CHAPTER 8

Xin J. (Joseph) Zhou • Fred G. Silva

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.

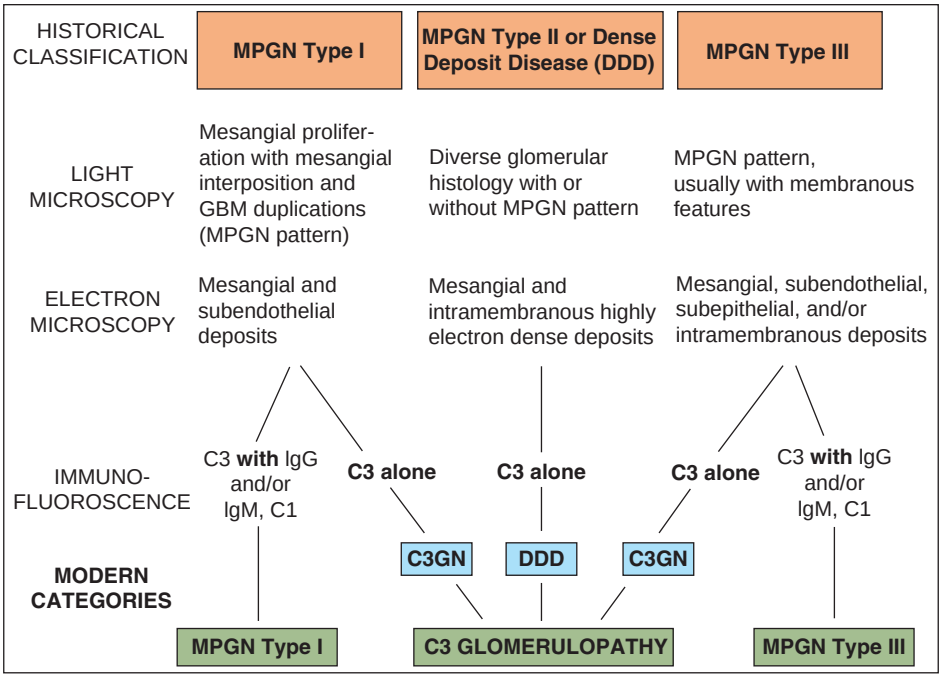

FIGURE 8.1 The evolving classification of membranoproliferative glomerulonephritis. Until recently, the classification of primary MPGN into types I, II, and III was based primarily on histologic features (light microscopy) and the ultrastructural location and electron density of the deposits (electron 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.

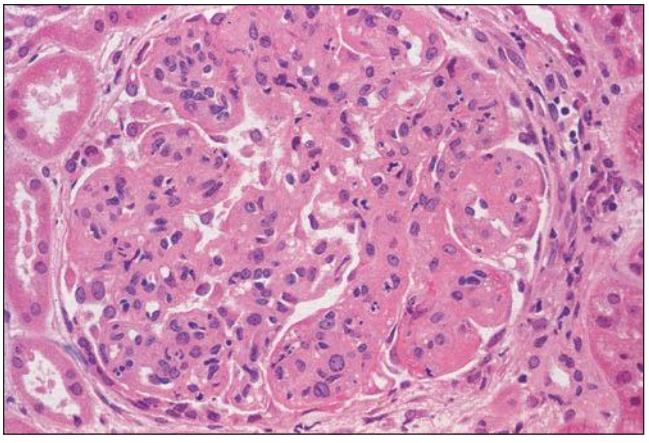

FIGURE 8.2 MPGN type I. There is increased lobulation, intracapillary hypercellularity (including mild neutrophil infiltration), and thickening of the capillary walls. (H&E, ×400.)

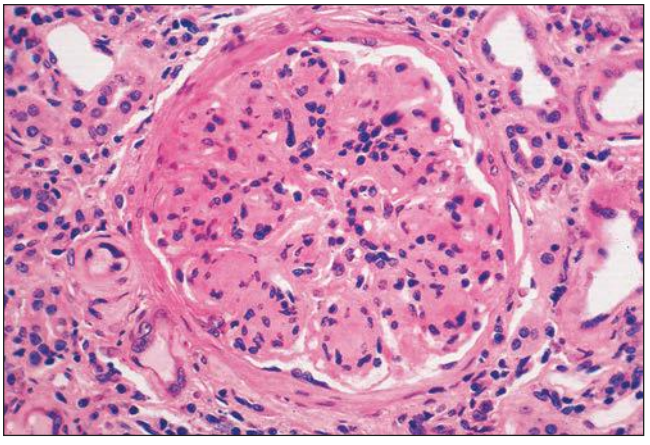

FIGURE 8.4 MPGN type I. Accentuation of the lobular pattern with sclerotic mesangial nodules. (H&E, ×400.)

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

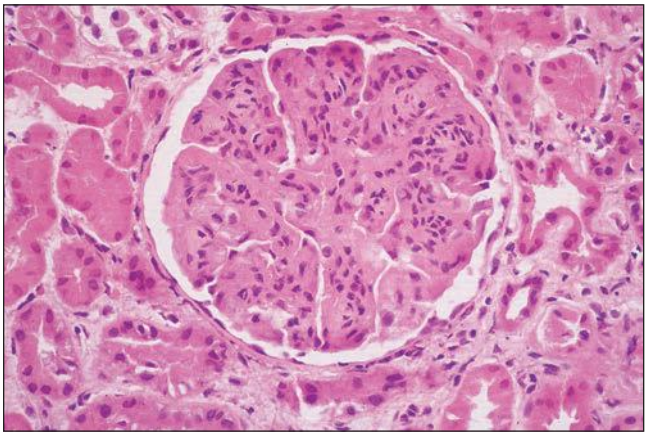

FIGURE 8.3 MPGN type I. There are capillary wall thickenings, increased cellularity, and pronounced lobulation. (H&E, ×360.)

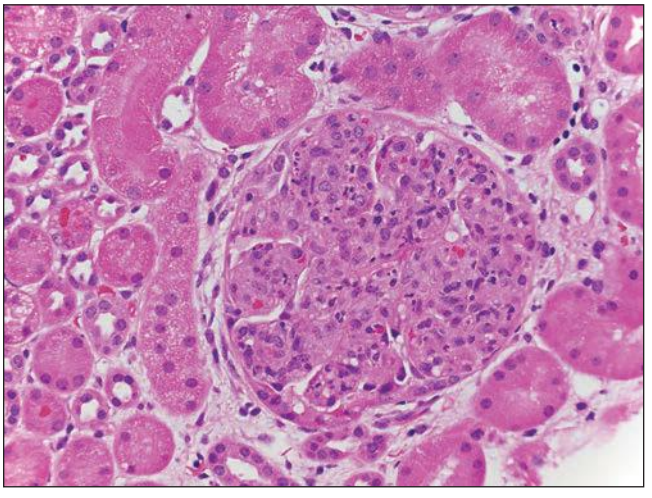

FIGURE 8.5 MPGN type I. There are numerous infiltrating neutrophils (exudative form) resembling acute postinfectious glomerulonephritis by light microscopy. (H&E, ×400.)

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

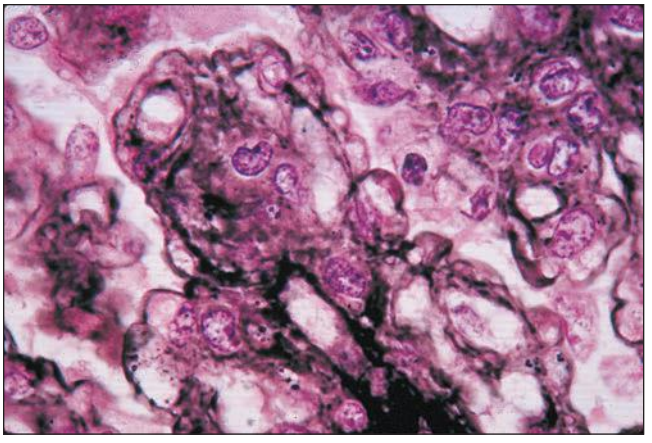

FIGURE 8.6 MPGN type I. Glomerulus with silver stain shows tram tracking or reduplication of the GBM. (Jones silver methenamine, ×600.)

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,

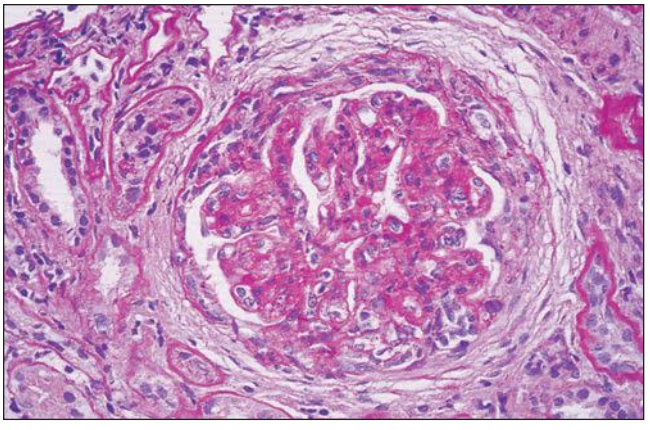

FIGURE 8.7 MPGN type I. Glomerulus from a case of MPGN type I with crescent. (PAS, ×400.)

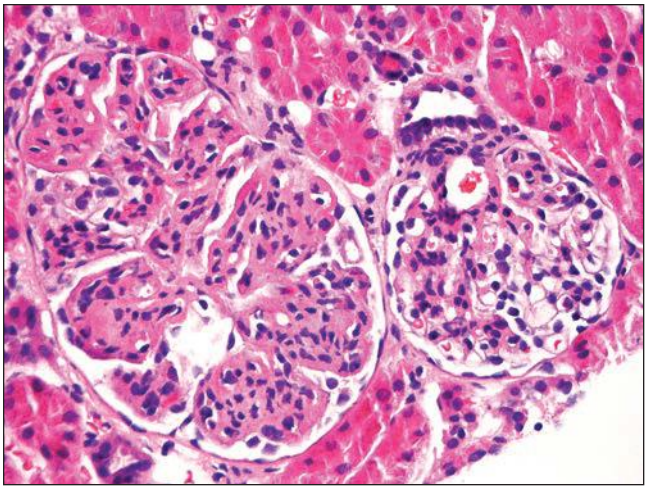

FIGURE 8.8 Focal MPGN type I. One glomerulus shows typical changes of MPGN type I, while the other glomerulus reveals only mild mesangial hypercellularity. (H&E, ×400.)

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

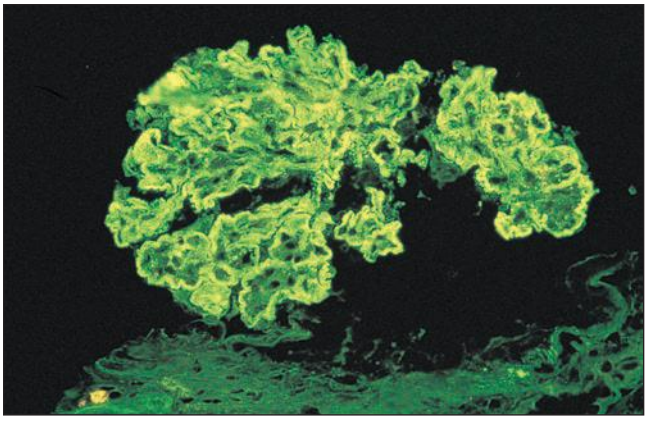

FIGURE 8.9 Immunofluorescence of MPGN type I. There is intense glomerular mesangial and capillary wall staining with anti-IgG antiserum. (×400.)

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

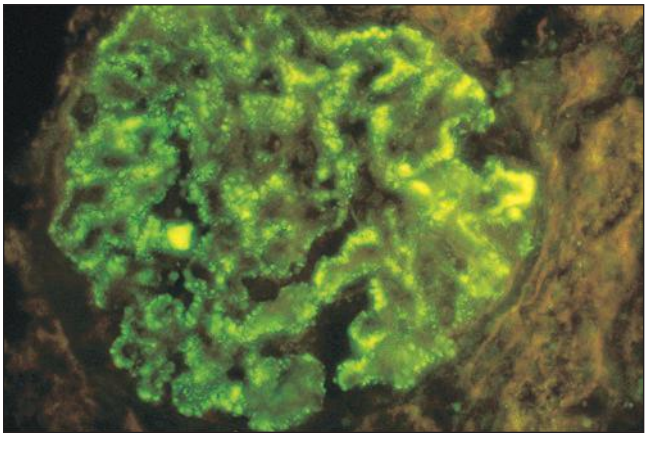

FIGURE 8.10 Immunofluorescence of MPGN type I. There is moderately intense staining for IgM along the glomerular capillary walls in a granular pattern. (×400.) (Courtesy of Dr. Zoltan Laszik.)

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.

