulosclerosis and the presence or cellular or fibrocellular crescents were significant predictors of a poor outcome in the same multivariate analysis. Unlike the original Oxford study cohort, that of Halling et al. (332) included children with an initial GFR of less than 30 mL/min/1.73 m^2. When these latter patients were omitted from the analysis, the significance of crescents as a predictor of a poor outcome was lost, although the effects of M1, E1, and $T \geq 1$ all remained significant (332).

Shima et al. (333) analyzed the value of the Oxford Classification as a predictor of poor renal outcome, defined as a decline in eGFR to less than 60 mL/min/1.73 m^2, in 161 consecutive Japanese children (less than 20 years old) with IgA nephropathy diagnosed between 1977 and 1989. Due to the fact that RAS blockers and long-term corticosteroid/combination therapies were infrequently used in Japan during the study interval, only 16% of the patients in this study received any form of immunosuppressive medication compared to 48% of children in the original Oxford cohort. A total of 64% of biopsies had mesangial hypercellularity, and segmental glomerulosclerosis was present in only 8.7% of the cases. Similar to the findings of Coppo et al. (324), mesangial and endocapillary hypercellularity were more frequent in patients less than 13 years old compared to older patients in the cohort. After a mean observation period of 7.4 ± 4.8 years, seven patients reached the end point renal outcome with five patients developing ESRD. By univariate and multivariate analyses, M and T scores and crescents were significant predictors of renal outcome. Stratifying the patients based on proteinuria at biopsy ≥0.5 g/24 h (n = 79) gave similar results, except that crescents lost significance (333).

Finally, Le et al. (334), in a study of 218 Chinese children meeting, found only S1 and T1/2 were significant predictors of poor outcome (greater than 50% reduction in eGFR or ESRD), whereas M1, E1, and crescents were not. Among pathologic parameters only T1/2 was an independent predictor of poor outcome in a multivariate analysis including clinical and pathologic parameters. However, it should be noted that patients in this study had the greatest frequency of treatment with immunosuppressive agents and blockers of the RAS among all of the pediatric studies, which may have influenced the findings, particularly with regard to the prognostic significance of the M and E scores.

In summary, validation studies of the Oxford Classification (see Table 12.13) have shown somewhat variable results, although in general, there was value of this histopathologic classification in predicting clinical outcomes and response to immunosuppressive therapy above that which could be determined by clinical parameters alone, in contrast to findings with previous histopathologic classification (63). Variability between the original Oxford study and the different validation studies might be accounted for by differences in patient populations, particularly fractions of patients with mild disease without glomerular hypercellularity (M0 and E0) and those with advanced disease (S1, T2), differences in the use of RAS inhibitors, and differences in study end points. Another difference between the original Oxford study and some of the validation studies involved the numbers of pathologists involved in scoring of the biopsies; this is particularly true with respect to grading of mesangial hypercellularity, which initially was a lesion in which there was considerable interobserver variability among the Oxford pathologists that had to be addressed using an initial circulation of test cases and a subsequent meeting of these pathologists at which sources of this variability were specifically addressed.

Some of the differences between studies appear to be instructive. Crescents, not a significant predictor of outcomes in the original Oxford cohort and other studies using the same entry criteria, mainly due to the fact that patients with rapidly progressive glomerulonephritis were excluded from these studies, may in fact have predictive value in patients with severe disease (eGFR less than 30 mL/min), and this deserves further study. Mesangial proliferative lesions may respond to RAS blockade with a decrease in time-averaged proteinuria (327), possibly accounting for the lack of association of M score with outcomes in cohorts in which most patients underwent treatment with ACEi/angiotensin receptor blockers (ARBs). In some studies, patients with mesangial hypercellularity were more likely to be treated with immunosuppressive therapy compared to the Oxford cohort, which may also explain failure to identify M1 as an independent predictor of ESRD. As such, pathologic variables that correlate with renal outcome in all clinical settings are still missing, the exception perhaps being the long recognized prognostic significance of the degree of TA and IF. Nevertheless, the Oxford Classification offers a

useful approach for predicting renal outcome and distinguishing between active and chronic lesions.

Segmental necrotizing lesions (see Figs. 12.33 and 12.34) in glomeruli are uncommon in IgA nephropathy, and for this reason, their clinical significance has not been extensively studied. Still, El Karoui et al. (326) did find a significant association between such lesions and the development of ESRD or doubling of serum creatinine by univariate (but not multivariate) analysis, and if not treated with immunosuppressive agents, these lesions may be associated with a greater probability of progression to ESRD (196).

Finally, routine immunofluorescence and electron microscopic findings appear to be of limited value with regard to predicting clinical outcomes in IgA nephropathy. Bellur et al. (337) examined the correlation of immunofluorescence findings with histologic findings and renal outcomes in the original Oxford study patient cohort. They found, consistent with some previous reports (127,149,150), that the presence of IgA deposits in glomerular capillary walls in addition to mesangial areas correlated with greater mesangial and endocapillary hypercellularity. In addition, the presence of IgG in addition to IgA was associated with more mesangial and endocapillary hypercellularity, consistent with some previous findings in human IgA nephropathy and an animal model of this disease (96,338,339). However, in the Oxford cohort, neither peripheral capillary IgA nor the presence of IgG was associated with a significantly greater rate of decline in eGFR, although patients with these immunofluorescence findings tended to receive more immunosuppression, and there was a trend toward worse renal survival in patients with glomerular IgG deposits (337). While some prior studies identified mesangial deposition of IgG as a risk factor for disease progression in human IgA nephropathy (96,339), this has not been found to be the case in the majority of studies (50,93,340). The same can be said of IgA deposition in glomerular capillary walls in addition to mesangial areas (see Table 12.10). Likewise, isolated studies have identified glomerular IgM deposition as a risk factor for progression (50,341), although this may be a nonspecific finding associated with segmental glomerulosclerosis (341) and has also been reported to be a nonspecific finding related to proteinuria (277), which is a known risk factor for progression of IgA nephropathy as discussed above. A decrease in the number of podocytes per glomerulus has been found to be correlated with the extent of glomerular sclerosis and impairment of GFR in patients with IgA nephropathy and may contribute to proteinuria and disease progression in these patients (342), although quantitation of podocyte number clearly cannot be routinely performed in renal biopsy evaluations.

Prognosis of IgA Nephropathy in Children Versus Adults

A limited number of studies have examined renal survival rates in children diagnosed with IgA nephropathy. The Southwest Pediatric Nephrology Study Group reported that of 80 children with IgA nephropathy followed for at least 4 years, 12 (15%) developed ESRD. Major risk factors for progression were similar to those noted in adults: glomerular sclerosis, proteinuria, and hypertension (161). A study of 103 pediatric IgA nephropathy patients from Kentucky and Tennessee showed an actuarial renal survival rate of 87% at 10 years and 70% at 20 years (59). Adults with IgA nephropathy in the same region of the United States had earlier been shown to have a 10-year renal survival rate of 78% (343). A Japanese study comparing outcomes in children and adults with IgA nephropathy found 10- and 20-year renal survival rates of 95% and 80%, respectively, in children versus 82% and 50%, respectively, in adults (162). The difference in renal survival between adults and children was attributed to less severe glomerular injury and a lower incidence of hypertension in the former (162). In the United States, a lower incidence of hypertension among IgA nephropathy patients has also been noted in children than in adults (343). In our renal biopsy series of IgA nephropathy patients from the Eastern and Midwestern United States, the frequency of minimal histologic lesions (Oxford M0 E0 S0 T0) was 24% in children versus 14% in adults and that of advanced sclerotic lesions (with greater than 40% globally sclerotic glomeruli and/or greater than 40% estimated TA/IF) was 3% in children versus 17% in adults (122). Mina and Murphy (119) likewise noted far less TA and IF in renal biopsies of children than of adults with IgA nephropathy. Overall, these findings suggest the possibility that IgA nephropathy is more often a mild disease in children than in adults. However, an alternative explanation for the apparently better outcomes of IgA nephropathy in children as compared with adults may be that children are simply diagnosed earlier in the course of their disease. In our series, renal survival in children was significantly better than in adults, even when excluding patients with minimal histologic and advanced sclerotic lesions. Furthermore, the difference in renal survival was independent from the fraction of globally sclerotic glomeruli and the estimated percent interstitial fibrosis (122). This suggests that IgA nephropathy may indeed be a more benign condition when diagnosed in childhood than in adulthood, although additional studies in patients with more complete clinical data sets (e.g., time-averaged proteinuria, rate of renal functional decline) are needed to confirm this.

IgA Nephropathy in Pregnancy

The effect of pregnancy on the course of IgA nephropathy appears to depend on the severity of renal disease at conception. Abe (344,345) and Jungers et al. (346) have observed that in most cases, pregnancy did not adversely affect the course of IgA nephropathy. However, in women with IgA nephropathy characterized clinically by hypertension and moderate renal insufficiency at conception, and histologically by moderate to severe diffuse proliferative glomerulonephritis with TA, IF, and arteriolosclerosis, pregnancy may indeed result in an accelerated course toward ESRD (344,346). Packham et al. (347) examined outcomes of 116 pregnancies in 70 women with IgA nephropathy and found that the presence of focal and segmental endocapillary proliferative lesions and crescents, but not focal and segmental glomerular sclerosis, correlated with poor maternal outcomes, the latter including deterioration of renal function, development of hypertension, and a persistent increase in proteinuria. Increased rates of fetal loss were not associated with active or sclerosing glomerular lesions but were significantly associated with the presence of severe vascular lesions (arterial fibrointimal hyperplasia, hyaline arteriolosclerosis) (347).

Treatment of Primary IgA Nephropathy

There is no cure for IgA nephropathy, and there is no consensus on its treatment (47,348–350). Still, there are a number of treatment options that have been shown to be effective in slowing and possibly arresting the progress of the disease in

different cohorts of patients with IgA nephropathy, including some with moderate or even severe disease. These treatments can be grouped into two general classes, although the effects of some agents may not be limited to one or the other of these: (a) those aimed at treating the glomerulonephritis itself, which include treatments aimed at preventing and suppressing glomerular inflammation, and (b) those aimed at reducing modifiable risk factors for disease progression, such as proteinuria and hypertension (47,351). The first of these classes includes corticosteroids, other immunosuppressive agents, cytotoxic agents, fish oil, and tonsillectomy. The second includes primarily ACE inhibitors and angiotensin receptor antagonists. These treatment options are summarized below, although for more complete information, the reader is referred to two recent reviews (262,352).

Corticosteroids and Other Immunosuppressive/ Cytotoxic Agents

Immunosuppressive agents, particularly corticosteroids, have long been used to treat patients with IgA nephropathy, although the strongest evidence for their efficacy comes from four randomized controlled trials in Italy, China, and the United Kingdom. The initial Italian study (353) examined the effect of a 6-month course of steroids alone (pulse methylprednisolone, 1 g/d for 3 days, at induction and at the start of months 2 and 4, plus alternate-day oral prednisone for 6 months) in patient with proteinuria of at least 1 g/d. RAS blockade was limited in this study. The steroid treatment reduced proteinuria and increased renal survival over a 10-year period (353). A more recent Italian study (354) and a Chinese study (355) each compared treatment with corticosteroids and RAS blockade with RAS blockade alone in patients with well-preserved renal function and proteinuria of more than 1 g/24 h despite treatment with an ACEi. In the Italian study, patients treated with a 6-month course of oral prednisolone were less likely to develop ESRD or a doubling of serum creatinine than those given an ACEi alone (354). The Chinese study reached a similar conclusion, with a significantly lower fraction of steroid-treated patients showing a doubling of serum creatinine (355). While these latter two studies have received some criticism based on possible suboptimal RAS blockade (262,356), a recent meta-analysis of steroid therapy in IgA nephropathy, including these two studies, concluded that steroids significantly reduced proteinuria and the risk of ESRD in IgA nephropathy (357). Furthermore, a recent summary (358) of nine controlled trials of corticosteroid trials in patients with IgA nephropathy with proteinuria of greater than1 g/d without elevated serum creatinine levels or reduced eGFR reached a similar conclusion; the nine studies included the Italian and Chinese trials noted above plus a number of smaller studies performed between 1986 and 2009. These authors also concluded that short-term, relatively high-dose steroid therapy was superior to low-dose, long-term steroid treatment in preserving renal function in proteinuric IgA nephropathy (358). However, it should be stressed that these studies did not address the potential benefit of steroid therapy in individuals with reduced renal function, even though these patients represent a major proportion of IgA nephropathy patients at risk for developing ESRD.

In the UK study, oral prednisolone, tapered over 2 years, was combined with a 3-month course of cyclophosphamide and azathioprine over the ensuing 21 months in patients with a serum creatinine level between 1.5 and 2.8 mg/dL; a significantly larger fraction of those patients treated with this immunosuppressive regimens showed good preservation of renal function over a 2- to 5-year follow-up period (359). However, a subsequent randomized controlled trial with a median follow-up interval of almost 5 years showed no benefit of addition of azathioprine to a 6-month high-dose corticosteroid regimen on preservation or renal function or proteinuria (360).

In two separate Japanese studies, repeat renal biopsies were performed following treatment of IgA nephropathy patients with diffuse mesangial proliferative glomerulonephritis with pulse methylprednisolone followed by oral prednisolone for 1 year with (65) or without (361) tonsillectomy. In both studies, the posttreatment biopsies showed a reduction in mesangial matrix compared with the pretreatment biopsies. The tonsillectomy study (65) also showed disappearance of crescents, which were present in 91% of the pretreatment biopsies, and a significant reduction in interstitial inflammation.

Another study suggests that combination therapy with corticosteroids and cyclophosphamide may be effective in slowing the progression of severe, crescentic IgA nephropathy. Repeat biopsies performed after 6 months of therapy showed a significant decrease in active histologic lesions (mesangial and endocapillary hypercellularity, crescents, necrosis, and interstitial inflammation) with no significant increase in chronicity (glomerular sclerosis, tubular atrophy, interstitial fibrosis), with a stable mean serum creatinine and reduction in proteinuria 2.5 years later (362,363). However, crescentic IgA nephropathy still appears to be less responsive to treatment with corticosteroids and cyclophosphamide than is ANCA-associated crescentic glomerulonephritis (195).

A number of small case series suggested that mycophenolate mofetil (MMF) might be an effective agent for treating primary IgA nephropathy (364–366). However, in a 3-year prospective, placebo-controlled, and randomized study of 34 adults with IgA nephropathy and moderate to severe renal insufficiency, proteinuria of at least 1 g/d, and/or hypertension, no significant differences were seen in the rate of change of serum creatinine, proteinuria, or other markers of renal function between patients treated with MMF and an ACEi versus those treated with an ACEi alone (367). A meta-analysis of four studies also suggested no significant effect of MMF on proteinuria (368). Still, a recent study of 40 Chinese patients with mild histologic lesions did show a positive effect of MMF in reducing progression to an end point of ESRD or doubling of serum creatinine (369). Clearly, additional randomized controlled trials of MMF are needed to assess its potential benefit in those IgA nephropathy patients most at risk for disease progression, namely those with persistent proteinuria despite RAS blockade and histologic lesions associated with renal functional decline (261).

Cruzado et al. (370) recently reported a randomized controlled trial of sirolimus in 23 patients with high-risk IgA nephropathy (GFR 30 to 60 mL/min and/or proteinuria greater than 1 g/d); all patients were treated with a statin and an ACEi. Twenty of the patients underwent protocol renal biopsies 1 year after the original biopsy. After 1 year of treatment, patients receiving sirolimus had a significantly higher mean GFR compared to control patients treated with only the statin and ACEi. Sirolimus-treated patients, but not controls, also showed improvement in mean M and E scores on

the 1-year protocol biopsies compared to scores on baseline biopsies (370). The findings of this study indicate that further investigation into the efficacy of sirolimus is warranted and also suggest a role for follow-up biopsies graded using the Oxford Classification in clinical drug trials in IgA nephropathy.

Fish Oil

Fish oil preparations, rich in long chain, omega-3 polyunsaturated fatty acids, have emerged as a somewhat controversial treatment for IgA nephropathy. Donadio et al. (371,372) at the Mayo Clinic have provided the strongest evidence that treatment with fish oil for a minimum of 2 years significantly slows the rate of decline in renal function and the risk of developing ESRD in IgA nephropathy patients with proteinuria greater than 1 g/d and renal insufficiency (serum creatinine 1.5 to 3.0 mg/dL). Many potential mechanisms for this effect have been postulated, including reduction of blood pressure, suppression of various immunologic and inflammatory responses, and inhibition of mesangial cell proliferation (reviewed in Ref. (373)). Other studies, however, have failed to demonstrate a significant effect of fish oil on renal function in patients with IgA nephropathy (374,375), and a meta-analysis of five reported trials of fish oil in IgA nephropathy concluded that there was a 75% probability that fish oil was beneficial, although the mean effect when all results were combined was not statistically significant (376).

Tonsillectomy

Tonsillectomy is a popular practice in Japan for patients with IgA nephropathy, especially those who have episodes of macroscopic hematuria associated with bouts of recurrent tonsillitis (47,350,377). The rationale for tonsillectomy is not entirely clear, although it is presumably based on removal of potential antigenic stimuli and reduction in circulating levels of IgA1 and IgA1-containing immune complexes (351,378). There is also some evidence that IgA (but not IgG or IgM) antibodies against *H. parainfluenzae*, a common bacterium on the tonsils, and/or immune complexes comprising such antibodies and *H. parainfluenzae* outer membrane antigens, may play a role in the pathogenesis of some cases of IgA nephropathy and IgA vasculitis (HSP nephritis) (378–381). One recent retrospective study reported that tonsillectomy significantly improved long-term renal survival in patients with IgA nephropathy (382); however, several other similar studies have not found such a benefit of tonsillectomy (351,383), and to date, there have not been prospective, controlled studies of the effect of tonsillectomy on the progression of IgA nephropathy. A recent meta-analysis showed that while tonsillectomy alone did not improve outcomes in IgA nephropathy, there may be a benefit of tonsillectomy when this is combined with steroid therapy (384). Still, in the absence of a randomized controlled trial, it is currently recommended that tonsillectomy be reserved only for those IgA nephropathy patients with episodes of macroscopic hematuria associated with recurrent tonsillitis (350).

ACE Inhibitors and Angiotensin Receptor Antagonists

Randomized, controlled trials have found that administration of ACEi and/or ARBs to control blood pressure and reduce proteinuria are beneficial in slowing the rate of renal functional decline in both adults and children with IgA nephropathy, proteinuria of at least 0.5 g/d and preserved renal function at the time of diagnosis (385–387). A retrospective study of IgA nephropathy patients with hypertension and proteinuria of at least 1 g/d found that ACEi therapy was superior to other antihypertensive agents in stabilizing renal function and reducing proteinuria (388).

In one study, the effects of losartan (ARB) and enalapril (ACEi) in reducing proteinuria in IgA nephropathy patients with initial proteinuria of greater than 1 g/d were additive (389), raising the possibility that dual therapy with an ACEi and an ARB may be superior to monotherapy for patients with IgA nephropathy and significant proteinuria. However, there are some safety concerns with this dual therapy, and an added benefit of dual therapy (compared with ACEi or ARB alone) on preservation of renal function has not yet been demonstrated (262,390). Because ACE inhibitors and ARBs do not have direct immunosuppressive or anti-inflammatory effects, it is also likely that these drugs may provide added benefit to patients with active IgA nephropathy receiving corticosteroids and/or other immunosuppressive agents, as noted above.

Renal Transplantation in Patients With IgA Nephropathy

Recurrence of IgA nephropathy in the renal allograft was initially documented in a single patient by Berger (2). Berger et al. (391) later reported glomerular deposits of IgA in 7 of 12 renal allografts from patients whose original renal disease was IgA nephropathy. Each of the seven patients had or later developed microscopic hematuria and the majority also developed mild proteinuria, although no graft losses due to recurrent IgA nephropathy were seen. Subsequent studies, summarized in Table 12.14, have documented that recurrence of IgA nephropathy in renal allografts is rather common, developing in 28% of the 840 patients pooled from the 14 studies represented in this table, in which immunofluorescence studies for immunoglobulins were performed on all renal allograft biopsies. The rate of recurrence is noted to vary considerably between different studies. This is because of different criteria for performing a renal allograft biopsy in the different studies and different criteria used to define a recurrence of IgA nephropathy. For example, in the studies of Freese et al. (394) and Choy et al. (397), in which biopsies were only performed in patients with graft dysfunction, proteinuria of $\geq$1 g/d or macroscopic hematuria (in the latter study only), and in which mesangial cell proliferation plus predominant mesangial deposits of IgA were required for a diagnosis of recurrent IgA nephropathy, the recurrence rates were less than 20%. By contrast, higher recurrence rates were reported in studies with more liberal biopsy policies (e.g., microscopic hematuria included as an indication for biopsy) and in which mesangial IgA deposits alone were accepted as criteria for recurrent IgA nephropathy. How different diagnostic criteria can affect reported recurrence rates is illustrated by the study of Kessler et al. (404), in which 13 of 28 (46%) patients had renal allograft biopsies showing mesangial IgA deposits, but only 9 (32%) had glomerular abnormalities by light microscopy in addition to the IgA deposits. Finally, in a review of 12 studies comprising 659 graft recipients with an original renal disease of IgA nephropathy, Choy et al. (405) found a significantly higher rate of recurrent disease in grafts from related donors (90/302; 29.8%) versus those from unrelated donors (81/362; 22.7%), although diagnostic criteria for recurrent IgA nephropathy varied between the different studies included in this analysis.

TABLE 12.14 Renal transplantation in patients with ESRD due to IgA nephropathy: incidence of recurrence and of graft loss due to recurrence

Reference	Recurrence rate	Time posttransplant to recurrence	Graft loss due to recurrence	Time posttransplant to graft loss
Briganti et al. (392)	—	—	15/532 (2.8%)	—
Ponticelli et al. (393)	37/106 (34.9%)	33 mo (median)	4/106 (3.8%)	52 mo (median)
Freese et al. (394)	13/104 (12.5%)	—	6/104 (5.8%)	—
Jeong et al. (395)	40/90 (44.4%)	By 10 y	4/90 (4.4%)	—
Andresdottir et al. (396)	17/79 (21.5%)	13–145 mo	1/79 (1.3%)	—
Choy et al. (397)	14/75 (18.6%)	67 mo (mean)	3/75 (4.0%)	142 mo (mean)
Courtney et al. (398)	13/75 (17.3%)	—	7/75 (9.3%)	
Ohmacht et al. (399)	20/61 (32.8%)	—	10/61 (16.3%)	32–102 mo
Bumgardner et al. (400)	18/61 (29.5%)	31 mo (mean)	6/61 (9.8%)	63 mo (mean)
Frohnert et al. (401)	14/53 (26.4%)	—	3/53 (5.7%)	—
Wang et al. (402)	14/48 (29.2%)	52 mo (median)	4/48 (8.3%)	60–120 mo
Soler et al. (403)	6/31 (19.4%)	46 mo (mean)	3/31 (9.7%)	52–96 mo
Odum et al. (236)	17/29 (58.6%)	46 mo (mean)	1/29 (3.4%)	74 mo
Kessler et al. (404)	13/28 (46.4%)	68 mo (mean)	4/28 (14.3%)	69–119 mo
Pooled Data	**236/840 (28.1%)**		**71/1375 (5.2%)**	

While recurrence of IgA nephropathy in renal allografts is relatively common, in the great majority of cases, this does not result in graft loss, and 10-year renal allograft survival in patients whose original renal disease was IgA nephropathy is not significantly different from that in pooled populations of patients with other causes of renal failure (393,397). Furthermore, in a multivariate analysis, recurrent IgA nephropathy defined by the presence of mesangial IgA deposits was not found to be a significant risk factor for graft loss (393,404). Still, recurrent IgA nephropathy is not as benign as once thought and clearly can cause late graft loss. For grafts surviving greater than 12 years, the rate of graft loss in IgA nephropathy patients was found to exceed that in a pooled population of patients with other causes of renal failure (397). To date, there are no known pretransplant clinical parameters or histologic features on native kidney biopsy that predict a poor outcome in IgA nephropathy patients undergoing a renal transplant (394). Despite the higher recurrence rate of IgA nephropathy in grafts from related donors (see above), Choy et al. (405) found similar rates of graft loss due to recurrent disease in recipients of grafts from related (5.5%) and unrelated donors (5.0%). However, a number of posttransplant factors, including proteinuria of ≥1 g/d and the presence of crescents on a renal transplant biopsy with mesangial IgA deposits, have been found to be associated with reduced graft survival in these patients (393,406–408). Graft loss due to recurrent IgA nephropathy during the first year posttransplantation, while very rare overall, may occur when crescents are present on the allograft biopsy (407,408). Data from two retrospective studies suggest that RAS blockade using an ACEi or ARB may slow the rate of decline of graft function and reduce graft loss due to recurrent disease in patients with recurrent IgA nephropathy (398,409), although this needs to be confirmed, preferably in a controlled, prospective study. A study of registry data from Australia and New Zealand suggested that immunosuppressive protocols involving withdrawal of corticosteroids are likely to be associated with a higher rate of recurrent IgA nephropathy (410).

As noted earlier, glomerular IgA deposits have been noted in a significant fraction of kidneys from healthy organ donors (e.g., 16% in one Japanese study (186)). While it has been noted that such deposits are resorbed and disappear, as early as within 2 weeks of transplantation (411), in one Japanese study (412), the presence of IgA deposits in the donor kidney was found to be a significant risk factor for the development of recurrent IgA nephropathy and graft loss due to recurrent disease, although the numbers of patients in this study were small (49 total, 13 [26.5%] with recurrent disease). Whether bound IgA in a donor kidney indicates an organ that is more likely to develop clinical disease when transplanted into a recipient with IgA nephropathy is an important question, and investigation of this may also provide some additional insight into glomerular factors associated with disease progression.

FAMILIAL IgA NEPHROPATHY

The first documentation of familial cases of biopsy-proven IgA nephropathy was in two HLA-identical brothers of Lebanese origin, in 1978 (292). The younger brother developed ESRD and received a kidney transplant from his brother who had normal renal function. A perioperative biopsy of the donor kidney showed minimal histologic abnormalities; however, immunofluorescence showed granular mesangial deposits of IgA and C3. The recipient did well posttransplant and had no hematuria or proteinuria after 1 year (292).

Subsequent to this, a review of IgA nephropathy patients reported to the MRC (United Kingdom) glomerulonephritis registry revealed that 3.8% of these patients had a family history of renal disease (413). Julian et al. (414) reported 14 individuals of potentially related pedigrees, the majority born in central and eastern Kentucky, with biopsy-proven IgA nephropathy; six of the patients shared a common ancestor. Furthermore, there was no evidence that a shared environmental factor or a high degree of inbreeding accounted for this familial clustering of IgA nephropathy (414).

More recently, familial clustering of individuals with IgA nephropathy has been reported in a population of Australian Aborigines (415) and in Caucasian populations from northern (416) and southern (417) Italy. In these Italian studies, individuals with a family history of IgA nephropathy comprised 14% and 51%, respectively, of the total number of cases of IgA nephropathy at the centers involved, indicating that in some regions of the world, cases of familial IgA nephropathy are likely to comprise a substantial fraction of the total number of cases of IgA nephropathy.

As discussed above (see Genetic Factors and the Role of the Renin-Angiotensin System), a number of different genetic loci have been identified that appear to confer increased or decreased susceptibility to developing IgA nephropathy. One of these, on chromosome 6q22-23, was linked to 30 IgA nephropathy kindreds, 24 from Italy and 6 from the United States (418), although other Italian IgA nephropathy families did not show linkage to this locus (419), indicating that familial IgA nephropathy is genetically heterogeneous.