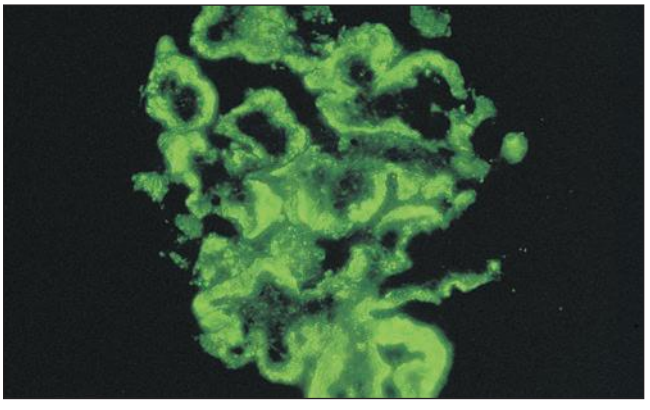

FIGURE 8.11 Immunofluorescence of MPGN type I. There is intense staining aong all glomerular capillary walls for C3. The granular staining is quite broad in this instance. (×400.)

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

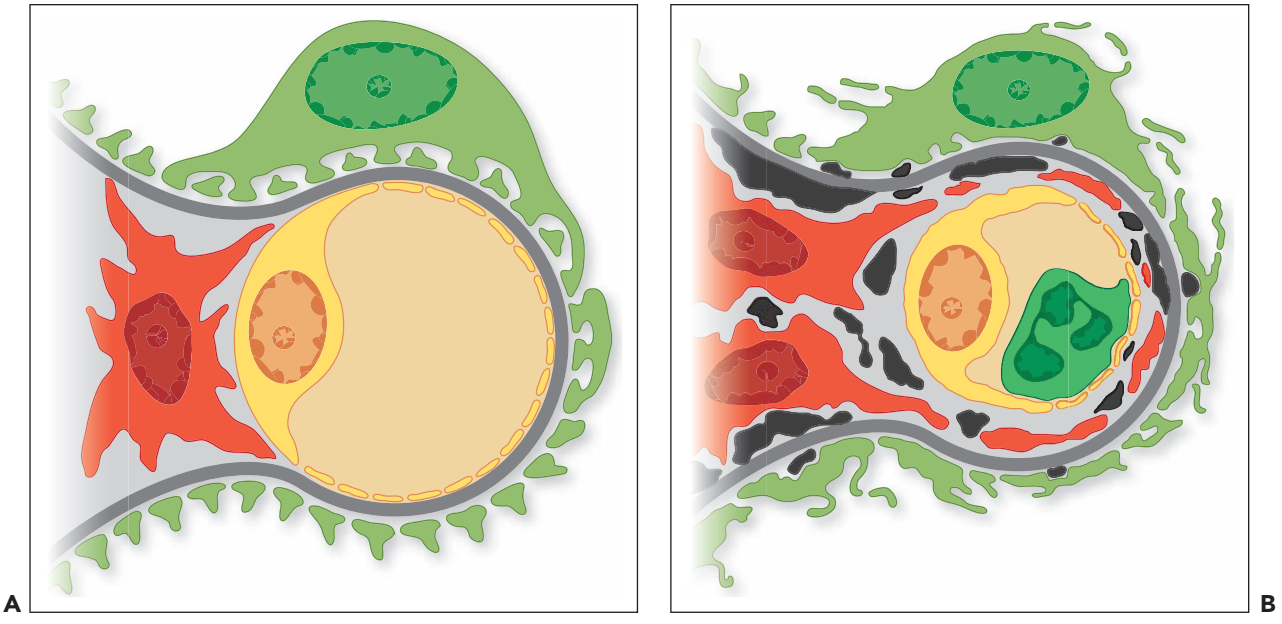

FIGURE 8.12 Drawing depicting a normal glomerular capillary and adjacent mesangium **(A)** compared to the ultrastructural changes of MPGN type I **(B)**. Note the subendothelial, mesangial and few subepithelial dense deposits (*black*), capillary wall mesangial interposition (*red*), new layers of subendothelial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

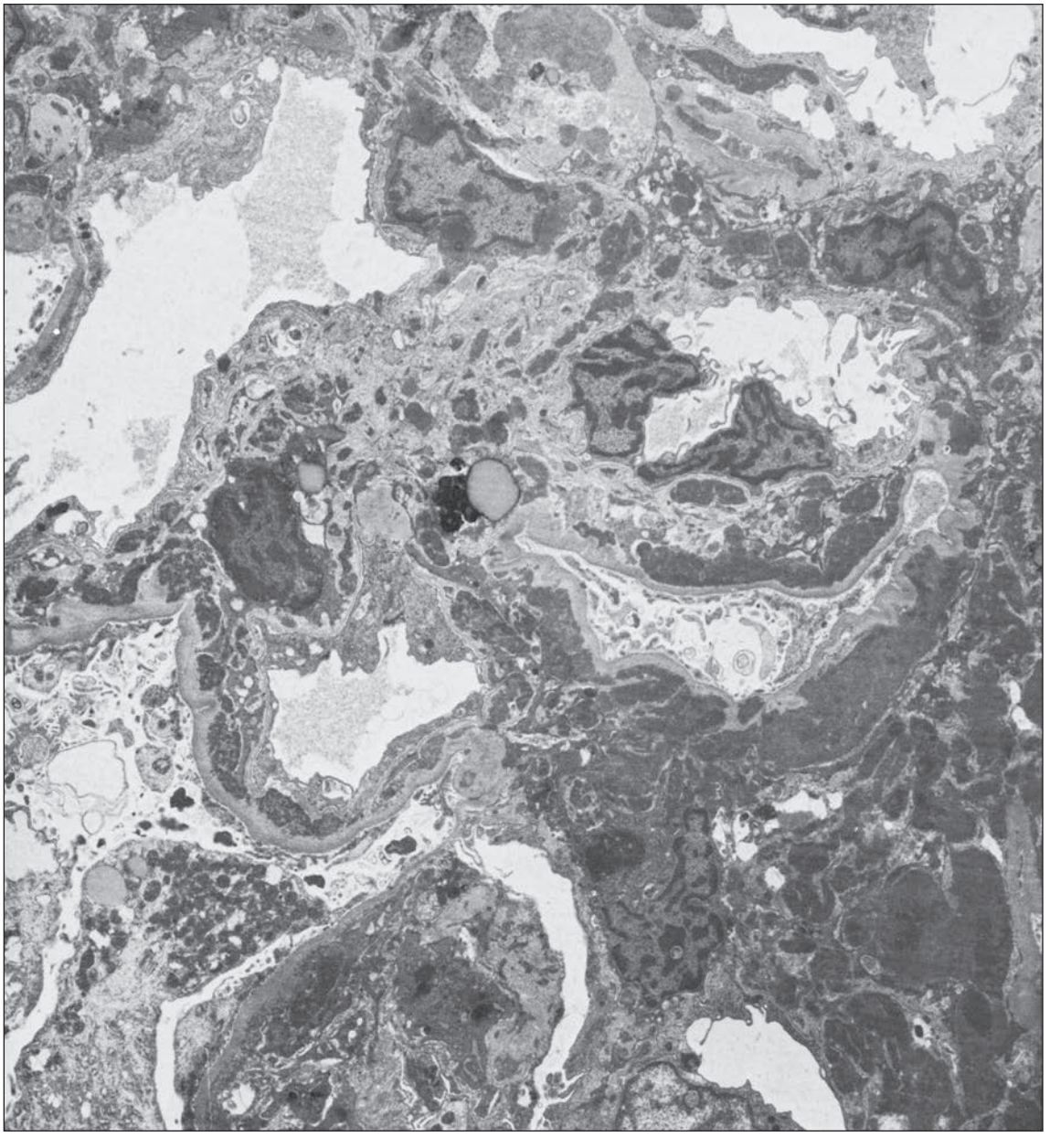

FIGURE 8.13 MPGN type I. Note the presence of a large number of discrete electron-dense osmiophilic deposits throughout the glomerular structures. There are numerous large subendothelial deposits and scattered mesangial deposits. Some of the glomerular capillaries are closed, and others are patent. (Uranyl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

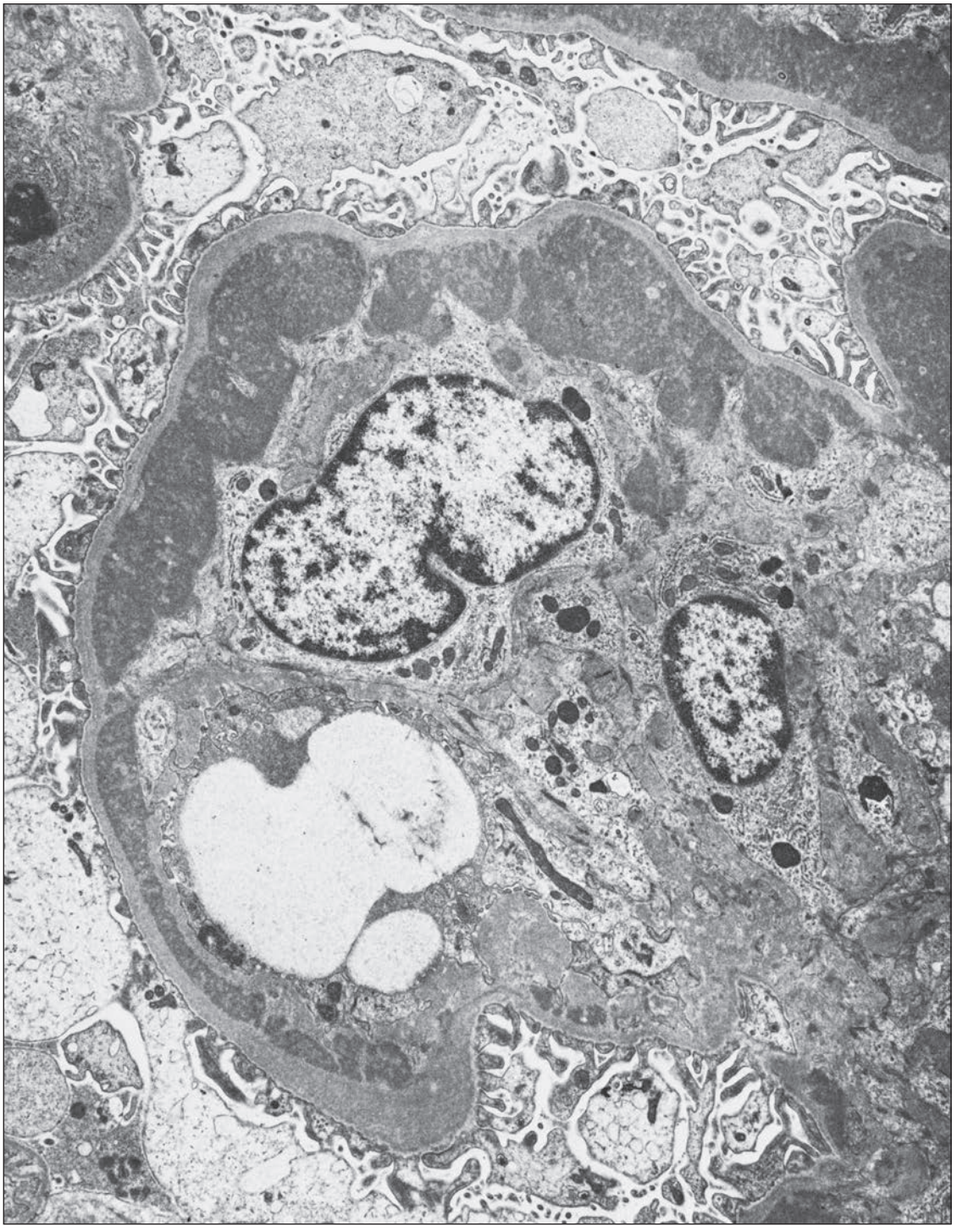

FIGURE 8.14 **MPGN type I.** Electron micrograph shows a segment of a glomerular capillary with large, discrete, electron-dense deposits in the subendothelial space. (Uranyl acetate and lead citrate, ×5844.) (Courtesy of Dr. Edith Hawkins.)