Schena et al. (416) compared clinical presentation, renal biopsy findings, and renal survival rates in 39 patients with familial IgA nephropathy (from 19 families, familial defined as having ≥2 family members with biopsy-proven IgA nephropathy) with those in 25 patients with sporadic IgA nephropathy from the same region of Italy. No significant differences between the two groups of patients were found in age of onset, male:female ratio, mean creatinine clearance, level of proteinuria, or frequency of hypertension at the time of the diagnostic renal biopsy, and no significant differences were found in the severity of histologic findings on the biopsies. However, 15-year renal survival from the time of the biopsy was only 36% in patients with familial IgA nephropathy compared with 92% in those with sporadic IgA nephropathy. Among patients with familial disease, those with familial involvement limited to a single generation (suggestive of autosomal recessive inheritance) had a significantly poorer outcome than those with involvement of two or more generations (suggestive of autosomal dominant inheritance) (416). However, a much larger subsequent study, also from Italy, failed to confirm that familial IgA nephropathy has a worse prognosis than the sporadic form (420). The different findings in these studies may reflect the genetic heterogeneity of familial IgA nephropathy, the small sample size in the original study, and/or possibly earlier detection of familial forms of the disease in this study.

SECONDARY IgA NEPHROPATHY

A large number of conditions have been reported to be associated with the development of glomerular IgA deposits, with associated glomerular histologic changes and clinical manifestations such as hematuria and proteinuria. Most of these are listed in Table 12.15, which classifies these conditions into categories of diseases and provides literature references for each. Of those conditions listed, by far that most commonly associated with IgA nephropathy is cirrhosis of the liver, whether resulting from ethanol abuse, viral hepatitis, toxic injury, biliary disease, or other causes (421). Of the remaining classes of illnesses, the most common associations with IgA nephropathy are seen with inflammatory lesions of secretory mucosae, most notably those of the gastrointestinal (GI) tract, and various forms of inflammatory arthritis (Table 12.15). It is also notable that IgA nephropathy is one of a number of immune complex–related glomerular lesions that can be seen in patients infected with HIV (178,461–467).

TABLE 12.15 Conditions associated with secondary IgA nephropathy

Hepatobiliary diseases
Cirrhosis secondary to
- Alcoholic liver disease (421–430)
- Viral hepatitis (423,424,430)
- Toxic liver disease (431)
- Biliary cirrhosis/biliary atresia (430,432–434)
- Cystic fibrosis (434,435)

Noncirrhotic portal hypertension (436)
Interleukin-2 therapy for hepatocellular carcinoma (437)

Gastrointestinal diseases
Celiac disease (438–440)
Crohn disease (441–443)
Ulcerative colitis (444,445)

Rheumatologic diseases
Ankylosing spondylitis (446–452)
Rheumatoid arthritis (453–455)
Psoriatic arthritis (451,452,456)
Reiter syndrome (451,452,456)
Behcet disease (457–460)

Infectious diseases
Human immunodeficiency virus (178,461–467)
Yersinia enterocolitica (468,469)
Campylobacter jejuni (470)
Clostridium difficile (471)
Mycoplasma pneumoniae (472)
Tuberculosis (473–475)
Brucellosis (476,477)
Leprosy (478)

Neoplastic and myeloproliferative diseases
Renal cell carcinoma (479–481)
Non-Hodgkins lymphomas (482)
Mycosis fungoides/Sézary syndrome (483,484)
Various carcinomas including squamous cell, bronchial small cell, and adenocarcinomas (485–487)
Mixed cryoglobulinemia (488,489)
Polycythemia vera (490,491)

Ophthalmologic diseases
Scleritis (492)
Uveitis with retinal vasculitis (493)

Dermatologic diseases
Dermatitis herpetiformis (494)
Psoriasis (495,496)

Miscellaneous pulmonary/systemic diseases
Sarcoidosis (497–500)
Silicosis (501)
Bronchiolitis obliterans (502)

IgA Nephropathy in Hepatobiliary Disease

Pathology

Berger et al. (422) examined renal tissue from 100 autopsies of patients with cirrhosis of the liver, 90 with alcoholic cirrhosis. They found granular mesangial deposits of IgA in 61 cases. Nakamoto et al. (429) similarly found glomerular IgA deposits in the kidneys from 28 of 43 (65%) cirrhotics, mostly at autopsy, although a small number of renal biopsies were included, and Kawaguchi and Koike (430) found glomerular IgA at autopsy in 17 of 30 (57%) individuals with cirrhosis of varying etiologies. Eight additional autopsy series reviewed by Newell (428) showed glomerular abnormalities by light microscopy, immunofluorescence, and/or EM in 25% to 100% of cases and in 50% to 68% of cases in those series in which all three diagnostic modalities were employed. The IgA deposits seen in the glomeruli of cirrhotics are predominantly mesangial, with some but not all cases also showing deposits in peripheral capillary loops that are typically segmental (422,429,503,504). As in primary IgA nephropathy, the glomerular deposits of IgA are frequently accompanied by deposits of IgG and/or IgM that are of lesser intensity than those of IgA (127,422,430,503,504) and, in some cases, by mesangial deposition of fibrinogen (429,504). Likewise, C3 is present in the majority of cases, although Nakamoto et al. (429), Callard et al. (503), and Kawaguchi and Koike (430) noted an absence of C3 in 18%, 30%, and 47% of cases, respectively, of cirrhosis-associated IgA nephropathy, which are clearly higher percentages than are noted in primary IgA nephropathy (see Table 12.7). Kawaguchi and Koike (430) and Woodroffe et al. (126) noted glomerular staining for C1q in 12 of 17 (71%) and 5 of 10 cases (50%) of cirrhosis-associated IgA nephropathy, respectively; by contrast, the latter investigators noted C1q deposition in only 11 of 78 (14%) cases of primary IgA nephropathy (126).

There are no specific histologic features that differentiate primary versus secondary forms of IgA nephropathy. As with primary IgA nephropathy, the histologic appearance of cirrhosis-associated IgA nephropathy is quite variable, ranging from histologically normal to diffuse proliferative glomerulonephritis. In the majority of cases, the histologic changes in cirrhosis-associated IgA nephropathy are mild, consisting of mild to moderate mesangial matrix expansion with or without accompanying mesangial hypercellularity or less commonly normal histology (422,429,430,503,504). A minority of cases show diffuse proliferative glomerulonephritis with a pattern resembling type I MPGN, with mesangial interposition and double contours of the glomerular basement membrane apparent on periodic acid-Schiff (PAS) and silver stains (Fig. 12.36). While relatively uncommon in autopsy-based series, these MPGN-like lesions are more frequently observed in biopsy-based series in which patients have sufficiently severe urinary abnormalities and/or renal insufficiency to warrant a renal biopsy. For example, in the study of Berger et al. (422), only 2 of 61 cirrhotics whose kidneys showed glomerular IgA deposits at autopsy had MPGN-like glomerular histology, whereas 5 of 11 cirrhotics undergoing a renal biopsy had such histologic changes, all with IgA as the predominant immunoglobulin present. In another biopsy series, 8 of 22 (36%) cirrhotics showed MPGN-type lesions, with IgA present in all but one of these (504). Crescentic glomerulonephritis is a very rare manifestation of cirrhosis-associated IgA nephropathy (429).

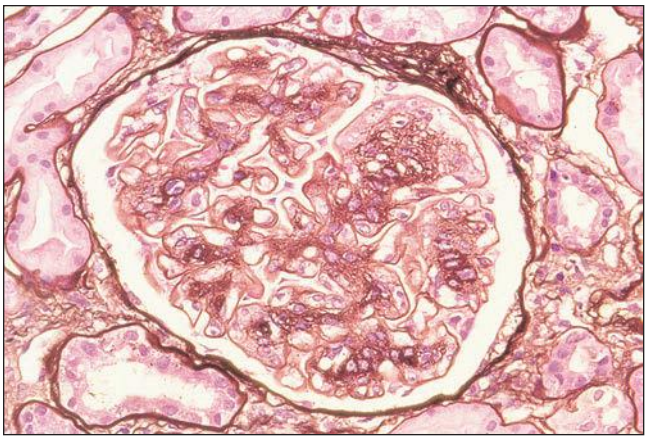

FIGURE 12.36 IgA nephropathy in a patient with cirrhosis of the liver. The glomerular histopathology resembles that of type I MPGN, with multiple double contours of the glomerular basement membrane. (Jones methenamine silver stain, ×400.)

EM shows the presence of electron-dense deposits in locations within the glomerulus corresponding to the IgA deposits seen by immunofluorescence, mainly in the mesangial areas. Subendothelial deposits are seen in some cases, particularly those with MPGN-like histology (503). Callard et al. (503) and Nochy et al. (504) noted an unusual change within some of the deposits in cirrhosis-associated IgA nephropathy, consisting of lucent areas 50 to 110 nm in diameter, not bound by a membrane, either isolated or in clusters. In addition, some of these lucent areas contained irregular aggregates of material of electron density that was equal to or greater than that of the main body of the immune complex deposit. These structures were noted within the mesangial matrix and/or glomerular basement membrane adjacent to the deposits, as well as within the deposits themselves (503), as illustrated in Figure 12.37. What these structures represent remains unclear; their appearance is not typical for immune complex deposits simply undergoing resorption, although in one such case, we have seen (Fig. 12.38) the large mesangial deposits present did show alternating zones of varying electron density, suggesting early resorption.

Clinical Presentation and Outcome

Secondary IgA nephropathy in the setting of cirrhosis is often an incidental finding discovered at autopsy and as such many if not most cases are subclinical. In their autopsy series, Kawaguchi and Koike (430) noted a history of persistent microscopic hematuria or moderate proteinuria in only 3 of 28 cirrhotics, not including 2 with underlying diabetic nephropathy, despite the fact that 23 of the 28 cases showed at least mild histologic changes (mesangial proliferation) and 16 showed glomerular IgA deposits. Among 249 consecutive patients with cirrhosis, Nakamoto et al. (429) found nephritic urinary changes (defined as hematuria with greater than 5 RBCs/high-power field, RBC casts, and/or significant cellular and granular casts) in 9.2% and proteinuria of greater than 3.5 g/d in 1.6%. They also noted a 25% incidence of these urinary abnormalities in those cirrhotics with histologically documented glomerular lesions (with glomerular IgA in 65% and dominant

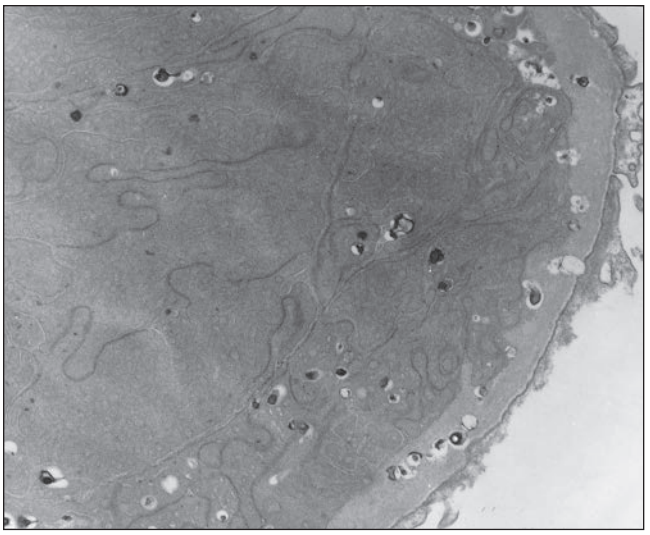

FIGURE 12.37 IgA nephropathy in a patient with cirrhosis of the liver. Electron micrograph shows areas of electron lucency within a large mesangial immune complex deposit and the adjacent basement membrane; contained within many of these areas are aggregates of highly electron-dense material. The curved lines and alternating zones of varying electron density within the deposit suggest early resorption. (Uranyl acetate and lead citrate, original magnification ×5000.)

glomerular IgA deposits in 54%), particularly mesangial cell proliferation (as opposed to just an increase in matrix), mesangial interposition, and segmental sclerosis (429). A similar correlation between urinary symptoms and glomerular histology was noted by Berger et al. (422) in an autopsy-based series and by Nochy et al. (504) in a series of cirrhotics undergoing renal biopsies. Not surprisingly, all of the patients in the latter series had some degree of proteinuria, although this was less than 1 g/d in the majority of cases. The majority of patients with MPGN-like histology had nephrotic-range proteinuria,

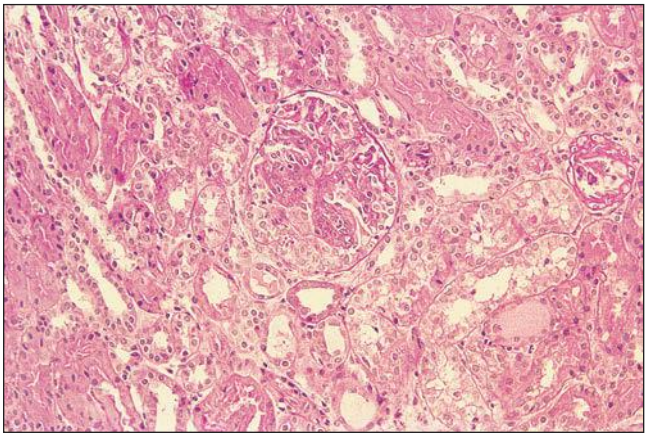

FIGURE 12.38 Acute IgA vasculitis (HSP) nephritis in a 4-year-old child. The glomerulus in the center of the field shows segmental endocapillary cell proliferation and a segmental cellular crescent. A sclerotic glomerulus (possibly an atrophic immature glomerulus) is present at the far right; however, there is minimal TA or IF. (PAS, ×200.)

and all but one had renal insufficiency, whereas in patients with purely mesangial lesions, nephrotic-range proteinuria was observed in less than 10% of cases and renal insufficiency in 40% (504). There is no consistent evidence that the severity of the renal disease is correlated with the severity of the liver disease (421,428), although there is one reported case where surgical correction of portal hypertension resulted in remission of nephrotic-range proteinuria in a patient with noncirrhotic liver disease and secondary IgA nephropathy (436). Even in renal biopsy series, progression to ESRD among patients with cirrhosis-associated IgA nephropathy is quite uncommon (504), an apparent contrast with primary IgA nephropathy, although a direct comparison of renal outcomes in primary versus cirrhosis-associated IgA nephropathy has not been done. Another feature of cirrhosis-associated IgA nephropathy that apparently differs from primary IgA nephropathy is the incidence of hematuria. While microscopic hematuria is present in the vast majority of patients with primary IgA nephropathy and one or more episodes of macroscopic hematuria can be documented in approximately 40% (see Table 12.5), it is not unusual for patients with cirrhosis-associated IgA nephropathy not to have microscopic hematuria (429,503,504), and macroscopic hematuria is uncommon (421,430). Finally, in a preliminary study, patterns of proteinuria in primary IgA nephropathy were found to be different than those in cirrhosis-associated IgA nephropathy by protein electrophoresis and Western blotting (505).

Pathogenesis

While there have not been direct studies of the mechanism of mesangial IgA deposition in cirrhosis-associated IgA nephropathy, the mesangial IgA deposits in this condition, like those in primary IgA nephropathy, have been shown to be composed primarily of IgA1 (135,430). In addition, in most cases, J chain is present and secretory component is absent, indicating the presence of pIgA within the deposits (135,430). However, how the IgA1 in cirrhosis-associated IgA nephropathy compares to that in primary IgA nephropathy with respect to a number of properties including glycosylation of the hinge region remains to be determined.

The mesangial deposition of IgA in cirrhotics may simply reflect an overabundance of circulating IgA immune complexes. Most patients with cirrhosis and cirrhosis-associated IgA nephropathy have elevated serum pIgA levels and circulating, IgA-containing immune complexes (127,506). This may result from a number of factors, including increased IgA production and impaired hepatic removal of pIgA and of IgA immune complexes from the circulation (421,506,507). Animal models in which rats were rendered cirrhotic by exposure to carbon tetrachloride (508) or being fed a lipotrope-deficient (LD) diet plus whiskey (426) resulted in most of these animals developing hematuria, proteinuria, and glomerular deposits of IgA, IgG, and C3. As with many humans with cirrhosis, these animals developed an increase in serum IgA levels, including the presence of IgA antibodies specific for dietary antigens such as ovalbumin, casein, and gliadin in animals fed an LD diet and whiskey (426,508). It is possible that a number of factors acting in concert, including impaired hepatic clearance of IgA and IgA immune complexes, polyclonal B-cell activation with enhanced IgA secretion, and increased intestinal permeability to macromolecules, contribute to the development of

secondary IgA nephropathy (426), although clearly much additional work is needed to elucidate the underlying pathogenic mechanisms.

IgA Nephropathy in HIV Infection

Combining data from six series (178,463–467), IgA nephropathy comprises 12% (15/123) of cases of immune complex–mediated glomerular lesions in HIV-infected patients. Like primary IgA nephropathy, IgA nephropathy associated with HIV infection appears to be uncommon in patients of black race (178,463). In four patients studied by Katz et al. (461) and another by Kimmel et al. (462), IgA antibodies directed against one or more HIV viral proteins were detected in sera from each patient. Furthermore, in their patient with HIV-associated IgA nephropathy, Kimmel et al. (462) demonstrated the presence of circulating immune complexes composed of IgA complexed with HIV p24 antigen, and both this antigen and IgA antibody reactive with it were eluted from this patient's renal biopsy tissue. It is also of interest that a number of studies have demonstrated circulating IgA immune complexes in a substantial fraction of patients with the acquired immune deficiency syndrome (509–511) and that in one of these studies, the IgA in the immune complexes was restricted to the IgA1 subclass (511).

IgA VASCULITIS (HENOCH-SCHÖNLEIN PURPURA) NEPHRITIS

The condition that became known as HSP appears to have first been described by Heberden in 1801 (9), when he reported a 5-year-old boy with a purpuric rash, abdominal pain, melena, joint pain, and hematuria. In 1837, Schönlein (10) described the association of arthralgia and purpura, and later Henoch, a former student of Schönlein, reported the association of GI and renal involvement in this disease (512,513). Schönlein and Henoch were pediatricians, and all of their patients were children. Sir William Osler and other internists observed identical signs and symptoms in adults, and until underlying immunopathologic differences were discovered, this syndrome could not be separated into multiple different forms of small vessel vasculitis. Most of Osler's patients probably had microscopic polyangiitis rather than IgA vasculitis. Osler (514) postulated that the disease was caused by an anaphylactic reaction, and "anaphylactoid purpura" (515) was commonly used as a name for this syndrome throughout the first half of the 1900s and is still occasionally used today, although it is now well established that the pathogenesis of neither IgA vasculitis (HSP) nor microscopic polyangiitis involves an anaphylactic reaction (516). As noted in the Introduction of this chapter, Baart de la Faille-Kuyper et al. (8) demonstrated mesangial deposits of IgA in renal biopsies of patients with IgAV (HSP) nephritis several years after the original description of similar deposits in IgA nephropathy by Berger and Hinglais (1). IgA vasculitis (HSP) is now classified as a form of systemic vasculitis with IgA1-dominant immune deposits, affecting small vessels (predominantly capillaries, venules, or arterioles) that often involves the skin and GI tract, and frequently causes arthritis and glomerulonephritis that is indistinguishable from IgA nephropathy (11,20). However, most of the literature to date that will be referenced used only clinical features to make a diagnosis of IgAV (HSP). The two major justifications for the change in the name from HSP to IgA vasculitis are, first, to recognize the distinctive feature if not pathogenic significance of IgA deposits in vessel walls and, second, to clarify that the syndrome of purpura, abdominal pain, arthralgias, nephritis, and other features of small vessel vasculitis do not allow distinguishing among many different forms of vasculitis that have very different etiologies, pathogenesis, prognoses, and appropriate treatments (11). As discussed later, there soon may be serologic markers (e.g., abnormally glycosylated IgA1) that may facilitate diagnosis of IgA vasculitis, similar to the availability of ANCA, anti-GBM, and cryoglobulins as markers for other forms of small vessel vasculitis.

Clinical Presentation of IgA Vasculitis (Henoch-Schönlein Purpura)

IgAV (HSP) may occur at any age, but is primarily a disease of children, with the majority of affected children presenting before the age of 10. In both children and adults, males are affected more often than females, with a male:female ratio between 1.3:1 and 2.3:1 (516–519). As with IgA nephropathy (see Table 12.3), IgAV (HSP) has been reported to be less common in African Americans than in Caucasians (37,518). The majority of cases of IgAV (HSP) arise during the winter and fall months, and the onset of symptoms often occurs during or shortly after an upper respiratory infection, particularly in children and adults under the age of 30 (121,517–519).

Table 12.16 lists the clinical features in 100 children (ages 1 to 15 years, median age 5.5 years) with IgAV (HSP) reported by Saulsbury (516). Only the nonthrombocytopenic purpura was present in all 100 children, although 98 also had arthritis, GI symptoms (abdominal pain, with or without GI bleeding), and/or nephritis. The purpuric lesions were concentrated

TABLE 12.16 Clinical features of 100 children with IgA vasculitis (Henoch-Schönlein purpura)

	Percent of patients
Purpura (nonthrombocytopenic)	100
Arthritis	82
Lower extremities only	52
Lower and upper extremities	30
Abdominal pain	63
Nephritis	40
Hematuria (macro- or microscopic)	40
Macroscopic hematuria	7
Proteinuria	25
Nephrotic syndrome	3
Gastrointestinal bleeding	33
Occult bleeding (guaiac-positive stools)	23
Gross bleeding (bloody stools, melena)	10
Orchitis	5 (9% of boys)
Seizures	2
Duodenal obstruction	1
Recurrence of symptoms	33

Modified from Saulsbury FT. Henoch-Schönlein purpura in children: report of 100 patients and review of the literature. *Medicine* 1999;78:395–408.

on the lower extremities and buttocks (516), although such lesions may be seen on the arms, face, and ears, mainly in children under the age of 2 (516,518,520,521). Arthritis, the second most common manifestation of IgAV (HSP), routinely involves joints of the lower extremities (knees, ankles, feet) and involves the upper extremities in approximately one third of the cases (516,518). GI involvement, manifest as colicky abdominal pain, vomiting, and occult or overt GI bleeding, occurs in 50% to 75% of cases (516,518). Any portion of the bowel may be involved, the jejunum and ileum most commonly. Potentially serious complications of GI involvement in IgAV (HSP), while uncommon, include bowel infarction, perforation, and intussusception (516,518). Arthritis and/or GI symptoms often precede the purpuric rash of IgAV (HSP) by up to 2 weeks (516). These symptoms represent an acute illness and, in the majority of cases, resolve within 8 weeks, although recurrences are not uncommon. Most recurrences occur within 4 months of the original illness and tend to be milder and of shorter duration (516).

The American College of Rheumatology criteria for diagnosis of IgAV (HSP) require the presence of at least two of the following: age ≤20 years at disease onset, palpable purpura, acute abdominal pain, biopsy showing histologic changes of leukocytoclastic vasculitis involving small arterioles/venules (522). The sensitivity and specificity of these criteria are 87.1% and 87.7%, respectively (522,523); however, at the time this calculation was made, microscopic polyangiitis was not included in the study as a specific variant of vasculitis, and IgA vascular deposits were not considered a defining feature of HSP. More recently, the Pediatric Rheumatology European Society (PRES), European League Against Rheumatism (EULAR), and Pediatric Rheumatology International Trials Organization (PRINTO) proposed and validated an updated set of criteria for IgAV (HSP) diagnosis with improved sensitivity (100%) without loss of specificity (87%). These criteria include the presence of purpura or petechiae with the lower limb predominance (mandatory) plus at least one of the following: abdominal pain, histopathologic changes or glomerulonephritis with predominant IgA deposits, arthritis or arthragia, renal involvement as evidenced by hematuria and/or proteinuria (523).

The manifestation of IgAV (HSP) that may become chronic and ultimately results in the greatest morbidity is nephritis. In the series shown in Table 12.16, 40% of children developed nephritis, manifest clinically as hematuria with or without accompanying proteinuria, within 9 weeks of the onset of other symptoms (516). While the great majority of cases of IgAV (HSP) nephritis will become manifest within such a time frame, delays in the onset of nephritis of between 3 months and 5 years have been reported (121,516,524,525). Only very rarely does nephritis precede all other symptoms of IgAV (HSP) (516,519).

The reported incidence of renal involvement in patients with IgAV (HSP) varies considerably between different studies, in part because of different criteria used to define renal involvement (e.g., microscopic hematuria alone vs. microscopic hematuria with proteinuria or hypertension; the number of red blood cells required to define hematuria on urinalysis) and variability in the length of follow-up after the onset of the acute illness. In different series, the incidence of renal involvement (defined by the presence of hematuria) in children with IgAV (HSP) is 20% to 56% (overall 34%), whereas in adults, it is 49% to 78% (overall 59%) (see Table 12.17). In a study of 223 children with IgAV (HSP), Jauhola et al. (527) found that the mean age of those with renal involvement was significantly higher than that of those without such involvement. Kaku et al. (525) examined potential factors associated with the development of renal disease in children with IgAV (HSP). They found in a multivariate analysis that persistent purpura for ≥1 month, GI bleeding (gross or occult), and decreased plasma factor XIII activity were significantly correlated with the development of renal disease, defined as the presence of macroscopic or microscopic hematuria. Of these, persistent purpura had by far the strongest association with the development of renal disease (525). In a smaller series of children, Sano et al. (532) found that persistent purpura, GI bleeding, decreased factor XIII activity, and age greater than 4 years were significantly associated with the development of renal disease in a univariate analysis, with all but the latter remaining significant by multivariate analysis. In a series of 57 adults, Tancrede-Bohin et al. (531) found a significant correlation between renal involvement and purpura above the waist, fever, and a recent upper respiratory infection by univariate analysis.

Clinical and Laboratory Features of IgAV (HSP) Nephritis

The clinical presentation of IgAV (HSP) nephritis, like that of IgA nephropathy, is quite variable, although nearly all patients (approximately 95% of adults and greater than 95% of children) with IgAV (HSP) nephritis have hematuria (121,516,519,520,522,525,529). Macroscopic hematuria is not uncommon in children, and in series from individual centers, this has been reported in as many as 64% of children with

TABLE 12.17 Frequency of renal involvement (hematuria) in IgA vasculitis (Henoch-Schönlein purpura)

Reference	No. of patients	% Renal involvement
Children		
Stewart et al. (526)	270	20
Jauhola et al. (527)	223	46
Kaku et al. (525)	194	34
Koskimies et al. (528)	141	28
Allen et al. (518)	131	38
Blanco et al. (517)	116	22
Saulsbury (516)	100	40
Garcia-Porrua et al. (529)	73	56
Mills et al. (522)	60	47
Pooled data	**1308**	**34**
Adults		
Cream et al. (530)	75	51
Tancrede-Bohin et al. (531)	57	49
Blanco et al. (517)	46	78
Garcia-Porrua et al. (529)	31	58
Mills et al. (522)	25	76
Pooled data	**234**	**59**

TABLE 12.18 Clinical syndromes in children with IgA vasculitis (HSP) nephritis

Reference	% Patients presenting with				
	Hematuria alone	Hematuria + proteinuria	Acute nephritic syndrome	Nephritic + nephrotic	Nephrotic syndrome[a]
Jauhola et al. (527) (102 patients)[b]	14	56	0	1	20
Meadow et al. (120) (88 patients)	6	45	10	30	9
Yoshikawa et al. (533) (83 patients)	24	14	18	35	8
Halling et al. (534) (73 patients)	16	37	23	15	8
Stewart et al. (526) (55 patients)	22	45	15	18	0
Koskimies et al. (528) (29 patients)	3	69	3	3	21
Pooled data (430 patients)	**15**	**43**	**11**	**18**	**11**

[a]Nearly all patients with nephrotic syndrome also had hematuria.

[b]Nine patients in this series had isolated, subnephrotic proteinuria.

IgAV (HSP) nephritis (120), although in the series of Saulsbury (516), only 7 of 40 children (18%) with IgAV (HSP) nephritis had macroscopic hematuria (see Table 12.16). Macroscopic hematuria tends to be less common in adults, with Pillebout et al. (519) reporting this in only 10% of 236 adults with IgAV (HSP) and hematuria. Approximately 30% of children (Table 12.18) and adults (519) will present with an acute nephritic (or mixed nephritic/nephrotic) syndrome, characterized by new-onset hypertension and/or an elevated serum creatinine level in addition to hematuria. The majority of children and adults with IgAV (HSP) nephritis have proteinuria in addition to hematuria, and in several series, 20% to 45% of patients had nephrotic-range proteinuria, often in combination with acute nephritic syndrome (121,519,528,533,534).