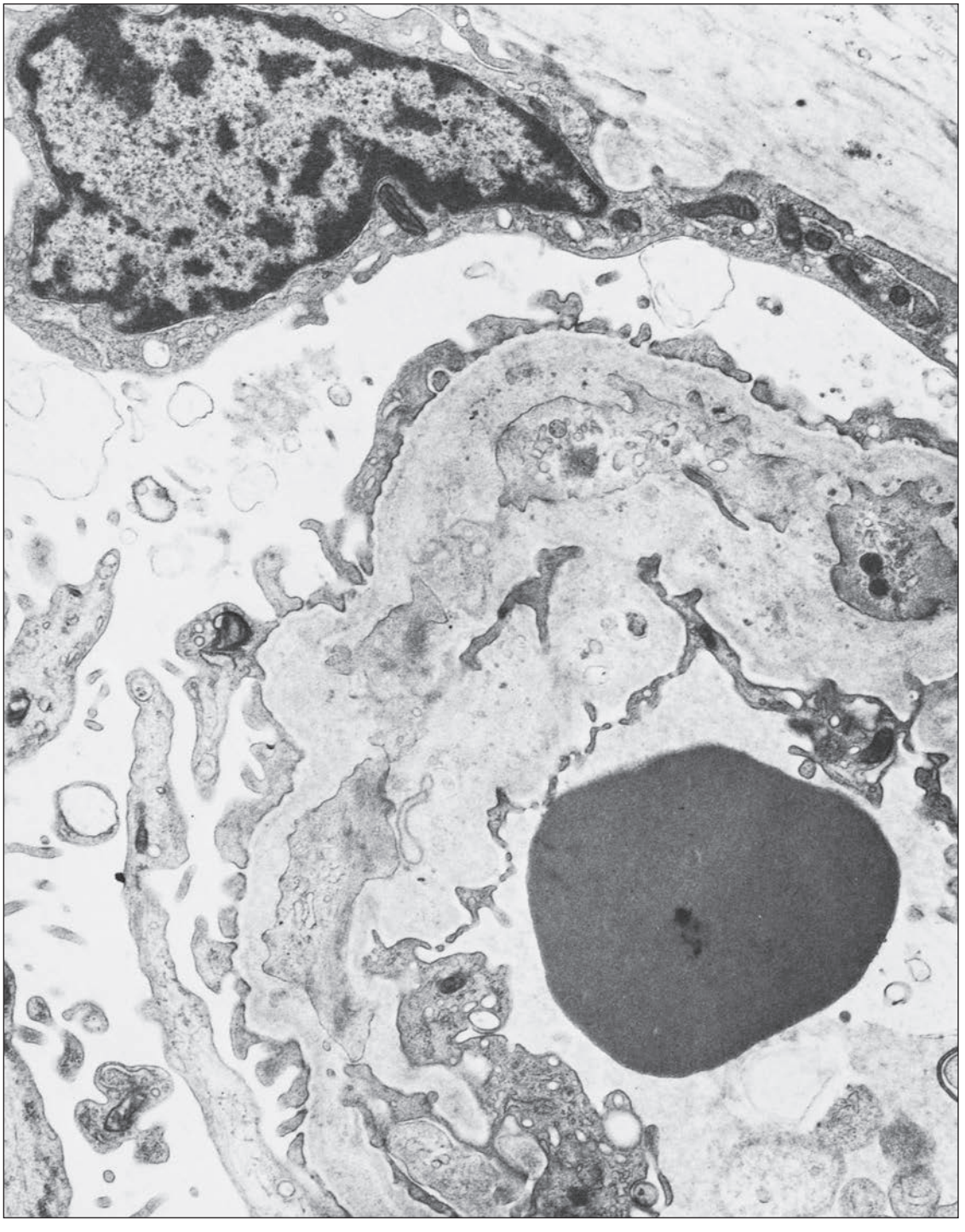

FIGURE 8.15 MPGN type I. Electron micrograph of portions of the glomerular capillary wall shows double basement membrane–like material. The mesangial cell has interposed itself between the endothelium and basement membrane and in so doing has also produced an inner (subendothelial) mesangial matrix/basement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

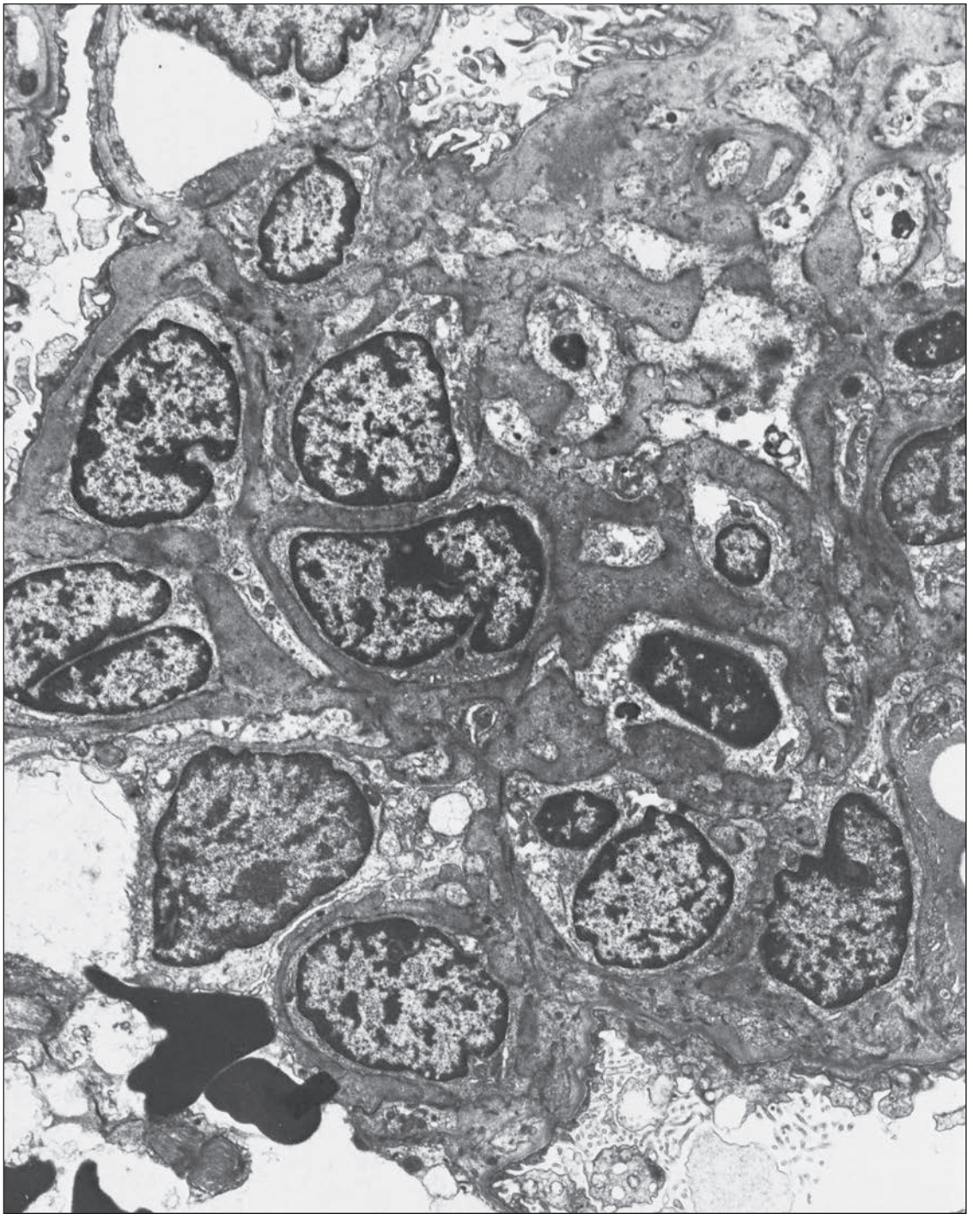

FIGURE 8.16 **MPGN type I.** A portion of a glomerulus shows increased numbers of cells in the mesangial or centrilobular regions. Although a number of these cells may represent native mesangial cells, it is also possible that many of them are migrant monocytes from the peripheral circulation (i.e.,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

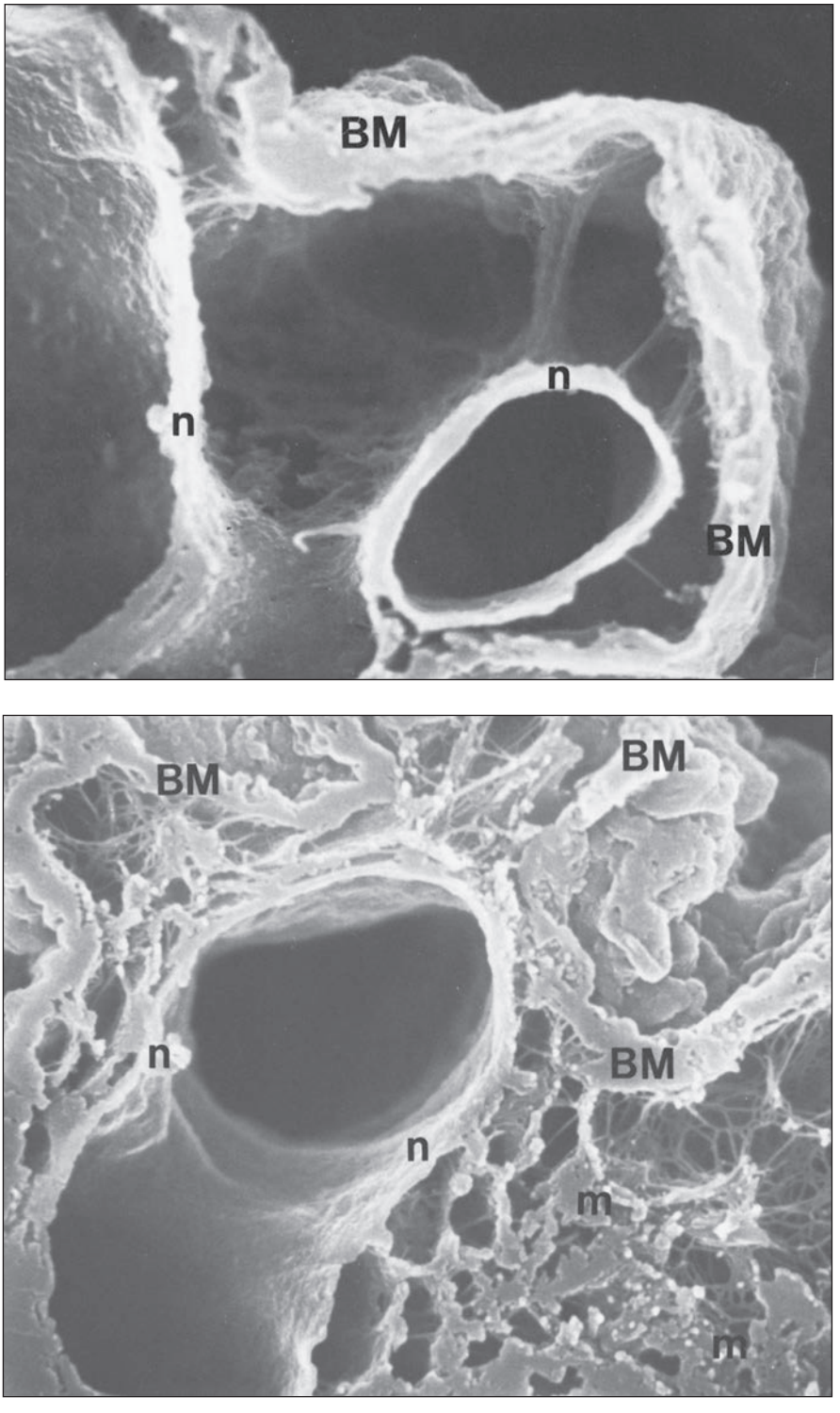

FIGURE 8.17 MPGN type I. Scanning electron microscopic technique of Bonsib (222) in which the cellular elements and deposits have been removed by enzymatic digestion, leaving behind only extracellular basement membranes and basement membrane–like material from a renal biopsy of MPGN type I. **A:** The 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).

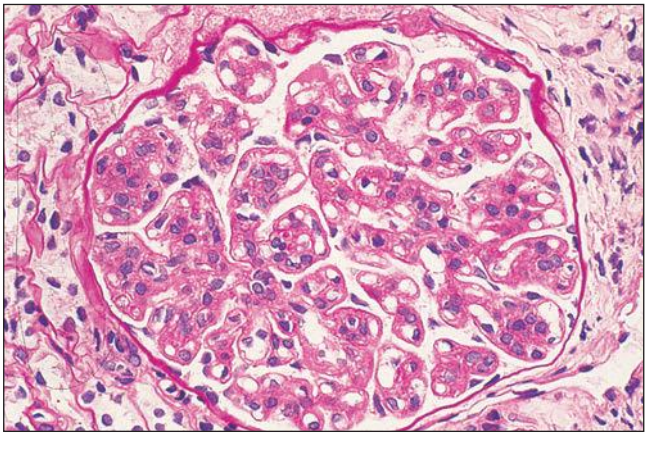

FIGURE 8.18 MPGN type III of Strife/Anders. This representative glomerulus shows a global increase in cellularity in the tuft. There is accentuation of the lobular pattern, and the light microscopic pattern is similar (if not identical) to MPGN type I. (PAS, ×400.) (Courtesy of Dr. Zoltan Laszik.)

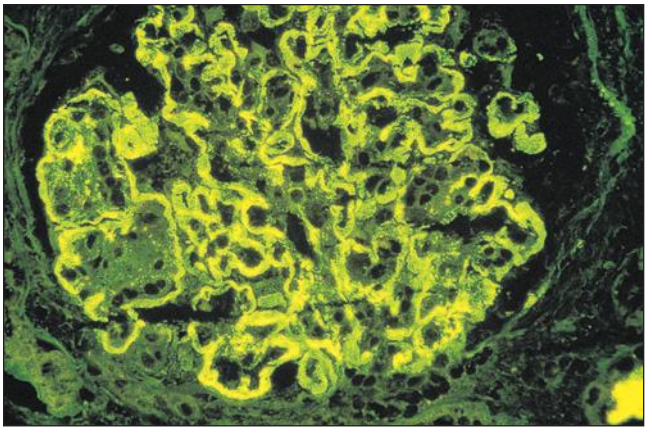

FIGURE 8.19 Immunofluorescence of MPGN type III of Strife/Anders. Note the intense granular to band-like glomerular capillary wall and mesangial staining for C3. (×400.)

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.

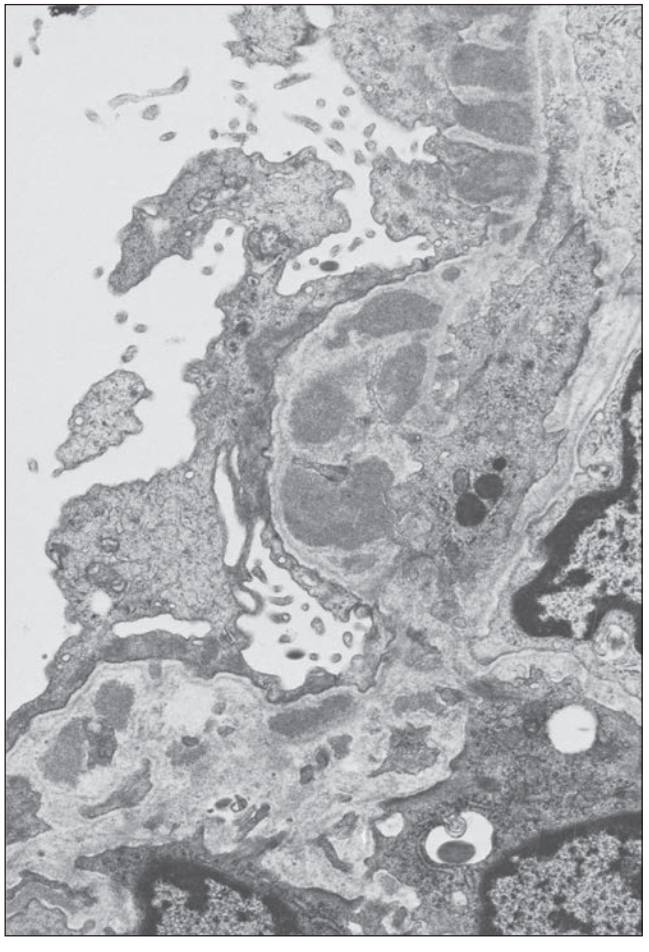

FIGURE 8.20 MPGN type III of Burkholder. There are large intramembranous deposits surrounded by a matrix and subepithelial deposits with adjacent spikes of GBM-like material (top right). (×15,000.) (Courtesy of Dr. A. James McAdams.)

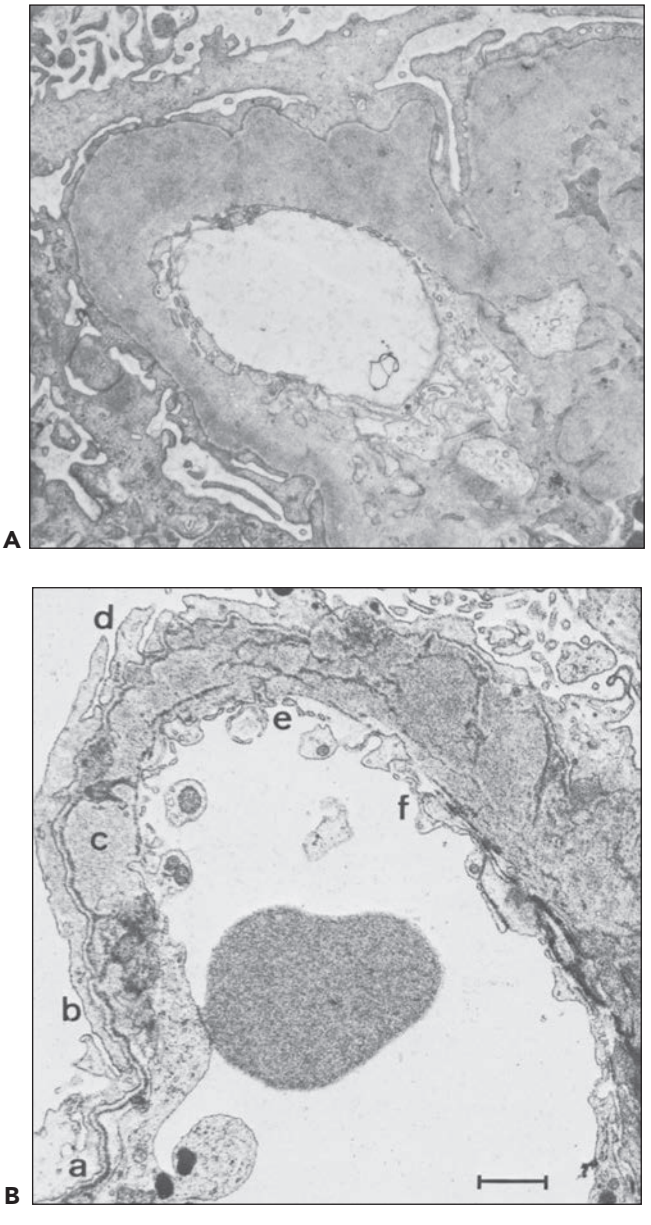

FIGURE 8.21 MPGN type III of Strife/Anders. A: Electron micrograph (not impregnated with silver) shows diffuse, ill-defined basement membrane thickening. **B:** Silver-impregnated material allows resolution of basement memabrane thickening. Several stages are shown starting from lower left: *a*, intact 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

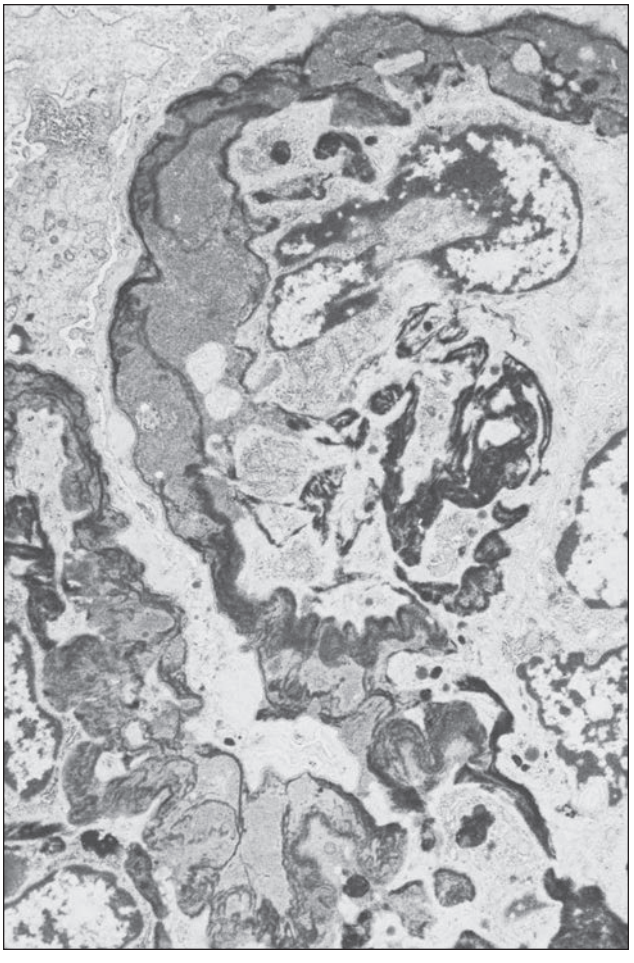

FIGURE 8.22 MPGN type III of Strife/Anders. Higher magnification of the silver impregnation of the plastic-embedded sections for transmission electron microscopy; a segment of a glomerulus from a patient with MPGN type III of strife. The remnant GBM is quite argyrophilic (electron dense) but contains 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

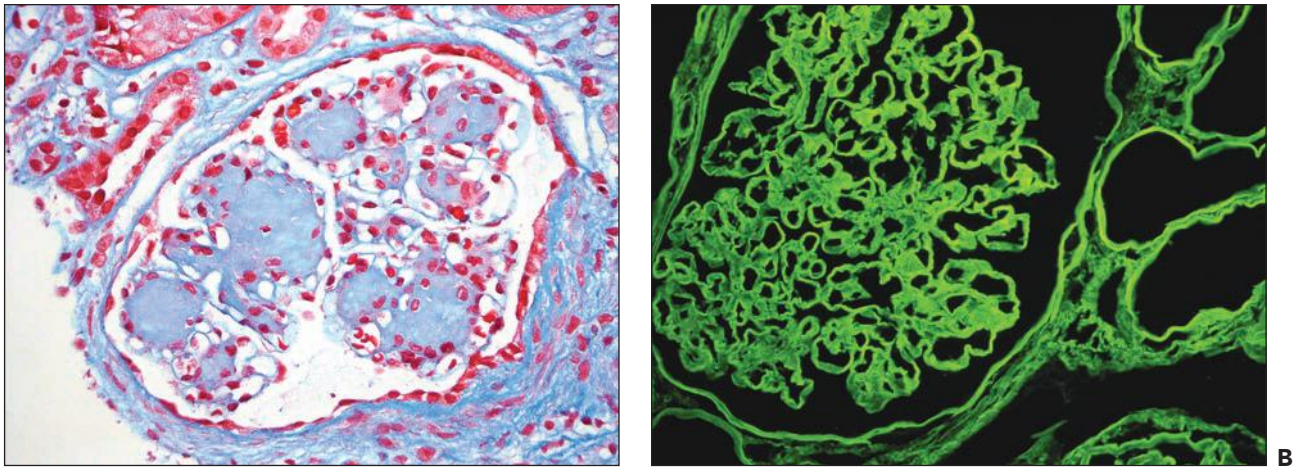

FIGURE 8.23 Kappa light chain deposition disease. A: There is solidification in mesangial areas that also show higher numbers of cells. Lobulation is accentuated. (Trichrome, ×400.) **B:** Immunofluorescence microscopy reveals extensive staining of the expanded mesangial regions, glomerular basement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

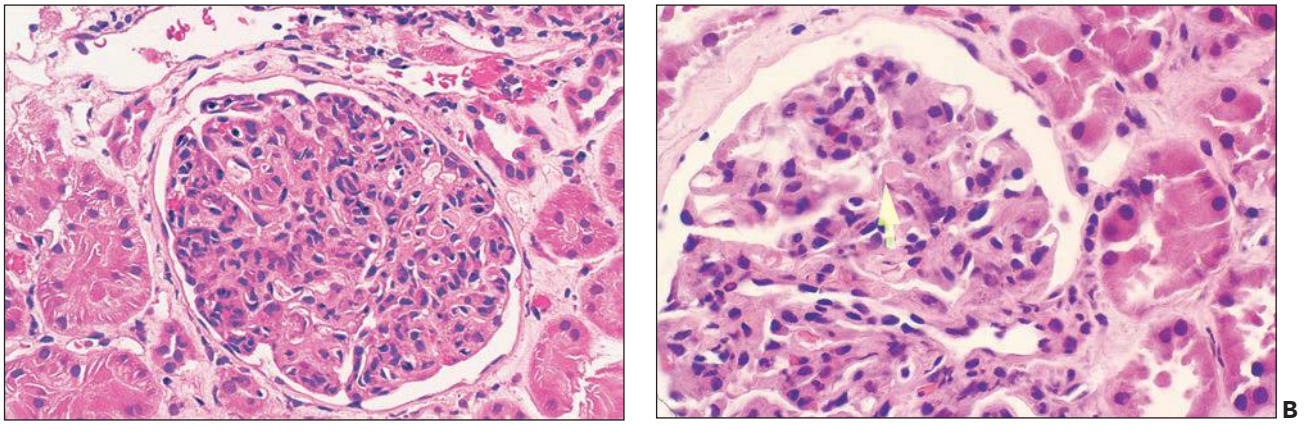

FIGURE 8.24 Cryoglobulinemic MPGN type I. There are thickened capillary walls and hypercellularity **(A,B)** and a few hyaline thrombi (**B,** *arrow*). (H&E, **A:** ×350, **B:** ×500.)

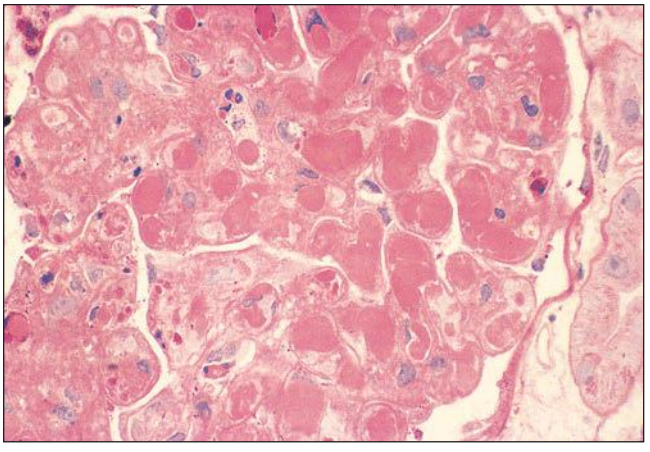

FIGURE 8.25 Cryoglobulinemic glomerulonephritis. There are numerous acidophilic hyaline thrombi in capillary lumens. (PAS, ×750.)

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 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).