During the initial presentation of IgAV (HSP) nephritis, the majority of children and adults will have normal renal function (516,517,519,534,535), although it remains debatable whether renal insufficiency at presentation is more commonly seen in adults than in children. Blanco et al. (517) found a serum creatinine level greater than 1.5 mg/dL in none of 26 children presenting with IgAV (HSP) and hematuria, compared with 6 (17%) of 36 adults, although Coppo et al. (535) reported impaired renal function in 37% of children (creatinine clearance of 60 to 90 mL/min/1.73 m^2 in 25% and less than 60 in 12%) and 25% of adults (serum creatinine 1.6 to 3.0 mg/dL in 14% and greater than 3.0 in 11%). Halling et al. (534) found reduced inulin clearance in 66% of children with IgAV (HSP) nephritis and nephrotic-range proteinuria but in only 8% of those with subnephrotic or absent proteinuria. Pillebout et al. (519) found some degree of renal insufficiency in 81 of 250 (32%) adults with IgAV (HSP) and suspected nephritis, 94% of whom had hematuria. Severe renal insufficiency, defined as a creatinine clearance ≤30 mL/min, was present in 35 (14%) of these patients. As with IgA nephropathy, rare cases of IgAV (HSP) nephritis may present as acute, reversible renal failure following a severe or relatively prolonged (≥3 days) episode of macroscopic hematuria; this may occur with very mild glomerular lesions and is felt to be related to tubular epithelial injury and/or tubular obstruction due to red blood cell casts (536,537).

Increased serum IgA levels are seen in a significant fraction of patients with IgAV (HSP), often in the range of approximately 50%, although the fraction varies considerably (18% to 62%) in different studies (516,517,529). In addition, circulating immune complexes containing IgA have been reported in over 50% of patients with IgAV (HSP), including those who did and did not develop nephritis (233,538,539). The highest levels of immune complexes are found during the initial 2 to 4 weeks of the disease (233,538). Levels of circulating, IgA-containing immune complexes in patients with IgAV (HSP) nephritis were found by Coppo et al. (232) to be highest during clinically active disease, defined by an increase in the severity of microscopic hematuria or the presence of macroscopic hematuria. These immune complex levels also positively correlated with the fraction of glomeruli with cellular crescents and were significantly higher than those in patients with clinically active IgA nephropathy. Serum C3 and C4 levels are normal in the great majority of patients with IgAV (HSP) with or without nephritis, with depressed levels of either C3 or C4 seen in less than 10% of patients (233,517,540,541), although low levels of properdin, consistent with alternative pathway activation, may be present in up to 30% of patients (541).

A controversial area concerns the value of ANCA of IgA class (IgA-ANCA) as serologic markers for IgAV (HSP). Ronda et al. (542) detected IgA-ANCA in 11 of 14 adults with IgAV (HSP), although in only one of these patients were the IgA-ANCA directed against myeloperoxidase (and this patient also had IgG antimyeloperoxidase antibodies) and in none against proteinase 3. It was also reported in one adult IgAV (HSP) patient that IgA-ANCA levels correlated with the activity of his renal disease (543). However, a number of other studies failed to detect IgA-ANCA in ≥75% of patients with IgAV (HSP) (544–547), and it has been suggested that the detection of circulating IgA-ANCA in these patients may be a false-positive result due to the presence of IgA rheumatoid factors or a lectin-like binding between abnormal carbohydrate side chains of IgA (see Pathogenesis, below) and neutrophil antigens (544,545).

Correlation of Clinical Parameters With Clinical Outcomes in IgAV (HSP) Nephritis

In children with IgAV (HSP) nephritis followed for ≥2 years, Meadow et al. (120) found that an initial presentation of mixed nephritic and nephrotic syndrome was correlated with the worst prognosis, with approximately 20% of patients

developing ESRD or dying, and another approximately 20% having active renal disease at most recent follow-up. By contrast, death and ESRD were extremely rare with any of the remaining four types of clinical presentation listed in Table 12.18, with approximately 20% of patients presenting with acute nephritic or nephrotic syndrome (but not both) having active renal disease at most recent follow-up. Coppo et al. (535) found in adults that presentation with serum creatinine greater than 1.5 mg/dL, proteinuria of greater than 1.5 g/d, and hypertension each correlated with a significantly increased risk of developing ESRD, although none of these factors were associated with a significant risk for the development of ESRD in children. In a more recent and larger study of adults with IgAV (HSP) nephritis undergoing a renal biopsy, Pillebout et al. (519) found that age ≥50 years, a history of macroscopic hematuria, serum creatinine greater than 1.35 mg/dL, and proteinuria greater than 1 g/d at the time of biopsy each correlated with a significantly increased risk of developing severe renal failure (creatinine clearance ≤30 mL/min) or ESRD by univariate analysis, with only the latter two factors remaining significant in a multivariate analysis that included morphologic as well as clinical factors. Other than the effect of macroscopic hematuria, which is correlated with improved renal survival by univariate analysis in IgA nephropathy, these clinical risk factors for a poor outcome in IgAV (HSP) nephritis closely mirror those in IgA nephropathy (see Table 12.6).

Pathologic Findings in IgAV (HSP) Nephritis

Gross Pathology

There are extremely few descriptions of the gross pathology of the kidneys of individuals with active IgAV (HSP) nephritis. Osler (514), describing autopsy findings in a patient who died 6 weeks after the onset of purpura, noted that the kidneys were enlarged with pale cortices and distinct striations with a few small hemorrhages and glomeruli standing out as translucent nodules, although it is possible that this patient had microscopic polyangiitis rather than IgAV (HSP). Histologic examination showed extensive crescent formation. Frost (548), reporting findings of an autopsy of a 15-year-old boy who died 2 months following the onset of purpura, also described enlarged kidneys and cortical pallor, but in addition noted numerous petechiae on the cut surface of the cortex, giving it a "flea-bitten" appearance. Microscopic examination showed glomerulonephritis involving a large number of glomeruli.

Light Microscopy

As with IgA nephropathy, the histologic appearance of IgAV (HSP) nephritis is highly variable, with glomeruli ranging from histologically normal to showing diffuse proliferative and crescentic glomerulonephritis (57,121,535,549,550). However, more severe glomerular lesions, and particularly crescents, are more commonly seen in IgAV (HSP) nephritis than in IgA nephropathy, particularly in children (60,545,551). Perhaps reflecting this, the two most commonly used histologic classification systems for IgAV (HSP) nephritis each place a considerable degree of emphasis on the fraction of glomeruli with crescents. The first of these, that of Meadow et al. (120) (Table 12.19), consists of five histologic grades that are distinguished primarily by the degree of mesangial proliferation and fraction of glomeruli with crescents, although tubulointerstitial changes are also considered. Meadow et al. (120) found that the majority of children with IgAV (HSP) nephritis in their renal biopsy series had grade II (27%) or grade III (30%) lesions, although lesions of all five grades were seen at least in 11 (13%) of the 88 patients (all children) in the series of Meadow et al. (120).

More commonly used than the Meadow et al. (120) classification is the International Study Group of Kidney Disease in Childhood (ISKDC) classification for IgAV (HSP) nephritis (549). As seen in Table 12.20, this classification schema places a very strong emphasis on crescents, with the fraction of glomeruli containing crescents being the sole discriminator between lesions of grades II, III, IV, and V, although it has been noted that the majority of biopsies with grades III, IV, and V lesions show endocapillary in addition to mesangial cell proliferation (534) (see Fig. 12.38). As can be seen in Table 12.21, the majority of cases of IgAV (HSP) nephritis from five different series cluster in grades II and III, with relatively few lesions of grades I, V, and VI, although the paucity of grade I lesions can probably be attributed to these being mild and usually not warranting a biopsy. Notably, cases of IgAV (HSP) nephritis have been routinely excluded in studies examining the clinical

TABLE 12.19 Histologic classification of IgA vasculitis (Henoch-Schönlein purpura) nephritis of Meadow et al. (120)

Histologic grade	Glomerular changes	Tubulointerstitial changes
I	Mostly normal Occasionally small areas of mesangial thickening ± mild hypercellularity may be present	Absent
II	Mesangial proliferation and/or sclerosis in <50% of glomeruli Rarely adhesions and/or small crescents	Absent
III	Mesangial proliferation in >50% of glomeruli Occasionally small crescents and/or adhesions may be present	Infrequent; mild when present
IV	Marked diffuse mesangial proliferation Frequent segmental and/or global glomerulosclerosis Crescents/adhesions in up to 50% of glomeruli	Tubular atrophy, interstitial fibrosis, interstitial inflammation often present
V	Marked diffuse mesangial proliferation Crescents in >50% of glomeruli, often large Prominent segmental and global glomerulosclerosis	Extensive tubular atrophy, interstitial fibrosis, and inflammation

TABLE 12.20 ISKDC histologic classification of IgA vasculitis (Henoch-Schönlein purpura) nephritis

I.	Minimal histologic alterations
II.	Pure mesangial proliferation
III.	Focal (IIIa) or diffuse (IIIb) mesangial proliferation with <50% crescents
IV.	Focal (IVa) or diffuse (IVb) mesangial proliferation with 50%–75% crescents
V.	Focal (Va) or diffuse (Vb) mesangial proliferation with >75% crescents
VI.	Membranoproliferative-like glomerulonephritis

applicability of the Oxford Classification, and it remains to be determined if and to what extent this classification is predictive of clinical outcomes in IgAV (HSP) nephritis.

Tubulointerstitial changes in IgAV (HSP) nephritis largely mirror the glomerular changes (121,519,549,552), with minimal changes in most grade I and II lesions of either major classification, except for varying numbers of red blood cells within tubular lumens. White (552) has noted a small number of cases in children with renal insufficiency in which there was widespread interstitial inflammation with only mild glomerular changes. With more severe lesions, particularly those with multiple crescents, there is interstitial edema and inflammation composed mainly of mononuclear leukocytes, although eosinophils may also be present (553). Tubular epithelial injury may be prominent, particularly in older adults with underlying chronic vascular disease (519). Interstitial foam cells may accompany TA and IF in some more chronic lesions (120).

Although IgAV (HSP) is a form of small vessel vasculitis, necrotizing arteritis is only rarely seen on renal biopsy. In their series of renal biopsies from 250 adults with IgAV (HSP) nephritis, Pillebout et al. (519) noted necrotizing and granulomatous arteritis involving interlobular arteries in only two cases. An additional vascular lesion that we have noted in two cases of IgAV (HSP) nephritis is a focal, necrotizing capillaritis involving the peritubular capillaries of the renal medulla (Fig. 12.39A). This lesion, which resembles the dermal leukocytoclastic vasculitis seen in IgAV (HSP) (see Extrarenal Pathology, below), has been well documented in patients with ANCA-associated vasculitis and glomerulonephritis (554), and as is generally the case with the ANCA-associated lesions, the capillaritis in our IgAV (HSP) cases was limited to the medulla and no arterial lesions were seen. However, neither of our IgAV (HSP) patients was positive for antimyeloperoxidase or anti–proteinase 3 antibodies, and both biopsies showed prominent endocapillary proliferation in addition to focal crescents, changes far more typical of IgAV (HSP) nephritis than of ANCA-associated (pauci-immune) GN (190). Furthermore, one of these cases showed focal granular staining for IgA, but not for IgG or IgM, in and around inflamed medullary peritubular capillaries by immunofluorescence (Fig. 12.39B), a finding we have not observed in cases of ANCA-associated GN. Gough et al. (555) noted peritubular capillary basement membrane reduplication in one of two cases of IgAV (HSP) nephritis and in two of nine cases of ANCA-associated crescentic glomerulonephritis (but none of 17 cases of IgA nephropathy) examined ultrastructurally. It is possible that this reduplication may represent healed peritubular capillaritis.

Immunohistologic Findings

The glomerular immunohistologic findings in IgAV (HSP) nephritis are not distinguishable from those in IgA nephropathy (134,550,556) (see Table 12.7). IgA is the dominant or codominant immunoglobulin, although IgG and/or IgM are not infrequently present as well, and C3 is present in the overwhelming majority of cases. Early complement components, C1q and C4, are absent in most cases (550,556). The IgA deposits, like those in IgA nephropathy, are composed exclusively or almost exclusively of IgA1 (134,135,557), and J chain is typically present (135,557). IgA deposition is always present in the mesangium, with peripheral capillary wall deposits seen in some cases but not all (Fig. 12.40). Fibrinogen staining is often present within cellular crescents and associated with segmental necrotizing lesions. In addition (and as in IgA nephropathy; see Fig. 12.17), mesangial staining for fibrinogen is seen in the majority of cases of IgAV (HSP) nephritis (549).