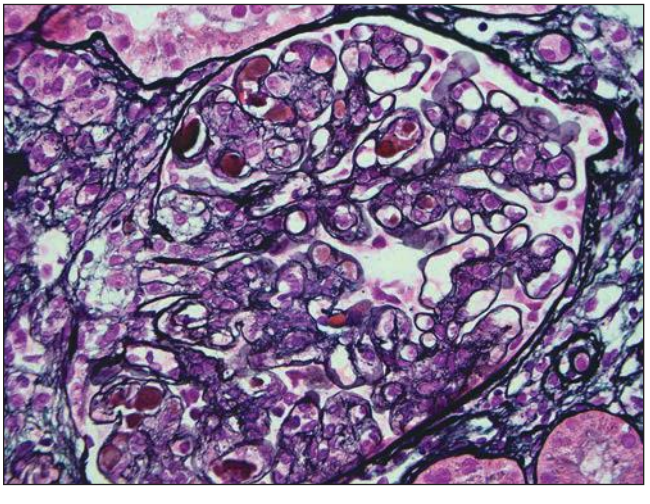

FIGURE 8.26 Cryoglobulinemic MPGN type I. There are multiple silver-negative hyaline thrombi and segmental double contours. (Jones silver, ×400.)

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

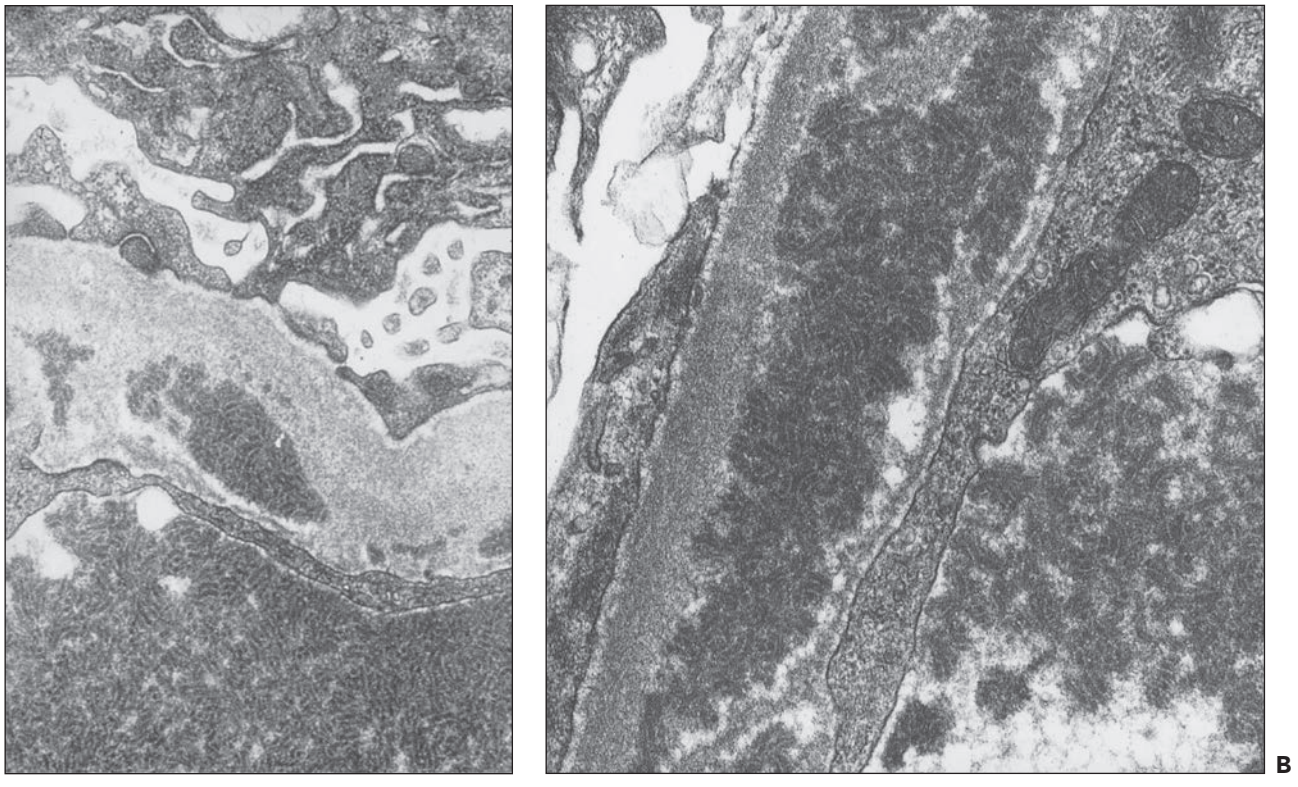

FIGURE 8.27 Hepatitis C–associated cryoglobulinemic glomerulonephritis. A & B: There are subendothelial and intraluminal electron-dense deposits with a microtubular substructure. Note the short parallel stacks of microtubules. The intramembranous deposits correspond to hyaline thrombi by light microscopy.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

REFERENCES

1. Fabrizi F, Colucci P, Ponticelli C, et al. Kidney and liver involvement in cryoglobulinemia. *Semin Nephrol* 2002;22:309.
2. Mazzucco G, Monga G, Casanova S, et al. Cell interposition in glomerular capillary walls in cryoglobulinemic glomerulonephritis (CRYGN): ultrastructural investigation of 23 cases. *Ultrastruct Pathol* 1986;10:355.
3. Hiramatsu R, Hoshino J, Suwabe T, et al. Membranoproliferative glomerulonephritis and circulating cryoglobulins. *Clin Exp Nephrol* 2014;18(1):88–94.
4. Fabrizi F, et al. Hepatitis C virus infection, mixed cryoglobulinemia and kidney disease. *Am J Kidney Dis* 2013;61:623–637.
5. Sheeran TP, White RH, Raafat F, et al. Hypocomplementaemia, C3 nephritic factor and type III mesangiocapillary glomerulonephritis progressing to systemic lupus erythematosus [Letter]. *Br J Rheumatol* 1995;34:90.
6. Markpwitz GS, D'Agati VD. Classification of lupus nephritis. *Curr Opin Nephrol Hypertens* 2009;18:220–225.
7. Clardy CW, Forristal J, Strife CF, et al. A properdin dependent nephritic factor slowly activating C3, C5, and C9 in membranoproliferative glomerulonephritis, types I and III. *Clin Immunol Immunopathol* 1989;50:333.
8. Goules A, Masouridi S, Tzioufas AG, et al. Clinically significant and biopsy-documented renal involvement in primary Sjögren syndrome. *Medicine (Baltimore)* 2000;79:241–249.
9. Orfila C, Lepert JC, Modesto A, et al. Henoch–Schonlein purpura and membranoproliferative-like glomerulonephritis. *Nephron* 1996;74:209.
10. Constantin A, Laroche M, Moulinier L, et al. Membranoproliferative glomerulonephritis, p-antineutrophil cytoplasmic antibodies, and rheumatoid arthritis. Report of a case. *Rev Rhum Engl Ed* 1996;63:141.
11. Haffner D, Schindera F, Aschoff A, et al. The clinical spectrum of shunt nephritis. *Nephrol Dial Transplant* 1997;12:1143.
12. Salmon D, Fantin B, Bricaire F, et al. Endocarditis due to *Pasteurella multocida* with glomerulonephritis. *Am J Med* 1989;86:493.
13. Frew AJ, Higgins RM. Empyema and mesangiocapillary glomerulonephritis with nephrotic syndrome. *Br J Dis Chest* 1988;82:93.
14. Ceylan K, Karahocagil MK, Soyoral Y, et al. Renal involvement in *Brucella* infection. *Urology* 2009;73:1179–1183.
15. Pecchini F, Bufano G, Ghiringhelli P. Membranoproliferative glomerulonephritis secondary to tuberculosis. *Clin Nephrol* 1997;47:63.
16. Weiner ID, Northcutt AD. Leprosy and glomerulonephritis: Case report and review of the literature. *Am J Kidney Dis* 1989;13:424.
17. Kirmizis D, Efstratiadis G, Economidou D, et al. MPGN secondary to Lyme disease. *Am J Kidney Dis* 2004;43:544.
18. McCausland FR, Niedermaier S, Bijol V, et al. Lyme disease-associated glomerulonephritis. *Nephrol Dial Transplant* 2011;26:3054–3056.
19. Sais MH, Layani MP, Colon S, et al. *Mycoplasma pneumoniae*-associated nephritis in children. *Pediatr Nephrol* 1999;13:39.
20. Hulton SA, Risdon RA, Dillon MJ. Mesangiocapillary glomerulonephritis associated with meningococcal meningitis, C3 nephritic factor and persistently low complement C3 and C5. *Pediatr Nephrol* 1992;6:239.
21. Zhang L, Meng H, Han X, et al. The relationship between HBV serum markers and the clinicopathological characteristics of hepatitis B virus-associated glomerulonephritis (HBV-GN) in the northeastern Chinese population. *Virol J* 2012;9:200.
22. Gilbert RD, Wiggelinkhuizen J. The clinical course of hepatitis B virus-associated nephropathy. *Pediatr Nephrol* 1994;8:11.
23. Chan TM. Hepatitis B and renal disease. *Curr Hepat Rep* 2010;9:99–105.
24. Johnson RJ, Couser WG. Hepatitis B infection and renal disease: Clinical, immunopathogenetic and therapeutic considerations. *Kidney Int* 1990;37:663.
25. Chan MK, Chan KW, Chan PC, et al. Adult-onset mesangiocapillary glomerulonephritis: A disease with a poor prognosis. *Q J Med* 1989;72:599.
26. Brzosko WJ, Krawczynski K, Nazarewicz T, et al. Glomerulonephritis associated with hepatitis B surface antigen immune complexes in children. *Lancet* 1974;2:477.
27. Stratta P, Camussi G, Ragni R, et al. Hepatitis B antigenaemia associated with active chronic hepatitis and mesangioproliferative glomerulonephritis. *Lancet* 1975;2:179.
28. Li PK, Lai FM, Ho SS, et al. Acute renal failure in hepatitis B virus–related membranous nephropathy with mesangiocapillary transition and crescentic transformation. *Am J Kidney Dis* 1992;19:76.
29. Johnson RJ, Gretch DR, Yamabe H, et al. Membranoproliferative glomerulonephritis associated with hepatitis C virus infection. *N Engl J Med* 1993;328:465.
30. Kidney Disease: Improving Global Outcomes (KDIGO). KDIGO clinical practice guidelines for the prevention, diagnosis, evaluation, and treatment of hepatitis C in chronic kidney disease. *Kidney Int* 2008;73(Suppl 109):S69–S77.
31. Ferris S, Dal Pero F, Bortoletto G, et al. Detailed analysis of the E2-IgM complex in hepatitis C-related type II mixed cryoglobulinemia. *J Viral Hepat* 2006;13:166–176.
32. D'Amico G. Renal involvement in hepatitis C infection: Cryoglobulinemia glomerulonephritis. *Kidney Int* 1998;54:650.
33. Perico N, Cattanco D, Bikbov B, et al. Hepatitis C infection and chronic renal disease. *Clin J Am Soc Nephrol* 2009;4:207–220.
34. Kim KK, Factor SM. Membranoproliferative glomerulonephritis and plexogenic pulmonary arteriopathy in a homosexual man with acquired immunodeficiency syndrome. *Hum Pathol* 1987;18:1293.
35. Nebuloni M, di Belgiojoso GB, et al. Glomerular lesions in HIV-positive patients: a 20-year experience from Northern Italy. *Clin Nephrol* 2009;72:38–45.

36. Mustonen K, Makela S, Helin H, et al. Mesangiocapillary glomerulonephritis caused by Puumala hantavirus infection. *Nephron* 2001;89:402.
37. Miettinen M, Mäkelä S, Haapala M, et al. Glomerulonephritis emerging shortly after Puumala hantavirus infection: A report on 7 patients. *Clin Nephrol* 2011;75:550–556.
38. Donini U, Rossi L, Palanchetti F, et al. BK papovavirus immune complexes in glomerulonephritis. *Proc Eur Dial Transplant Assoc* 1980;17:637.
39. Andresdottir MB, Assmann KJ, Hilbrands LB, et al. Primary Epstein–Barr virus infection and recurrent type I membranoproliferative glomerulonephritis after renal transplantation. *Nephrol Dial Transplant* 2000;15:1235–1237.
40. Chesney RW, O'Regan S, Guyda HJ, et al. *Candida* endocrinopathy syndrome with membranoproliferative glomerulonephritis: Demonstration of glomerular *Candida* antigen. *Clin Nephrol* 1976;5:232.
41. Date A, Neela P, Shastry JC. Membranoproliferative glomerulonephritis in a tropical environment. *Ann Trop Med Parasitol* 1983;77:279.
42. Covic A, Mititiuc I, Caruntu L, et al. Reversible nephrotic syndrome due to mesangiocapillary glomerulonephritis secondary to hepatic hydatid disease. *Nephrol Dial Transplant* 1996;11:2074.
43. Sethi S, Zand L, Leung N, et al. Membranoproliferative glomerulonephritis secondary to monoclonal gammopathy. *Clin J Am Soc Nephrol* 2010;5:770–782.
44. Kowalewska J, Nicosia RF, Smith KD, et al. Patterns of glomerular injury in kidneys infiltrated by lymphoplasmacytic neoplasms. *Hum Pathol* 2011;42:896–903.
45. Walker JF, O'Neil S, Campbell E, et al. Carcinoma of the oesophagus associated with membranoproliferative glomerulonephritis. *Postgrad Med J* 1981;57:592.
46. Enriquez R, Sirvent AE, Cabezuelo JB, et al. Membranoproliferative glomerulonephritis and gastric adenocarcinoma. *Nephrol Dial Transplant* 1999;14:242.
47. Usalan C, Emri S. Membranoproliferative glomerulonephritis associated with small cell lung carcinoma. *Int Urol Nephrol* 1998;30:209.
48. Sartelet H, Melin JP, Wynckel A, et al. Membranoproliferative glomerulonephritis (MPGN) and pulmonary carcinoid tumour. *Nephrol Dial Transplant* 1997;12:2405.
49. Reshi AR, Mir SA, Gangoo AA, et al. Nephrotic syndrome associated with transitional cell carcinoma of urinary bladder. *Scand J Urol Nephrol* 1997;31:295.
50. Rahman RC, Pollono D, Drut R, et al. Malignancy-associated membranoproliferative glomerulonephritis. *Pediatr Nephrol* 1997;11:208.
51. Salazar-Exaire D, Rodriguez A, Galindo-Rujana ME, et al. Membranoproliferative glomerulonephritis associated with a mixed-cell germinal ovary tumor. *Am J Nephrol* 2001;21:51–54.
52. D'Agati VD, Bomback AS. C3 glomerulopathy: what's in a name? *Kidney Int* 2012;82:379–381.
53. Sethi S, Fervenza FC. Membranoproliferative glomerulonephritis—a new look at an old entity. *N Engl J Med* 2012;366:1119–1131.
54. West CD, McAdams AJ. The alternative pathway C3 convertase and glomerular deposits [Review]. *Pediatr Nephrol* 1999;13:448.
55. Marder HK, Coleman TH, Forristal J, et al. An inherited defect in the C3 convertase, C3b, Bb, associated with glomerulonephritis. *Kidney Int* 1983;23:749.
56. Goodship T, Pappworth IY, Toth T, et al. Factor H autoantibodies in membranoproliferative glomerulonephritis. *Mol Immunol* 2012;52:200–206.
57. Coleman TH, Forristal J, Kosaka T, et al. Inherited complement component deficiencies in membranoproliferative glomerulonephritis. *Kidney Int* 1983;24:681.
58. Loirat C, Levy M, Peltier AP, et al. Deficiency of the second component of complement: its occurrence with membranoproliferative glomerulonephritis. *Arch Pathol Lab Med* 1980;104:467.
59. Suzuki J, Suzuki S, Nozawa R, et al. Membranoproliferative glomerulonephritis associated with heredity deficiency of 4th component of complement. *Clin Nephrol* 2003;60:279.
60. Soto K, Wu YL, Ortiz A, et al. Familial C4b deficiency and immune complex glomerulonephritis. *Clin Immunol* 2010;137:166–175.
61. Roord JJ, van Diemen-van Steenvoorde RA, Schuurman HJ, et al. Membranoproliferative glomerulonephritis in a patient with congenital deficiency of the third component of complement. *Am J Kidney Dis* 1989;13:413.
62. Coleman TH, Forristal J, West CD. Hereditary C6 deficiency in membranoproliferative glomerulonephritis (MPGN) type I. *Pediatr Res* 1979;13:446.
63. Miura T, et al. Membranoproliferative pattern of glomerular injury associated with complement 9 deficiency due to Arg95stop mutation. *Clin Exp Nephrol* 2011;15:86–91.
64. Servais A, Noel LH, Dragon-Durey MA, et al. Heterogeneous pattern of renal disease associated with homozygous factor H deficiency. *Hum Pathol* 2011;42:1305–1311.
65. Dragon-Durey MA, Frémeaux-Bacchi V, Loirat C, et al. Heterogeneous and homozygous factor H deficiencies associated with hemolytic uremic syndrome or membranoproliferative glomerulonephritis: report and genetic analysis of 16 cases. *J Am Soc Nephrol* 2004;15:789–795.
66. Berry PL, McEnery PT, McAdams AJ, et al. Membranoproliferative glomerulonephritis in two siblings. *Clin Nephrol* 1981;16:101.
67. Strife CF, Hug G, Chuck G, et al. Membranoproliferative glomerulonephritis and alpha-1-antitrypsin deficiency in children. *Pediatrics* 1983;71:88.
68. Elzouki AN, Lindgren S, Nilsson S, et al. Severe alpha 1-antitrypsin deficiency (PiZ homozygosity) with membranoproliferative glomerulonephritis and nephritic syndrome, reversible after orthotopic liver transplantation. *J Hepatol* 1997;26:1403.
69. Stutchfield PR, White RH, Cameron AH, et al. X-linked mesangiocapillary glomerulonephritis. *Clin Nephrol* 1986;26:150.
70. Bogdanovic RM, Dimitrijevic JZ, Nikolic VN, et al. Membranoproliferative glomerulonephritis in two siblings: report and literature review. *Pediatr Nephrol* 2000;14:400.
71. Sherwood MC, Pincott JR, Goodwin FJ, et al. Dominantly inherited glomerulonephritis and an unusual skin disease. *Arch Dis Child* 1987;62:1278.
72. Said SM, Cornell LD, Sethi S, et al. Acquired glomerular lesions in patients with Down syndrome. *Hum Pathol* 2012;43:81–88.
73. Halevi R, Davidovitz M, Mann S, et al. Gaucher's disease and mesangiocapillary glomerulonephritis in childhood: a coincidence? *Pediatr Nephrol* 1993;7:438.
74. Egbert BM, Schwartz E, Kempson RL. Kartagener syndrome: Report of a case with mesangiocapillary glomerulonephritis. *Arch Pathol Lab Med* 1977;101:95.
75. Kinberg JA, Angle CR, Wilson RB. Nephropathy-gonadal dysgenesis, type 2: Renal failure in three siblings with XY dysgenesis in one. *Am J Kidney Dis* 1987;9:507.
76. Robson WL, Leung AK. Membranoproliferative glomerulonephritis in a child with Prader-Willi syndrome. *Am J Med Genet* 1992;43:858.
77. Goodyer PR, Fong JS, Kaplan BS. Turner's syndrome, 46X, del (X) (p11), persistent complement activation and membranoproliferative glomerulonephritis. *Am J Nephrol* 1982;2:272.
78. Pan CG, Strife CF, Ward MK, et al. Long-term follow-up of nonsystemic lupus erythematosus glomerulonephritis in patients with hereditary angioedema: report of four cases. *Am J Kidney Dis* 1992;19:526.
79. Akpolat T, Akpolat I, Karagoz F, et al. Familial Mediterranean fever and glomerulonephritis and review of the literature. *Rheumatol Int* 2004;24:43.
80. Paydas S, Abayli B, Kocabas A, et al. Membranoproliferative glomerulonephritis associated pulmonary sarcoidosis. *Nephrol Dial Transplant* 1998;13:228.
81. Frey FJ, Trost B, Zimmerman A. Autoimmune adrenalitis, asthma and membranoproliferative glomerulonephritis. *Am J Nephrol* 1991;11:341.
82. Yuan XG, Hu W, Chen FF, et al. Renal complications of Castleman's disease: report of two cases and analysis of 75 cases. *Clin Exp Nephrol* 2011;15:921–926.
83. Jhaveri KD, D'Agati VD, Pursell R, et al.. Celiac sprue-associate membranoproliferative glomerulonephritis. *Nephrol Dial Transplant* 2009;24:3545–3548.
84. Miller RR. Membranoproliferative glomerulonephritis and amyloidosis. *Hum Pathol* 1984;15:1185.
85. Srikanta S, Malaviya AN, Rajagopalan P, et al. Association of type I (insulin-dependent) diabetes mellitus, autoimmunity, antinuclear antibody, and membranoproliferative glomerulonephritis. *Diabetes Care* 1983;6:71–74.
86. Meroni M, Sessa A, Battini G, et al. Alport syndrome with type I membranoproliferative glomerulonephritis [Letter]. *Nephron* 1993;65:479.

87. Villar MT, Bass P, Dewhurst G, et al. Autosomal dominant polycystic kidney disease complicated by glomerulonephritis. *Nephron* 1992;62:226.
88. Tatsumi T, Morishima T, Watarai T, et al. Recurrent Cushing's disease associated with nephrotic syndrome. *Intern Med* 1995;34:10.
89. Jaffe JA, Kimmel PL. Chronic nephropathies of cocaine and heroin abuse: A critical review. *Clin J Am Soc Nephrol* 2006;1:655–667.
90. Jha V, Murthy MS, Kohli HS, et al. Secondary membranoproliferative glomerulonephritis due to hemolytic uremic syndrome: an unusual presentation. *Ren Fail* 1998;20:845.
91. Kamei K, Nakagawa A, Otsuka Y, et al. Chronic glomerulonephritis associated with IgG subclass deficiency. *Pediatr Nephrol* 2007;22:2–9.
92. Surian M, Imbasciati E, Cosci P, et al. Glomerular disease and pregnancy, a study of 123 pregnancies. *Nephron* 1984;36:101.
93. Akoglu H, Dede F, Akoglu G, et al. Membranoproliferative glomerulonephritis associated with psoriasis vulgaris. *Ren Fail* 2009;31:858–861.
94. Leslie BR, Hamburger RJ, Stilmant MM, et al. Renal artery dysplasia in a patient with membranoproliferative glomerulonephritis. *Am J Med* 1979;66:528.
95. Velasquez Forero F, Garcia Prugue N, Ruiz Morales N. Idiopathic nephrotic syndrome of the adult with asymptomatic thrombosis of the renal vein. *Am J Nephrol* 1988;8:457.
96. Yoshikawa N, Truong LD, Mattioli CA, et al. Membranoproliferative glomerulonephritis in Takayasu's arteritis. *Am J Nephrol* 1988;8:240.
97. Navas-Palacios JJ, Usera-Sarraga G, GilMargin R, et al. Pathology of the kidney in "toxic oil epidemic syndrome." *J Toxicol Environ Health* 1984;13:1.
98. Rutherford PA, Veale D, Ashcroft T, et al. Mesangiocapillary glomerulonephritis as the presenting feature of cryptogenic organizing pneumonitis. *Nephrol Dial Transplant* 1992;7:1043.
99. Ashman N, Sheaff M, Raftery MJ. Mesangiocapillary glomerulonephritis associated with ulcerative colitis: A 6-year follow-up of 2 cases. *Clin Nephrol* 2003;60:146–148.
100. Wisnieski JJ, Baer AN, Christensen J, et al. Hypocomplementemic urticarial vasculitis syndrome. Clinical and serologic findings in 18 patients. *Medicine (Baltimore)* 1995;74:24.
101. Sakarcan A, Neuberg RW, McRedmoind KP, et al. Membranoproliferative glomerulonephritis develops in a child with autologous stem cell transplant. *Am J Kidney Dis* 2002;40:E19.
102. Little MA, Dupont P, Campbell E, et al. Severity of primary MPGN, rather than MPGN type, determines renal survival and post-transplantation recurrence risk. *Kidney Int* 2006;69:504.
103. Habib R, Antignac C, Hinglais N, et al. Glomerular lesions in the transplanted kidney in children. *Am J Kidney Dis* 1987;10:198.
104. Moroni G, Casati C, Qualini S, et al. Membranoproliferative glomerulonephritis type I in renal transplantation patients: A single-center study of a cohort of 68 renal transplants followed up for 11 years. *Transplantation* 2011;91:1222–1239.
105. Brigg JD, Jones E. Recurrence of glomerulonephritis following renal transplantation. *Nephrol Dial Transplant* 1999;14:564.
106. Briganti EM, Russ GR, McNeil JJ, et al. Risk of renal allograft loss from recurrent glomerulonephritis. *N Engl J Med* 2002;347:103.
107. Lorenz EC, Sethi S, Leung N, et al. Recurrent membranoproliferative glomerulonephritis after renal transplantation. *Kidney Int* 2010;177:721–728.
108. Angelo JR, Bell CS, Braun MC. Allograft failure in kidney transplant recipients with membranoproliferative glomerulonephritis. *Am J Kidney Dis* 2011;57:291–299.
109. Zhang PF, Rao KV, Anderson WR. An ultrastructural study of the membranoproliferative variant of transplant glomerulopathy. *Ultrastruct Pathol* 1988;12:185.
110. Nadasdy T, Satoskar A, Nadasdy G. Pathology of renal transplantation. In: Zhou XJ, et al., eds. *Silva's Diagnostic Renal Pathology*. New York: Cambridge University Press, 2009.
111. Andresdottir MB, Assmann KJ, Hoitsma AJ, et al. Recurrence of type I membranoproliferative glomerulonephritis after renal transplantation; analysis of the incidence, risk factors, and impact on graft survival. *Transplantation* 1997;63:1628.
112. Baid-Agrawal S, Farris AB III, Pascual M, et al. Overlapping pathways to transplant glomerulopathy: chronic humoral rejection, hepatitis C infection, and thrombotic microangiopathy. *Kidney Int* 2011;80:879–885.
113. Karakayali FY, Ozdemir H, Kivrakdal S, et al. Recurrent glomerular diseases after renal transplantation. *Transplant Proc* 2006;38:470–472.
114. Cahen R, Trolliet P, Dijoud F, et al. Severe recurrence of type I membranoproliferative glomerulonephritis after transplantation: remission on steroids and cyclophosphamide. *Transplant Proc* 1995;27:1746.
115. Lien YH, Scott K. Long-term cyclophosphamide treatment for recurrent type I membranoproliferative glomerulonephritis after transplantation. *Am J Kidney Dis* 2000;35:539.
116. Schwarz A, Krause PH, Offermann G, et al. Recurrent and de novo renal disease after kidney transplantation with or without cyclosporine A. *Am J Kidney Dis* 1991;17:524.
117. Smith RJ, Harris CL, Pickering MC. Dense deposit disease. *Mol Immunol* 2011;48:1604–1610.
118. Pickering MC, D'Agati VD, Nester CM, et al. C3 glomerulopathy: consensus report. *Kidney Int* 2013;84:1079–1089.
119. Zhou XJ, Laszik Z, Silva FG. Algorithmic approach to the interpretation of renal pathology. In: Zhou XJ, et al., eds. *Silva's Diagnostic Renal Pathology*. New York: Cambridge University Press, 2009.
120. Burkholder PM, Marchand A, Krueger RP. Mixed membranous and proliferative glomerulonephritis: a correlative light, immunofluorescence and electron microscopic study. *Lab Invest* 1970;23:459.
121. 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.
122. Strife CF, McEnery PT, McAdams AJ, et al. Membranoproliferative glomerulonephritis with disruption of the glomerular basement membrane. *Clin Nephrol* 1977;7:65.
123. Fahr T. Pathologische Anatomie des Morbus Brightii. In: Henke F, Lubarsch O, eds. *Handbuch der Speziellen Pathologischen Anatomie und Histologie*, Vol. 6. Berlin: Springer, 1925:156.
124. Cameron JS. The natural history of glomerulonephritis. In: Kincaid-Smith P, d'Apice A, Atkins R, eds. *Progress in Glomerulonephritis*. New York: Wiley, 1979:1.
125. MacCallum WG. Glomerular changes in nephritis. *Bull Johns Hopkins Hosp* 1934;55:416.
126. Ellis A. Natural history of Bright's disease: clinical, histological and experimental observations. *Lancet* 1942;1:1.
127. Bell ET. A clinical and pathological study of subacute and chronic glomerulonephritis, including lipoid nephrosis. *Am J Pathol* 1938;14:691.
128. Allen AC. *The kidney: Medical and surgical disease*. New York: Grune & Stratton, 1951.
129. Churg J, Grishman E. Subacute glomerulonephritis. *Am J Pathol* 1959;35:25.
130. Habib R, Michielsen P, DeMontera E, et al. Clinical, microscopic and electron microscopic data in the nephrotic syndrome of unknown origin. In: Wolstenholme GEW, Cameron MP, eds. *Renal Biopsy: Clinical and Pathological Significance*. London: Churchill Livingstone, 1961:70.
131. Jones DB. Nephrotic glomerulonephritis. *Am J Pathol* 1957;33:313.
132. Arakawa M, Kimmelstiel P. Circumferential mesangial interposition. *Lab Invest* 1969;21:276.
133. West CD, McAdams AJ, McConville JM, et al. Hypocomplementemic and normocomplementemic persistent (chronic) glomerulonephritis: clinical and pathologic characteristics. *J Pediatr* 1965;67:1089.
134. Gotoff SP, Fellers FX, Vawter GF, et al. The beta 1C globulin in childhood nephrotic syndrome: laboratory diagnosis of progressive glomerulonephritis. *N Engl J Med* 1965;273:524.
135. Kawamura T, Usui J, Kaseda K, et al. Primary membranoproliferative glomerulonephritis on the decline: decreased rate from the 1970s to the 2000s in Japan. *Clin Exp Nephrol* 2013;17:248–254.
136. Kumatowska I, Jedrzejka D, Malyska A, et al. Trends in the incidence of biopsy-proven glomerular disease in the adult population in central Poland in the years 1990–2010. *Kidney Blood Press Res* 2012;35:254–258.
137. Habib R, Kleinknecht C, Gubler MC, et al. Idiopathic membranoproliferative glomerulonephritis in children: report of 105 cases. *Clin Nephrol* 1973;1:194.
138. Takei T, Itabashi M, Moriyama T, et al. Positive C1q staining associated with poor renal outcome in membranoproliferative glomerulonephritis. *Clin Exp Nephrol* 2013;17:92–98.