Davin et al. (556) noted that the ratio of lambda:kappa light chains in circulating pIgA and mesangial IgA deposits, which is not infrequently greater than 1 in IgA nephropathy (125,130,148,207,208,211), is not elevated in patients with IgAV (HSP) nephritis. However, in-depth studies of the light chain composition of glomerular IgA deposits, such as those

TABLE 12.21 Frequency of histologic lesions of IgAV (HSP) nephritis, according to ISKDC classification

Reference	Population	No. of patients	Percentage of biopsies of histologic grade					
			I	II	III	IV	V	VI
Yoshikawa et al. (60)	Children	122	18	18	43	10	10	1
Kawasaki et al. (540)	Children	114	0	27	46	20	4	3
Coppo et al. (535)	Adults	95	2	56	33	2	0	5
	Children	57	2	56	33	2	0	7
Halling et al. (534)	Children	40	13	20	48	15	5	0
Heaton et al. (549)	Children	22	0	36	41	5	9	9
Jauhola et al. (527)	Children	21	0	33	57	5	0	5
Pooled data	**Children**	**376**	**7**	**29**	**44**	**12**	**6**	**3**

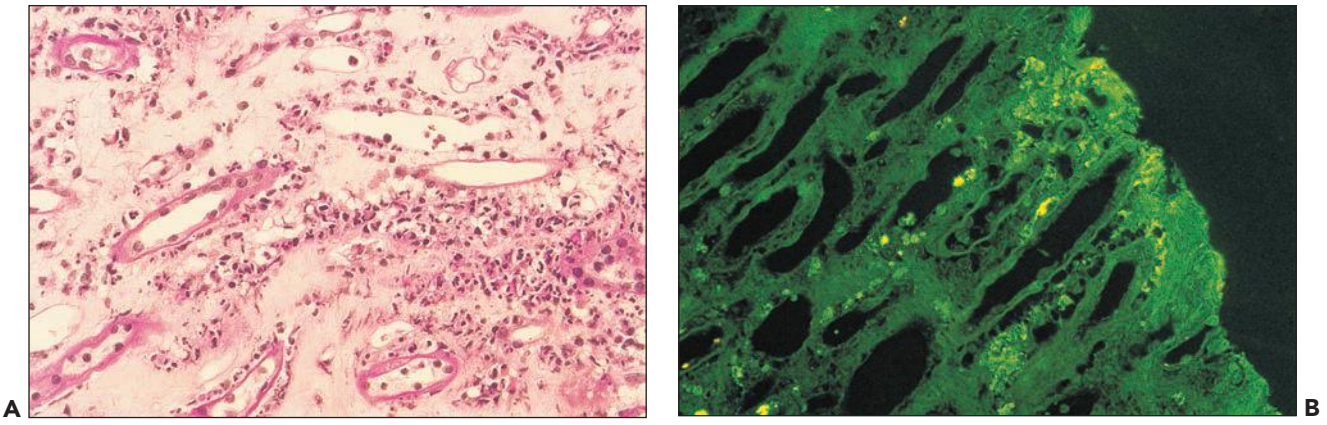

FIGURE 12.39 Necrotizing capillaritis involving peritubular capillaries of the renal medulla in a patient with IgA vasculitis (Henoch-Schönlein purpura) nephritis. A: There is a dense infiltrate of neutrophils with associated karyorrhectic debris in and around the peritubular capillaries. (H&E, ×400.) **B:** Immunofluorescence of the same biopsy, showing focal granular peritubular staining for IgA in the medulla (FITC anti-human IgA, ×400.)

done in IgA nephropathy (148,211), are lacking in IgAV (HSP) nephritis.

Electron Microscopic Findings

The diagnosis of IgAV (HSP) nephritis is typically made on the basis of the immunofluorescence and light microscopic findings, *together with the clinical findings*. As is the case with IgA nephropathy, EM is rarely needed to diagnose IgAV (HSP) nephritis. Furthermore, EM cannot be used to differentiate IgAV (HSP) nephritis from IgA nephropathy, although the former shows a higher frequency of subendothelial and to a lesser extent subepithelial immune complex deposits than the latter (see Table 12.8). All of our cases of IgAV (HSP) nephritis showed mesangial deposits, with subendothelial, subepithelial, and/or intramembranous deposits in approximately 60%. By contrast, only approximately 30% of cases of IgA nephropathy had peripheral capillary deposits in addition to mesangial deposits. Large subepithelial deposits ("humps") have been reported in a small fraction of cases of IgAV (HSP) nephritis (550,551). Such deposits are very rare in IgA nephropathy and would bring into consideration the possibility of an IgA-dominant postinfectious glomerulonephritis (see Differential Diagnosis, below). Yoshikawa et al. (533) have described mesangial and peripheral capillary deposits containing "lead shot" microparticles, 30 to 80 nm in diameter, in several children with IgAV (HSP) nephritis. After review of their published electron micrographs, however, I feel that this most likely represents microvesicular change, which is not infrequently seen in deposits undergoing resorption, rather than a change specific for IgAV (HSP).

Alterations of the glomerular basement membrane, including segmental thinning and splitting of the lamina densa (see Fig. 12.28) and irregularities suggestive of remodeling of the outer (epithelial) aspect of the glomerular basement membrane, are commonly seen in IgAV (HSP) nephritis (551,558,559). In the majority but not all cases showing such changes, subendothelial, subepithelial, and/or intramembranous immune complex deposits are present, often associated with or in the vicinity of the glomerular basement membrane alterations (558). Vogler et al. (558) did not observe any qualitative differences or differences in severity between the glomerular basement membrane changes in IgA nephropathy and IgAV (HSP) nephritis, although such changes may be more prevalent in IgAV (HSP) nephritis (559) simply because of the higher frequency of peripheral capillary deposits.

Extrarenal Pathology

Histologically, the characteristic skin lesion of IgAV (HSP) is a leukocytoclastic vasculitis involving the small blood vessels (arterioles and venules) of the dermis (516,521). There is neutrophil infiltration and nuclear debris from fragmented neutrophils present in and around the involved vessels, which may show fibrinoid necrosis (Fig. 12.41). Immunofluorescence or immunoperoxidase studies show granular deposits of IgA in the dermal blood vessels of the involved skin (Fig. 12.42). The IgA is usually accompanied by C3 and fibrinogen; IgG, IgM, and IgE may also be present, although staining for these immunoglobulins is less intense than that for IgA. As in the glomeruli of patients with IgAV (HSP) nephritis, early

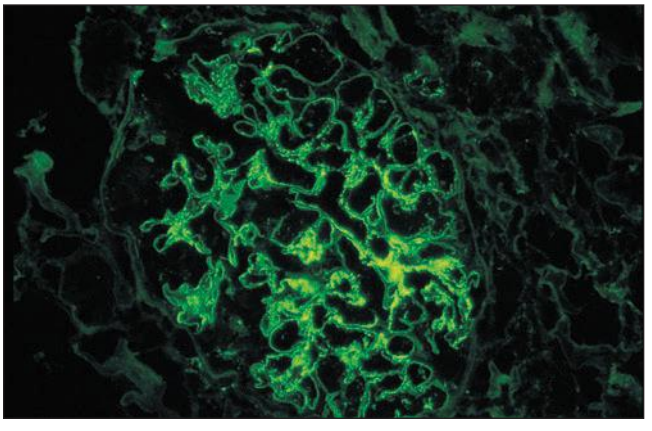

FIGURE 12.40 IgA vasculitis (Henoch-Schönlein purpura) nephritis. Granular staining for IgA in the mesangium and segmentally in the peripheral glomerular capillary walls. (FITC anti-human IgA, ×400.)

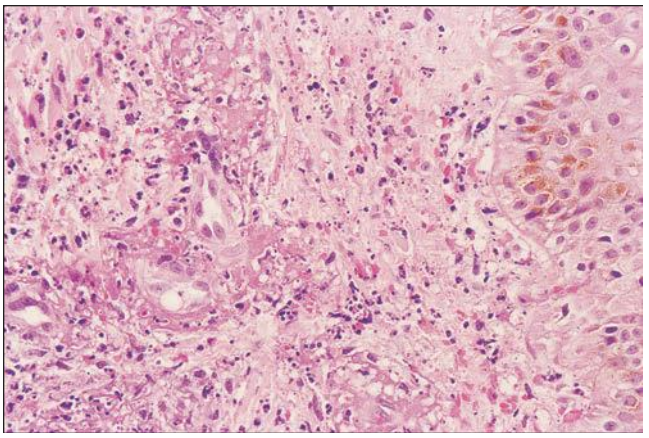

FIGURE 12.41 Dermal leukocytoclastic vasculitis in IgA vasculitis (Henoch-Schönlein purpura). There is fibrinoid necrosis of dermal blood vessels, with prominent associated karyorrhexis. The epidermis is at the right edge of the field. (H&E, ×400.)

complement components (C1q, C4) are typically absent (560). In performing a skin biopsy for immunofluorescence studies, the biopsy should be taken from the edge of a fresh purpuric lesion to optimize the probability of obtaining positive IgA staining. IgA may be resorbed from older lesions and may also be absent from the center of fresh lesions, possibly due to proteolysis (561).

Similar vasculitic lesions to those present in the skin have been described in other organs, most notably the small intestine, where granular deposits of IgA and C3 were likewise noted in submucosal blood vessels (562,563). A very rare but potentially fatal complication of IgAV (HSP) is pulmonary involvement with pulmonary hemorrhage (564–568). Examination of the lungs at autopsy revealed neutrophilic and necrotizing capillaritis involving the alveolar capillaries, with associated intra-alveolar hemorrhage and more variable involvement of small arteries (59,565). Immunofluorescence and immunoperoxidase studies have shown prominent deposition of IgA, with less extensive IgG deposits, along the alveolar septae (59). Extremely rare cases of IgAV (HSP)-related cardiac vasculitis with associated myocardial necrosis have also been reported (569,570).

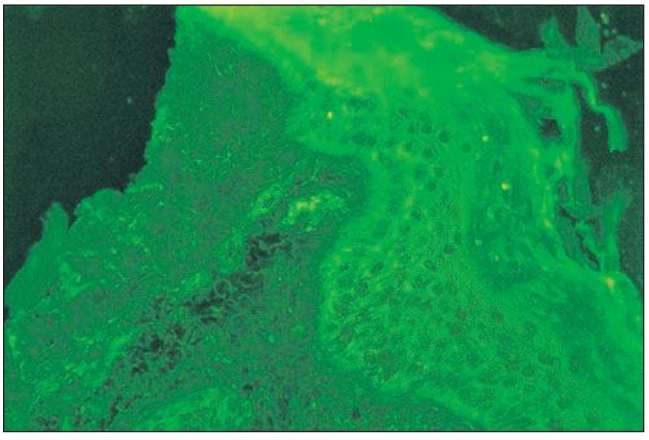

FIGURE 12.42 Dermal leukocytoclastic vasculitis in IgA vasculitis (Henoch-Schönlein purpura). Immunofluorescence shows granular staining for IgA in a blood vessel in the superficial dermis. (FITC anti-human IgA, ×400.)

Differential Diagnosis of IgAV (HSP) Nephritis

Because of the presence of extrarenal symptoms, the differential diagnosis of IgAV (HSP) nephritis is different from that for IgA nephropathy (see Table 12.9). It should again be emphasized here that IgAV (HSP) nephritis and IgA nephropathy cannot be distinguished from each other on a renal biopsy, and this distinction must be made on clinical grounds. A skin biopsy is often very useful in diagnosing IgAV (HSP) (whether or not renal involvement is present); however, the detection of vascular IgA deposits alone is clearly not diagnostic of IgAV (HSP), as such deposits may also be seen in skin from patients with IgA nephropathy, other glomerular diseases, or even healthy individuals (152,155).

Because of the extrarenal manifestations of IgAV (HSP), the primary differential diagnosis of IgAV (HSP) nephritis would include other systemic diseases associated with glomerulonephritis, namely ANCA-associated vasculitides (particularly microscopic polyangiitis but also granulomatosis with polyangiitis [Wegener's]), eosinophilic granulomatosis with polyangiitis (Churg-Strauss), SLE, and cryoglobulinemia, as well as IgA-dominant postinfectious glomerulonephritis, which may occur following the onset of a bacterial skin infection and may in rare instances mimic IgAV (HSP) with a purpuric rash, transient arthralgias, and GI symptoms (571,572). While ANCA-associated necrotizing and crescentic glomerulonephritis (ANCA-GN) is typically regarded as pauci-immune, with few or no glomerular immune complex deposits (573), a number of cases of ANCA-GN with mesangial IgA have been described (190–192), and in a study of 126 cases of ANCA-GN, we found significant (≥1+ on a 0 to 4+ scale) mesangial staining for IgA with accompanying mesangial electron-dense deposits on EM in 12 (9.5%) cases (193). ANCA-GN with mesangial IgA can usually be distinguished from IgAV (HSP) nephritis with crescents serologically, as the former is associated with a positive ELISA for antimyeloperoxidase and/or antiproteinase 3 in greater than 80% of cases, while the latter is associated with a negative ELISA for both of these antigens (197). Furthermore, most cases of IgAV (HSP) nephritis (and IgA nephropathy) with crescents show prominent mesangial and endocapillary hypercellularity at least focally, while in ANCA-GN, glomeruli and portions of glomeruli not involved by crescents or necrosis are usually normocellular or show at most mild mesangial hypercellularity (190).

Features distinguishing lupus nephritis and IgA-dominant postinfectious glomerulonephritis from IgAV (HSP) nephritis are the same as those that distinguish these lesions from IgA nephropathy and have been discussed earlier in this chapter (see Differential Diagnosis in section on Primary IgA Nephropathy). Mixed cryoglobulins may occasionally contain IgA (either a monoclonal IgA or an IgA-rheumatoid factor), and like the far more commonly observed IgG-IgM mixed cryoglobulins, these IgA-containing cryoglobulins (most often IgA-IgG) can produce cutaneous leukocytoclastic vasculitis and glomerulonephritis with IgA deposits in both locations, mimicking IgAV (HSP) (574–577). The glomerular lesions reported with IgA-containing cryoglobulins have ranged from

focal mesangial proliferative to diffuse crescentic glomerulonephritis, including MPGN. While intracapillary pseuothrombi composed of the cryoglobulin were noted in one case (576), none of the reported cases described the curved cylindrical and annular substructure of the glomerular deposits by EM that is seen in some cases of glomerulonephritis in IgG-IgM mixed cryoglobulinemia (578).

Pathogenesis

Several key features that were discussed in some detail in the earlier section on the pathogenesis of IgA nephropathy are also applicable to IgAV (HSP) and, particularly, IgAV (HSP) nephritis. The reader is referred to recent review articles discussing the pathogenesis of IgAV (HSP) (516,579–581).

As noted above (see Immunohistologic Findings), the glomerular deposits of IgA in IgAV (HSP) nephritis are composed almost exclusively of IgA1, and as in IgA nephropathy, this appears to be predominantly pIgA1, based on the presence of J chain and absence of secretory component within the deposits (135,557). Furthermore, there is significant evidence that abnormal glycosylation of IgA1 contributes to mesangial IgA1 deposition in IgAV (HSP) nephritis, as it does in IgA nephropathy. Allen et al. (582) found that serum IgA1 from IgAV (HSP) patients with renal involvement showed increased binding to the lectin *Vicia villosa*, highly consistent with abnormal *O*-glycosylation. By contrast, serum IgA1 from patients with IgAV (HSP) without renal involvement did not show abnormal lectin binding. Furthermore, two patients have been reported with IgA multiple myeloma presenting as IgAV (HSP) (204,205). In both patients, decreased sialylation of hinge region *O*-glycans of IgA1 was documented by mass spectroscopy (205). One of the two patients had documented IgAV (HSP) nephritis (204) and the other had a transient mild decrease in renal function with proteinuria but an inactive urine sediment, and a renal biopsy was not done (205). Like patients with these conditions, a large fraction of first-degree relatives of children with both IgA nephropathy and IgAV (HSP) nephritis also have elevated levels of galactose-deficient IgA1, consistent with a hereditary basis for this abnormality in both diseases (583).