139. Kim Y, Michael AF, Fish AJ. Idiopathic membranoproliferative glomerulonephritis. In: Brenner B, Stein J, eds. *Nephrotic Syndrome*. New York: Churchill Livingstone, 1982:237.
140. Levy M, Gubler MC, Habib R. New concepts in membranoproliferative glomerulonephritis. In: Kincaid-Smith P, d'Apice AJF, Atkins RC, eds. *Progress in Glomerulonephritis*. New York: Wiley, 1979:177.
141. Magil AB, Price JD, Bower G, et al. Membranoproliferative glomerulonephritis type I. Comparison of natural history in children and adults. *Clin Nephrol* 1979;11:239.
142. Pickering RJ, Herdman RC, Michael AF, et al. Chronic glomerulonephritis associated with low serum complement activity (chronic hypocomplementemic glomerulonephritis). *Medicine (Baltimore)* 1970;49:207.
143. West CD, Ruley EJ, Spitzer RE, et al. The natural history of membranoproliferative glomerulonephritis: Its relation to the hypocomplementemia. In: Kincaid-Smith P, Mathew TH, Becker EL, eds. *Glomerulonephritis: Morphology, Natural History, and Treatment, Part I*. New York: Wiley, 1973:531.
144. Servais A, Noël LH, Roumenina LT, et al. Acquired and genetic complement abnormalities play a critical role in dense deposits disease and other C3 glomerulopathies. *Kidney Int* 2012;82:454–464.
145. James S, Neiberger R, Donnelly W, et al. Membranoproliferative glomerulonephritis in a fifteen-month-old boy. *Child Nephrol Urol* 1990;10:218.
146. Cameron JS, Ogg CS, Turner DR, et al. Mesangiocapillary glomerulonephritis and persistent hypocomplementemia. In: Kincaid-Smith P, Mathew TH, Becker EL, eds. *Glomerulonephritis: Morphology, Natural History, and Treatment, Part 1*. New York: Wiley, 1973:541.
147. Donadio JV Jr, Slack TK, Holley KE, et al. Idiopathic membranoproliferative (mesangiocapillary) glomerulonephritis: a clinicopathologic study. *Mayo Clin Proc* 1979;54:141.
148. Cameron JS, Turner DR, Heaton J, et al. Idiopathic mesangiocapillary glomerulonephritis: comparison of types I and II in children and adults and long-term prognosis. *Am J Med* 1983;74:175.
149. Moutzouris D, Herlitz L, Appel GB, et al. Renal biopsy in the very elderly. *Clin J Am Soc Nephrol* 2009;4:1073–1082.
150. Pincon E, Rioux-Leclercq N, Frouget T, et al. Renal biopsies after 70 years of age: a retrospective longitudinal study from 2000 to 2007 on 150 patients in Western France. *Arch Gerontol Geriatr* 2011;5:e120–e124.
151. Cameron JS, Glasgow EF, Ogg CS, et al. Membranoproliferative glomerulonephritis and persistent hypocomplementaemia. *Br Med J* 1970;4:7.
152. Kawasaki Y, Suzuki J, Nozawa R, et al. Efficacy of school urinary screening for membranoproliferative glomerulonephritis type I. *Arch Dis Child* 2002;86:21.
153. Burgess E, Curtis M, Benediktsson H. Membranoproliferative glomerulonephritis presenting as malignant hypertension [Letter]. *Nephron* 1990;54:369.
154. Watson AR, Poucell S, Thorner P, et al. Membranoproliferative glomerulonephritis type I in children: correlation of clinical features with pathologic subtypes. *Am J Kidney Dis* 1984;4:141.
155. Tarshish P, Bernstein J, Tobin JN, et al. Treatment of mesangiocapillary glomerulonephritis with alternate-day prednisone: a report of the International Study of Kidney Disease in Children. *Pediatr Nephrol* 1992;6:123.
156. International Study of Kidney Disease in Children. Nephrotic syndrome in children: prediction of histopathology from clinical and laboratory characteristics at time of diagnosis. *Kidney Int* 1978;13:159.
157. Haas M, Meehan SM, Karrison TG, et al. Changing etiologies of unexplained adult nephritic syndrome: a comparison of renal biopsy findings from 1976–1979 and 1995–1997. *Am J Kidney Dis* 1997;30:621.
158. Johnson RJ, Hurtado A, Merszei J, et al. Hypothesis: Dysregulation of immunologic balance resulting from hygiene and socioeconomic factors may influence the epidemiology and cause of glomerulonephritis worldwide. *Am J Kidney Dis* 2003;42:575.
159. Hultberg B, Ravnskov U. The excretion of N-acetyl-beta-glucosaminidase in glomerulonephritis. *Clin Nephrol* 1981;15:33.
160. Futrakul P, Kullavanijaya P, Watana D, et al. Tubular functions in glomerulonephropathies in childhood. *Int J Pediatr Nephrol* 1981;2:17.
161. Luder AS, Cohen SL, Fisher C. Nephrotic syndrome complicated by tubular dysfunction: case report and review of possible mechanisms. *Postgrad Med J* 1980;56:282.
162. Yata N, Ikeda M, Ishikura K, et al. Typical MPGN with few urinary abnormalities. *Am J Kidney Dis* 2004;43:918.
163. Levy M, Gubler MC, Sich M, et al. Immunopathology of membranoproliferative glomerulonephritis with subendothelial deposits (type I MPGN). *Clin Immunol Immunopathol* 1978;10:477.
164. Habib R, Loirat C, Gubler MC, et al. Morphology and serum complement levels in membranoproliferative glomerulonephritis. *Adv Nephrol* 1974;4:109.
165. Varade WS, Forristal J, West CD. Patterns of complement activation in idiopathic membranoproliferative glomerulonephritis, types I, II, and III. *Am J Kidney Dis* 1990;16:196.
166. Border WA. Immune complex detection in glomerular diseases. *Nephron* 1979;24:105.
167. Davis CA, Marder H, West CD. Circulating immune complexes in membranoproliferative glomerulonephritis. *Kidney Int* 1981;20:728.
168. Woodroffe AJ, Border WA, Theofilopoulos AN, et al. Detection of circulating immune complexes in patients with glomerulonephritis. *Kidney Int* 1977;12:268.
169. Endoh M, Suga T, Sakai H. IgG, IgA, and IgM rheumatoid factors in patients with glomerulonephritis. *Nephron* 1985;39:330.
170. Barceló P, Lopez-Lillo J, Cabero L, et al. Successful pregnancy in primary glomerular disease. *Kidney Int* 1986;30:914.
171. Morton MR, Bannister KM. Renal failure due to mesangiocapillary glomerulonephritis in pregnancy: Use of plasma exchange therapy. *Clin Nephrol* 1993;40:74.
172. Tomura S, Tsutani K, Sakuma A, et al. Discriminant analysis in renal histological diagnosis of primary glomerular diseases. *Clin Nephrol* 1985;23:55.
173. Konvalinka A, Scholey JW, Diamandis EP. Searching for new biomarkers of renal diseases through proteomics. *Clin Chem* 2012;58:353–365.
174. Jones DB. Membranoproliferative glomerulonephritis: one or many diseases? *Arch Pathol Lab Med* 1977;101:457.
175. Laohapand T, Cattell V, Gabriel JR. Monocyte infiltration in human glomerulonephritis. *Clin Nephrol* 1983;19:309.
176. Soma J, Saito T, Sato H, et al. Intraglomerular immune cell infiltration and complement 3 deposits in membranoproliferative glomerulonephritis type I: a serial-biopsy study of 25 cases. *Am J Kidney Dis* 1994;23:365.
177. Yang N, Isbel NM, Nicolic-Paterson DJ, et al. Local macrophage proliferation in human glomerulonephritis. *Kidney Int* 1998;54:143.
178. Lan HY, Yang N, Nikolic-Paterson DJ, et al. Expression of macrophage migration inhibitory factor in human glomerulonephritis. *Kidney Int* 2000;57:499.
179. Wu Q, Tanaka H, Hirukawa T, et al. Characterization and quantification of proliferating cell patterns in endocapillary proliferation. *Nephrol Dial Transplant* 2012;27:3234–3241.
180. Ferrario F, Castiglione A, Colasanti G, et al. The detection of monocytes in human glomerulonephritis. *Kidney Int* 1985;28:513.
181. Monga G, Mazzucco G, di Belgiojoso GB, et al. The presence and possible role of monocyte infiltration in human chronic proliferative glomerulonephritides: light microscopic, immunofluorescence, and histochemical correlations. *Am J Pathol* 1979;94:271.
182. Patrakka J, Ruotsalainen V, Ketola I, et al. Expression of nephrin in pediatric kidney diseases. *J Am Soc Nephrol* 2001;12:289.
183. Wang SX, Rastaldi MP, Patari A, et al. Patterns of nephrin and a new proteinuria-associated protein expression in human renal diseases. *Kidney Int* 2002;61:141.
184. Nakamoto Y, Yasuda T, Imai H, et al. Circumferential mesangial interposition: a form of mesangiolysis [Review]. *Nephrol Dial Transplant* 1992;7:373.
185. Lee HS, Lee JS, Koh HI, et al. Intraglomerular lipid deposition in routine biopsies. *Clin Nephrol* 1991;36:67.
186. Bohle A, Biwer E, Christensen JA. Hyperperfusion injury of the human kidney in different glomerular diseases. *Am J Nephrol* 1988;8:179.
187. Miller MN, Baumal R, Poucell S, et al. Incidence and prognostic importance of glomerular crescents in renal diseases of childhood. *Am J Nephrol* 1984;4:244.
188. Jardim HM, Leake J, Risdon RA, et al. Crescentic glomerulonephritis in children. *Pediatr Nephrol* 1992;6:231.
189. Korzets Z, Bernheim J, Bernheim J. Rapidly progressive glomerulonephritis (crescentic glomerulonephritis) in the course of type I idiopathic membranoproliferative glomerulonephritis. *Am J Kidney Dis* 1987;10:56.