Noting the abnormal glycosylation of the hinge region of IgA1 in IgAV (HSP) nephritis, most of the same mechanisms involved in mesangial IgA deposition and subsequent events (e.g., mesangial cell proliferation, complement activation) discussed earlier in this chapter for IgA nephropathy would also be potentially involved in the pathogenesis of IgAV (HSP) nephritis, and this has indeed been documented in some instances. For example, in IgAV (HSP) nephritis as in IgA nephropathy, mesangial transferrin receptor (CD71) expression is enhanced and colocalizes with IgA (268). In both conditions, complement activation at the level of the glomerulus occurs through both alternative and MBL pathways (584,585).

Still, it remains unclear why IgAV (HSP) nephritis is associated with a systemic vasculitis and IgA nephropathy is not. One possibility involves a role of IgE. Plasma IgE levels are elevated significantly more often in children with IgAV (HSP) nephritis than in those with IgA nephropathy, and IgE deposits were demonstrated on cutaneous Langerhans and mast cells in four of six patients with IgAV (HSP) nephritis (586). It has been postulated that mast cells with bound IgE serve as a potential source of IL-8, a potent chemoattractant for neutrophils, which play a vital role in the pathogenesis of leukocytoclastic vasculitis (556). Differences in the composition of circulating, IgA-containing immune complexes could also be relevant here. For example, IgA-fibronectin complexes in children with IgAV (HSP) often contain IgG, whereas those from adults with IgA nephropathy do not (587), and a subset of immune complexes in patients with IgAV (HSP) are larger than those in patients with IgA nephropathy (556). If those immune complexes that are present in IgAV (HSP) but not IgA are more effective in binding to certain ligands on a variety of cells that secrete neutrophil chemoattractants such as IL-8, this could potentially play a role in the different pathologic manifestations of IgAV (HSP) and IgA nephropathy (556). Eosinophil activation may represent another pathogenic difference between IgAV (HSP) and IgA nephropathy. Children with IgAV (HSP) have higher levels of serum eosinophil cationic protein (ECP) than either those with IgA nephropathy of healthy controls, and ECP levels were higher in IgAV (HSP) patients with nephritis than those without (588). In another study, serum ECP levels were higher only in patients with active nephritis (575). While these studies suggest a possible role of ECP in the initiation of nephritis in patients with IgAV (HSP), the nature of this role remains undefined.

Genetic Factors

There are a small number of reports of IgAV (HSP) occurring in two or more members of the same immediate family, in most instances siblings (reviewed in Ref. (589)). In some but not all of these cases, the family members were exposed to a common infectious agent or other potential immunologic stimuli. Unlike the case with IgA nephropathy, specific chromosomal loci have not been identified that are linked to these familial cases of IgAV (HSP). Still, a number of genetic factors have been identified that may affect the probability of occurrence, likelihood of renal involvement, and severity of renal involvement in IgAV (HSP). These are discussed below and are summarized in Table 12.22.

Complement Deficiencies

Deficiencies in the fourth (C4) and second (C2) components of complement have been reported to be associated with an increased probability of developing IgAV (HSP). This association is better documented for C4, which is produced in two isotypes, C4A and C4B. Among multiple alleles encoding these isotypes, null alleles for both isotypes (C4AQ*0 and C4BQ*0) that produce no identifiable product are not rare. It has been found that C4BQ*0 is more common in IgAV (HSP) patients than in healthy controls (593,594). C4 null alleles are also more frequently found in patients with IgA nephropathy than controls (593). Individuals with complete C4 deficiency commonly develop immune complex–mediated diseases, including IgAV (HSP) and systemic lupus erythematosus (595). Furthermore, IgAV (HSP) patients with C4B deficiency, but not C4A deficiency, were found to have an increased incidence of renal disease (604), whereas renal disease in patients with C4A deficiency tended to be severe, although the numbers of the latter patients were small (604). C2 deficiency is quite rare; however, three individuals have been reported with C2 deficiency and IgAV (HSP) (590–592).

The association between these complement deficiencies and IgAV (HSP) would at first appear paradoxical, since both C2 and C4 are activated via the MBL pathway. Perhaps, the

TABLE 12.22 Genetic associations with IgA vasculitis (HSP) and IgAV (HSP) nephritis

	References
Increased probability of IgAV (HSP)	
C2 deficiency	(590–592)
C4B null allele (C4B*Q0)	(593,594)
Complete C4 (C4A + C4B) deficiency	(595)
HLA-DRB1*01	(596,597)
HLA-DRB1*11	(597)
MEFV (familial Mediterranean fever gene) mutations	(598–602)
TGF-β 509 TT genotype	(603)
Decreased probability of IgAV (HSP)	
HLA-DRB1*07	(596,597)
Increased likelihood of nephritis in patients with IgAV (HSP)	
C4B deficiency	(604)
HLA-B35	(605)
IL-8 2767 A allele	(606)
TGF-β 509 TT genotype	(603)
Increased proteinuria and/or likelihood of nephrotic syndrome	
ACE DD genotype	(607,608)
IL-1 beta 511 T allele	(609)
IL-1 receptor antagonist allele 2	(610)
Increased clinical severity of nephritis[a]	
C4A deficiency	(604)
IL-1 receptor antagonist allele 2	(610)

[a]Acute renal failure, persistent nephritis, or ESRD.

association of these complement deficiencies with IgAV (HSP) is related to an impaired clearance of IgA-containing immune complexes (594), although at present this is purely speculative.

ACE Gene Polymorphism

Two studies (607,608) have shown that patients with IgAV (HSP) nephritis who are homozygous for the ACE D allele (DD genotype) are more likely to have persistent and/or heavy proteinuria. However, in contrast to some studies of patients with IgA nephropathy (308–314), none of three studies of patients with IgAV (HSP) nephritis (607,608,611) found a significant difference between the DD and other ACE genotypes with respect to the development of chronic renal insufficiency. It remains possible that the apparent difference between IgA nephropathy and IgAV (HSP) nephritis with respect to the effect of ACE genotype on disease progression could be related to relatively small numbers of patients and/or a predominance of children in the IgAV (HSP) studies.

Other Associations

A number of HLA antigens have been reported to be associated with an increased probability of developing IgAV (HSP); these are listed in Table 12.22. While renal involvement in familial Mediterranean fever (FMF) is usually in the form of AA amyloidosis (600,602), patients with FMF have also been found to have an increased likelihood of developing certain forms of vasculitis, including IgAV (HSP) (598–602), and to a lesser extent polyarteritis nodosa (599,600,602). FMF results from mutations in the gene MEFV, which encodes the protein pyrin, also known as marenostrin. Pyrin and related proteins have been linked to a number of mediators of immune regulation (reviewed in Ref. (612)), and mice containing a truncated form of pyrin similar to that seen in many FMF patients show an increased susceptibility to bacterial lipopolysaccharide, elevated levels of macrophage-generated cytokines including IL-1 beta, and impaired apoptosis in macrophages (613). Variants of some cytokine gene polymorphisms, including carriage of specific alleles for IL-1 beta and IL-1 receptor antagonist genes, have been found to be associated with the likelihood of patients with IgAV (HSP) developing nephritis and/or the clinical manifestations of this nephritis, as summarized in Table 12.22 and reviewed by Yang et al. (579).

Prognosis of and Clinicopathologic Correlations in IgAV (HSP) Nephritis

Prognosis in Children and Adults

Coppo et al. (535) and Garcia-Porrua et al. (529) each compared long-term outcomes of children and adults with IgAV (HSP) nephritis, with different results. In their Italian cohort of 57 children and 95 adults, Coppo et al. (535) found no significant differences between the children and adults with respect to renal histology, fraction of patients with nephrotic-range proteinuria or renal insufficiency at initial presentation, remission rates, or actuarial renal survival rates at 5 and 10 years. The latter value was approximately 75% in both groups. By contrast, Garcia-Porrua et al. (529) found renal insufficiency at presentation and after a median follow-up of 5 years to be more severe in adults than in children, although the numbers of patients with IgAV (HSP) nephritis in this study were considerably smaller than in the study of Coppo et al. (535). In another small study, Hung et al. (614) found that none of 14 children with IgAV (HSP) nephritis developed chronic renal insufficiency, as compared with 6 of 12 adults.

In their study of children with IgAV (HSP) nephritis followed for ≥2 years, Meadow et al. (120) found that 5 (8%) of 62 patients developed severe renal insufficiency (creatinine clearance ≤45 mL/min/1.73 m^2) or died with severe renal sufficiency, while another 6 (10%) had active renal disease at the last follow-up. However, 34 (55%) of the patients had no evidence of renal disease, and 17 (27%) had only minor urinary abnormalities at the last follow-up. When these same 62 children plus 26 others were followed for a minimum of 6.5 years, 12 (14%) developed renal insufficiency (creatinine clearance less than 60 mL/min/1.73 m^2) or died, but 61 (69%) had no evidence of renal disease (615). Furthermore, when 78 of the latter 88 children were followed long term (mean 23.4 years), only one additional patient developed renal insufficiency (616). In 114 children followed for a mean of 9.8 years, Kawasaki et al. (540) found that 5 (4%) developed severe renal failure (creatinine clearance less than 40 mL/min/1.73 m^2), 15 (13%) had active renal disease at the last follow-up, and 94 (82%) had no evidence of renal disease or only minor urinary abnormalities at the last follow-up, findings quite similar to those of Meadow et al. (120). Most although not all studies of adults with IgAV (HSP) nephritis have reported a worse prognosis than this. Fogazzi et al. (617) reported that only 5 (31%)

of 16 adults followed for a mean of 91 months had no evidence of renal disease or only minor urinary abnormalities at the last follow-up, and 3 (19%) developed ESRD. Eight (45%) of 22 adults followed for a mean of 5.3 years by Cream et al. (530) developed renal insufficiency (creatinine clearance less than 60 mL/min or BUN greater than 60 mg/dL), although only one developed ESRD. Of 250 adults studied by Pillebout et al. (519) with a median follow-up of 14.8 years, only 20% had no evidence of renal disease at the last follow-up, 24% developed ESRD or severe renal failure (creatinine clearance less than 30 mL/min), and another 12% had a creatinine clearance of 30 to 50 mL/min at the last follow-up. By contrast, none of 17 adults with IgAV (HSP) nephritis (including four with histologic grade IV or V lesions by the classification of Meadow et al. (120)) reported by Lee et al. (618) developed chronic renal insufficiency, although follow-up (mean 3.2 years) in this study was considerably shorter than in the three other adult IgAV (HSP) studies cited above (519,530,617). It is also possible that the worse outcomes of adults with IgAV (HSP) nephritis in the latter studies may be related in part to initially more severe disease, although the fraction of patients presenting with nephrotic-range proteinuria was similar (30% to 40%) in the studies of Meadow et al. (120) in children and Pillebout et al. (519) in adults. While 11 of 16 patients in the study of Fogazzi et al. (617) had crescents in ≥5% of glomeruli, a direct comparison of biopsy findings between these studies is not possible because of their use of different histologic grading systems.

Clinicopathologic Correlations

In children, the ISKDC histologic grade (see Table 12.20) correlates reasonably well with clinical outcomes in IgAV (HSP) nephritis, as shown in Table 12.23, which summarizes results from four studies (533,615,619,620) with similar follow-up intervals. Patients with crescents in ≥50% of glomeruli or membranoproliferative-like lesions (ISKDC grades IV to VI) have a 32% likelihood of having chronic renal insufficiency and/or dying within approximately 6 years of diagnosis of nephritis, as compared with a 2% likelihood in patients with minimal or mild (ISKDC grade I or II) histologic lesions. In a similar analysis of children followed for a mean of 9.8 years, 31 of 31 children with ISKDC grade II lesions had no evidence of renal disease or only minor urinary abnormalities at the last follow-up, as compared with 18 of 31 (58%) children with ISKDC grade IV, V, or VI lesions (535). Furthermore, in the study of Halling et al. (620), ISKDC grade as well as proteinuria at 1 year postbiopsy were independent predictors of a poor outcome.

In adults, histologic findings that correlated with the development of severe renal failure (creatinine clearance less than 30 mL/min or ESRD) in 250 patients with a median follow-up of 14.8 years (minimum 13 years) by both univariate and multivariate analysis were necrosis in greater than 10% of glomeruli, global sclerosis of greater than 20% of glomeruli, and interstitial fibrosis involving greater than 10% of the sampled renal cortex (519). The presence or absence of crescents did not correlate with outcome by either univariate or multivariate analysis (519). Likewise, in one study of children with IgAV (HSP) nephritis followed for a mean of 9.8 years (540), a chronicity index composed of semiquantitative scores for glomerular sclerosis (segmental or global), TA, and IF was the only parameter that correlated significantly with an unfavorable outcome (active renal disease and/or renal insufficiency at last follow-up) in a multivariate analysis that included 15 different clinical and morphologic parameters. However, the fraction of glomeruli with crescents, glomerular macrophage infiltration, and interstitial inflammation each correlated significantly with unfavorable outcome by univariate analysis.

Treatment of IgAV (HSP) Nephritis

Most studies of treatment of IgAV (HSP) nephritis have focused on children (reviewed in Refs. (516,581,621)). These can be grouped into two major categories: prevention of nephritis in patients with IgAV (HSP) and treatment of IgAV (HSP) nephritis, the latter primarily involving patients with clinically and pathologically severe nephritis.

Prevention of IgAV (HSP) Nephritis

A small number of studies have examined the effect of corticosteroid therapy on the probability of children presenting with IgAV (HSP) and no urinary abnormalities developing nephritis, with mixed results. While a prospective study of 168 Italian children found a significant difference between children

TABLE 12.23 Correlation of ISKDC histologic grade with clinical outcome in childhood IgAV (HSP) nephritis

	Outcome (number [%] of patients)				
ISKDC grade	No renal abnormality	Minor urinary abnormality	Active renal disease	Renal insufficiency or death	All cases
I	17 (71%)	7 (29%)	0	0	24
II	45 (74%)	9 (15%)	5 (8%)	2 (3%)	61
III	78 (64%)	23 (19%)	13 (11%)	8 (7%)	122
IV	22 (42%)	9 (17%)	11 (21%)	10 (19%)	52
V	0	8 (31%)	3 (12%)	15 (58%)	26
VI	2 (33%)	0	2 (33%)	2 (33%)	6
All grades	164 (56%)	56 (19%)	34 (12%)	37 (13%)	291

Results are combined from the studies of Yoshikawa et al. (533) (83 patients, mean follow-up 5.8 years), Counahan et al. (615) (88 patients, minimum follow-up 6.5 years), Scharer et al. (619) (61 patients, mean follow-up 6.1 years), and Halling et al. (620) (59 patients, mean follow-up 5.2 years). Renal insufficiency was defined in these studies as a creatinine clearance of ≤30, <40, or <60 mL/min/1.73 m^2 in the different studies, and active renal disease was defined as proteinuria of >40 mg/h/m^2 or >1 g/d, urine albumin/creatinine of >200 mg/mmol, and/or hypertension, in the absence of renal insufficiency as defined above.

treated with oral prednisone for 2 weeks and untreated controls in the incidence of the development of urinary abnormalities (hematuria, with or without proteinuria) (622), a more recent, randomized, placebo-controlled study of 40 Canadian children did not (623), and a prospective study from Finland (527) found no effect of prednisone prophylaxis started at the onset of disease on the timing of nephritis in 102 children who subsequently developed renal symptoms. Ronkainen et al. (624) found in a double-blind, placebo-controlled study that while early prednisone therapy reduced the severity of joint pain and abdominal pain in children with IgAV (HSP), this was not effective in preventing the development of nephritis. Likewise, while two retrospective studies found steroid therapy to decrease the risk of developing nephropathy (525,625), another did not (626).

Treatment of IgAV (HSP) Nephritis in Children

While prospective, controlled trials are lacking, a number of case series (but clearly not all; Refs. (516,581)) suggest that high-dose corticosteroid therapy, often in combination with other immunomodulatory agents, is effective in treating severe IgAV (HSP) nephritis, characterized clinically by heavy (at least 1 g/d and often nephrotic-range) proteinuria and/or pathologically by crescentic GN (ISKDC grades IV and V). In a French study of 38 children treated with pulse methylprednisolone followed by oral prednisone, 27 had no evidence of renal disease and 3 others had only minor urinary abnormalities after 1 to 16 years of follow-up; 4 patients (all with ISKDC grade V lesions) developed ESRD (627). In two studies of combined therapy with corticosteroids, cyclophosphamide, and dipyridamole (one with additional therapy with heparin followed by warfarin), 21 of a total of 26 patients had no evidence of renal disease or only minor urinary abnormalities at the last follow-up, and only one of the remaining five patients developed chronic renal insufficiency (628,629). In a study of 21 children with IgAV (HSP) nephritis and a mean of 40% of glomeruli with crescents treated with steroids plus azathioprine, serum mean creatinine improved from 1.7 to 0.8 mg/dL and mean 24-hour urine protein decreased from 8.8 to 0.5 g after a mean follow-up of 32 months, although two patients (both with ISKDC grade V lesions) progressed to ESRD (630). Response to treatment was not different in patients given pulse methylprednisolone followed by oral prednisone versus oral prednisone alone (630). In a Japanese study in which patients with IgAV (HSP) nephritis (initially ISKDC grade III, IV, or V) underwent renal biopsies before and after treatment with pulse methylprednisolone and urokinase followed by oral prednisolone for 6 months, the mean activity index (determined from semiquantitative scores of mesangial proliferation, glomerular necrosis, cellular crescents, and interstitial inflammation with edema) decreased significantly, while there was no significant increase in chronicity index (glomerular sclerosis, fibrous crescents, tubular atrophy, and interstitial fibrosis) (631). Addition of oral cyclophosphamide to this therapeutic regimen further reduced both mean activity and chronicity indices on the follow-up biopsies (632). A more recent report also suggests that further addition of plasmapheresis to this regimen may be of benefit to children with rapidly progressive IgAV (HSP) nephritis (crescents in greater than 60% of glomeruli and a 50% reduction in creatinine clearance within 6 weeks), although the number of patients tested was small (633). However, evidence indicates that plasmapheresis alone is most likely not a particularly effective treatment for crescentic IgAV (HSP) nephritis (619,621).

Several studies have also suggested that cyclosporine A (CSA) may be an effective treatment for severe IgAV (HSP) nephritis. A randomized trial from Finland (634) compared CSA and methylprednisolone in 24 children with IgAV (HSP) nephritis and nephrotic-range proteinuria and/or crescents on renal biopsy. Resolution of proteinuria occurred within 3 months in 11/11 CSA-treated patients versus only 6/13 of patients treated with steroids alone, with additional treatment required for remission of proteinuria. After a mean of 6.1 years, three patients in each group had urinary abnormalities, although none had renal insufficiency (634). In a retrospective study of 29 Korean children with HSP nephritis and nephrotic-range proteinuria, all patients responded to CSA with remission of proteinuria within 3.5 months after initiation of therapy, although six of these patients became CSA dependent with relapses of proteinuria when CSA was discontinued (635).

Treatment of IgAV (HSP) Nephritis in Adults

Limited data are available on treatment of IgAV (HSP) nephritis in adults. In the retrospective study of Pillebout et al. (519), no significant effect of corticosteroids alone or of steroids plus cyclophosphamide on the development of severe renal insufficiency could be demonstrated. However, patients receiving these treatments had higher mean levels of proteinuria and serum creatinine than untreated patients, and patients receiving steroids and cyclophosphamide had more severe glomerular lesions than those receiving steroids alone. Thus, the potential efficacy of these treatments cannot be evaluated, and there is clearly a need for prospective studies, preferably a randomized, controlled trial. Pillebout et al. (519) also noted no differences in progression of renal disease between patients who received ACE inhibitors or ARBs and those that did not, although again these groups may not be sufficiently comparable to draw any conclusions regarding the possible efficacy of these agents.

A more recent study from these same investigators (636) confirmed that addition of cyclophosphamide to a regimen of steroid therapy produced no added benefit compared to steroids alone in treating adults with severe IgAV (HSP) nephritis. In a single case report, remission of IgAV (HSP) nephritis in an adult was seen after rituximab monotherapy, although a spontaneous remission cannot be excluded (637).

Recurrence of IgAV (HSP) Nephritis in Renal Transplants

Compared with IgA nephropathy, relatively little is known about recurrent IgAV (HSP) nephritis in renal allografts. In a study published in 1994, Meulders et al. (638) reviewed their experience and that of others with renal transplantation in patients with IgAV (HSP), comprising a total of 74 grafts in 67 patients. Biopsies of 45 grafts were performed in which immunofluorescence studies were done; of these, 24 (53%) showed segmental or diffuse, granular deposits of IgA within the glomeruli, although it was not stated how many of these biopsies showed histologic evidence of recurrent GN. With 13 grafts (18% of total), there was a "clinical recurrence" of IgAV (HSP) nephritis, defined as hematuria, with or without proteinuria,

unaccounted for by rejection. In nine of these cases, there was accompanying graft dysfunction, and seven grafts (9% of total) were lost due to recurrent IgAV (HSP) nephritis. All but one of these losses occurred with living-related grafts. Six of the patients with a clinical recurrence of IgAV (HSP) nephritis and two without such a recurrence showed systemic symptoms of IgAV (HSP), mainly purpura (638).

In seven patients with a clinical recurrence of IgAV (HSP) nephritis reported in two case series (638,639), the initial detection of urinary abnormalities occurred from 36 days to 35 months posttransplantation, although in all but two cases, this was documented within the first 9 months posttransplantation. Graft losses due to recurrent IgAV (HSP) nephritis occurred from 19 to 91 months posttransplantation (638,639).

Four reports published between 1997 and 2005 (392,403,519,640) reported graft loss due to recurrent IgAV (HSP) nephritis in 4/24, 0/12, 1/10, and 0/6 grafts, respectively. The frequency of clinical or histologic recurrence of IgAV (HSP) nephritis was only addressed in one of these studies (2/6; Ref. (403)). The single graft loss due to recurrent IgAV (HSP) nephritis in the study of Haubitz et al. (640) occurred with a cadaveric graft, 58 months posttransplantation.

A more recent study of Moroni et al. (641) examined outcomes in 17 patients (15 adults and 2 adolescents) with biopsy-proven IgAV (HSP) nephritis who received renal transplants; two of the patients received two transplants each. Graft survival in this cohort was not significantly different from that in an age-matched control cohort of 38 patients with an original renal disease other than IgAV (HSP) nephritis or IgA nephropathy. Eight of the 19 grafts (42%) developed recurrent IgAV (HSP) nephritis with associated graft dysfunction, proteinuria, and/or hematuria at a mean of 30 ± 41 months posttransplantation. Four grafts (21% of total) were lost due to recurrent IgAV (HSP) nephritis at a mean of 55 months posttransplantation. Interestingly, all four of these patients had necrotizing and/or crescentic lesions in their native kidney. Furthermore, the recurrence rate of IgAV (HSP) nephritis was higher in those patients whose original disease had necrotizing and/or crescentic lesions than in those whose original disease had no such lesions (71% vs. 12%, $P = 0.05$) (641).

Secondary IgA Vasculitis (Henoch-Schönlein Purpura)

As with IgA nephropathy, although much less commonly, secondary forms of IgAV (HSP) have been reported associated with a number of illnesses, each of which has also been reported to be associated with secondary IgA nephropathy (see Table 12.15). Conditions that have been reported to be associated with IgAV (HSP) with nephritis include cirrhosis (642,643), ankylosing spondylitis (644), Behcet disease (645), polycythemia vera (646), anterior uveitis (647), and various epithelial and hematologic malignancies (648,649).

Is IgAV (HSP) the Systemic Form of Primary IgA Nephropathy?

A number of investigators have suggested that IgAV (HSP) may be a systemic form of primary IgA nephropathy or conversely that IgA nephropathy is a renal-limited form of IgAV (HSP) (e.g., (650,651)). Perhaps, the strongest evidence for this comes from a number of reports of patients with biopsy-proven IgA nephropathy who subsequently developed typical IgAV (HSP) 2 to 13 years after the initial onset of renal symptoms (652–655). IgA nephropathy and IgAV (HSP) have also been reported in members of the same immediate family, including identical twins who presented with their respective illnesses at nearly the same time, shortly after each had developed an adenovirus infection (651).

TABLE 12.24 Similarities between IgA nephropathy and IgAV (HSP) nephritis

Clinical features
More frequent in males than in females
Uncommon in patients of black race
Macroscopic hematuria concurrent with a respiratory infection
Often leads to chronic renal insufficiency
May recur in renal allografts
Pathologic features
Dominant or codominant IgA deposits in mesangium ± glomerular capillary loops
IgA deposits are comprised mainly or exclusively of IgA1
Deposits usually contain C3, often IgG and/or IgM, rarely C1q
Variable histology, but often with mesangial proliferation
IgA deposits in dermal blood vessels
IgA immunologic abnormalities
Abnormal IgA1 glycosylation in patients and first-degree relatives
Increased plasma levels of IgA, pIgA, and IgA1
Circulating IgA immune complexes
Increased IgA synthesis
Other immunologic abnormalities
Reduced function of reticuloendothelial system
Low-grade complement activation
Increased plasma levels of IgE
Increased incidence of C4B null phenotype
Increased urinary excretion of TNF-alpha and IL-1
Glomerular deposits of IgA-binding staphylococcal M proteins

Modified from Davin J-C, ten Berge IJ, Weening JJ. What is the difference between IgA nephropathy and Henoch-Schonlein purpura nephritis? *Kidney Int* 2001;59:823–834.

The topic of the relationship between IgA nephropathy and IgAV (HSP) was reviewed by Davin et al. (556). As discussed by these authors, IgA nephropathy and IgAV (HSP) have a considerable number of clinical, pathologic, immunologic, and other similarities, many of which are listed in Table 12.24. There are also a number of notable differences, not the least of which is the typical age of onset (Table 12.25).

At present, however, considerations of the possible relationship between IgA nephropathy and IgAV (HSP) would appear to be limited by the concept that primary IgA nephropathy represents a single disease entity, when in all likelihood, it represents a group of entities with an essential common phenotypic expression (i.e., glomerular IgA1 deposits). The same may be true for IgAV (HSP) as well. Clearly, the entity we now know as primary IgA nephropathy is extremely heterogeneous with respect to its clinical presentation, pathologic expression, and long-term prognosis, and each of these are likely to be influenced by heterogeneous sets of genetic and environmental factors. It is anticipated that as we develop an increasing understanding of these factors, we will better understand

TABLE 12.25 Differences between IgA nephropathy (IgAN) and IgAV (HSP) nephritis

	IgAN	IgAV (HSP)
Clinical features		
Extrarenal symptoms	–	+
Usual age of onset	>15 y	<15 y
Nephritic/nephrotic syndrome	+	+++
Risk of chronic renal failure	+	++
Hypersensitivity	–	+
Secondary forms	++	+
Pathologic features		
Endocapillary proliferation	+	++
Crescents	+	++
IgA deposits in glomerular capillary loops	+	++
Subendothelial/subepithelial deposits by EM	+	++
Immunologic abnormalities		
Size of IgA immune complexes	7S–19S	>19S
Increased plasma levels of IgE	+	++
Increased plasma levels of eosinophil cationic protein	–	+
Increased expression of miR-418b[a]	**+**	**–**

[a]Levels within peripheral blood B cells of this microRNA that acts to reduce amounts of core 1, beta 1,3-galactosyltransferase 1 mRNA and protein within these cells (215).

Modified from Davin J-C, ten Berge IJ, Weening JJ. What is the difference between IgA nephropathy and Henoch-Schonlein purpura nephritis? *Kidney Int* 2001;59:823–834.

not only similarities and differences in the pathogenesis of IgA nephropathy and IgAV (HSP) but also what underlies the heterogeneity within each.

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