190. Gaffney EF. Prominent parietal epithelium: a common sign of renal glomerular injury. *Hum Pathol* 1982;13:651.
191. Taguchi T, Bohle A. Evaluation of change with time of glomerular morphology in membranoproliferative glomerulonephritis: a serial biopsy of 33 cases. *Clin Nephrol* 1989;31:297.
192. Striker LM-M, Killen PD, Chi E, et al. The composition of glomerulosclerosis. I. Studies in focal sclerosis, crescentic glomerulonephritis, and membranoproliferative glomerulonephritis. *Lab Invest* 1984;51:181.
193. Yoshikawa N, Yoshiara S, Yoshiya K, et al. Focal and diffuse membranoproliferative glomerulonephritis in children. *Am J Nephrol* 1988;8:102.
194. Kano K, Nishikura K, Kojima M, et al. A patient with membranoproliferative glomerulonephritis diagnosed by the third biopsy via endocapillary proliferative glomerulonephritis. *Clin Exp Nephrol* 2003;7:157.
195. D'Amico G, Ferrario F. Mesangiocapillary glomerulonephritis [Review]. *J Am Soc Nephrol* 1992;2:S159.
196. Hattori M, Kim Y, Steffes MW, et al. Structural-functional relationships in type I mesangiocapillary glomerulonephritis. *Kidney Int* 1993;43:381.
197. Schmitt H, Cavalcanti de Oliveira V, Bohle A. Tubulointerstitial alterations in type I membranoproliferative glomerulonephritis: an investigation of 259 cases. *Pathol Res Pract* 1987;182:6.
198. Fischbach H, Mackensen S, Grund KE, et al. Relationship between glomerular lesions, serum creatinine and interstitial volume in membranoproliferative glomerulonephritis. *Klin Wochenschr* 1977;55:603.
199. Mackensen-Haen S, Bohle A, Christensen J, et al. The consequences for renal function of widening of the interstitium and changes in the tubular epithelium of the renal cortex and outer medulla in various renal diseases. *Clin Nephrol* 1992;37:70.
200. Segerer S, Banas B, Wornle M, et al. CXCR3 is involved in tubulointerstitial injury in human glomerulonephritis. *Am J Pathol* 2004;164:635.
201. Davis BK, Cavallo T. Membranoproliferative glomerulonephritis: localization of early components of complement in glomerular deposits. *Am J Pathol* 1976;84:283.
202. Morel-Maroger L, Leathem A, Richet G. Glomerular abnormalities in nonsystemic diseases: relationship between findings by light microscopy and immunofluorescence in 433 renal biopsy specimens. *Am J Med* 1972;53:170.
203. Westberg NG, Naff GB, Boyer JT, et al. Glomerular deposition of properdin in acute and chronic glomerulonephritis with hypocomplementemia. *J Clin Invest* 1971;50:642.
204. Zucchelli P, Sasdelli M, Cagnoli L, et al. Membranoproliferative glomerulonephritis: correlations between immunological and histological findings. *Nephron* 1976;17:449.
205. Doi T, Mayumi M, Kanatsu K, et al. Distribution of IgG subclasses in membranous nephropathy. *Clin Exp Immunol* 1984;58:57.
206. Imai H, Hamai K, Komatsuda A, et al. IgG subclasses in patients with membranoproliferative glomerulonephritis, membranous nephropathy, and lupus nephritis. *Kidney Int* 1997;51:270.
207. Kawasaki Y, Suzuki J, Kakai N, et al. Evaluation of T-helper-1/-2 balance on the basis of IgG subclasses and serum cytokines in children with glomerulonephritis. *Am J Kidney Dis* 2004;44:42.
208. Orfila C, Rakotoarivony J, Manuel Y, et al. Immunofluorescence characterization of light chains in human nephropathies. *Virchows Arch A Pathol Anat Histopathol* 1988;412:591.
209. Yamashina M, Takami T, Kanemura T, et al. Immunohistochemical demonstration of complement components in formalin-fixed and paraffin-embedded renal tissues. *Lab Invest* 1989;60:311.
210. Kazatchkine MD, Fearon DT, Appay MD, et al. Immunohistochemical study of the human glomerular C3b in normal kidney and in 75 cases of renal diseases: loss of C3b receptor antigen in focal hyalinosis and proliferative nephritis of systemic lupus erythematosus. *J Clin Invest* 1982;69:900.
211. Lehman DH, Wilson CB, Dixon FJ. Extraglomerular immunoglobulin deposits in human nephritis. *Am J Med* 1975;58:765.
212. Murphy BF, d'Apice AJ. Identification of components of glomerular immune deposits using monoclonal antibodies. *Pathology* 1988;20:130.
213. Nakamura T, Oite T, Kazama T, et al. Monoclonal antibodies to human glomerular antigens. *Virchows Arch A Pathol Anat Histopathol* 1988;412:573.
214. Hara M, Mase D, Inaba S, et al. Immunohistochemical localization of glomerular basement membrane antigens in various renal diseases. *Virchows Arch A Pathol Anat Histopathol* 1986;408:403.
215. Büyükbabani N, Droz D. Distribution of the extracellular matrix components in human glomerular lesions. *J Pathol* 1994;172:199.
216. Rogers T, Rakheja D, Zhou XJ. Glomerular diseases associated with nephritic syndrome and/or rapidly progressive glomerulonephritis. In: Zhou XJ, et al., eds. *Silva's Diagnostic Renal Pathology*. New York: Cambridge University Press, 2009.
217. Anders D, Thoenes W. Basement membrane changes in membranoproliferative glomerulonephritis: a light and electron microscopic study. *Virchows Arch A Pathol Anat Histopathol* 1975;369:87.
218. Herrera G. Renal diseases associated with hematopoietic disorders or organized deposits. In: Zhou XJ, et al., eds. *Silva's Diagnostic Renal Pathology*. New York: Cambridge University Press, 2009.
219. Sato H. Ultrastructural study on membranoproliferative glomerulonephritis with special reference to subepithelial deposits [in Japanese]. *Nippon Jinzo Gakkai Shi* 1990;32:973.
220. Dowling JP, Mathews DC. Silver methenamine impregnation: A useful adjunct to renal electron microscopy. *Pathology* 1987;19:410.
221. Huh W, Kim DJ, Kim MK, et al. Expression of nephrin in acquired human glomerular disease. *Nephrol Dial Transplant* 2002;17:478.
222. Bonsib SM. Segmental subepithelial deposits in primary glomerulonephritis: Scanning electron microscopic examination of acellular glomeruli. *Hum Pathol* 1985;16:1115.
223. Cameron JS, Ogg CS, White RHR, et al. The clinical features and prognosis of patients with normocomplementemic mesangiocapillary glomerulonephritis. *Clin Nephrol* 1973;1:8.
224. Northway JD, McAdams AJ, Forristal J, et al. A "silent" phase of hypocomplementemic persistent nephritis detectable by reduced serum beta-1c-globulin levels. *J Pediatr* 1969;74:28.
225. McEnery PT, McAdams AJ, West CD. The effect of prednisone in a high-dose, alternate-day regimen on the natural history of idiopathic membranoproliferative glomerulonephritis. *Medicine (Baltimore)* 1985;64:401.
226. Schmitt H, Bohle A, Reineke T, et al. Long-term prognosis of membranoproliferative glomerulonephritis type I. Significance of clinical and morphological parameters: An investigation of 220 cases. *Nephron* 1990;55:242.
227. D'Amico G. Influence of clinical and histological features on actuarial renal survival in adult patients with idiopathic IgA nephropathy, membranous nephropathy, and membranoproliferative glomerulonephritis: Survey of the recent literature [Review]. *Am J Kidney Dis* 1992;20:315.
228. Braun MC, West CD, Strife CF. Differences between membranoproliferative glomerulonephritis types I and III in long-term response to an alternate-day prednisone regimen. *Am J Kidney Dis* 1999;34:1022.
229. Garcia-de la Puente S, Orozco-Loza IL, Zaltzman-Girshevich S, et al. Prognostic factors in children with membranoproliferative glomerulonephritis type I. *Pediatr Nephrol* 2008;23:929–935.
230. Orofino L, Quereda C, Lamas S, et al. Hypertension in primary chronic glomerulonephritis: analysis of 288 biopsied patients. *Nephron* 1987;45:22.
231. Arslan S, Saatci U, Ozen S, et al. Membranoproliferative glomerulonephritis in childhood: factors affecting prognosis. *Int Urol Nephrol* 1997;29:711.
232. Bazzi C, Petrini C, Rizza V, et al. Characterization of proteinuria in primary glomerulonephritides: urinary polymers of albumin. *Am J Kidney Dis* 1997;30:401.
233. Kawasaki Y, Suzuki J, Sakai N, et al. Predicting the prognosis of renal dysfunction by renal expression of alpha-smooth muscle actin in children with MPGN Type I. *Am J Kidney Dis* 2003;42:1131.
234. Schwertz R, Rother U, Anders D, et al. Complement analysis in children with idiopathic membranoproliferative glomerulonephritis: a long-term follow-up. *Pediatr Allergy Immunol* 2001;12:166.
235. Solling J. Circulating immune complexes in glomerulonephritis: a longitudinal study. *Clin Nephrol* 1983;20:177.
236. Soma J, Ootaka T, Sato H, et al. Tubulointerstitial changes are less important in membranoproliferative glomerulonephritis than in IgA nephropathy. *Nephron* 2000;86:230.
237. Soma J, Saito T, Ootaka T, et al. Differences in glomerular leukocyte infiltration between IgA nephropathy and membranoproliferative glomerulonephritis. *Nephrol Dial Transplant* 1998;13:608.
238. Ford DM, Briscoe DM, Shanley PF, et al. Childhood membranoproliferative glomerulonephritis type I. Limited steroid therapy. *Kidney Int* 1992;41:1606.

239. Brunt EM, Kissane JM, Cole BR, et al. Transmission and resolution of type I membranoproliferative glomerulonephritis in recipients of cadaveric renal allografts. *Transplantation* 1988;46:595.
240. West CD. Idiopathic membranoproliferative glomerulonephritis in childhood. *Pediatr Nephrol* 1992;6:96.
241. McEnery PT. Membranoproliferative glomerulonephritis: the Cincinnati experience—cumulative renal survival from 1957 to 1989. *J Pediatr* 1990;116:S109.
242. Edelmann CM Jr. Long-term low-dose prednisone ameliorates the course of membranoproliferative glomerulonephritis (MPGN): a report of the International Study of Kidney Disease in Children. *Pediatr Res* 1987;21:474.
243. International Study of Kidney Disease in Children. Alternate-day steroid therapy in membranoproliferative glomerulonephritis: a randomized controlled clinical trial. *Kidney Int* 1982;21:150.
244. Mota-Hernandez F, Gordillo-Paniagua G, Munoz-Arizpe R, et al. Prednisone versus placebo in membranoproliferative glomerulonephritis: long-term clinicopathological correlations. *Int J Pediatr Nephrol* 1985;6:25.
245. Yanagihara T, Hayakawa M, Yoshida J, et al. Long-term follow-up of diffuse membranoproliferative glomerulonephritis type I. *Pediatr Nephrol* 2005;20:585.
246. Levin A. Management of membranoproliferative glomerulone phritis: Evidence-based recommendations. *Kidney Int* 1999;55:S41.
247. Faedda R, Satta A, Tanda F, et al. Immunosuppressive treatment of membranoproliferative glomerulonephritis. *Nephron* 1994;67:59.
248. Toz H, Ok F, Unsai A, et al. Effectiveness of pulse cyclophosphamide plus oral steroid therapy in idiopathic membranoproliferative glomerulonephritis. *Nephrol Dial Transplant* 1997;12:1081.
249. Bagheri N, Nemati E, Rahbar K, et al. Cyclosporine in the treatment of membranoproliferative glomerulonephritis. *Arch Iran Med* 2008;11:26–29.
250. Jones G, Juszczak M, Kingdon E, et al. Treatment of idiopathic membranoproliferative glomerulonephritis with mycophenolate mofetil and steroids. *Nephrol Dial Transplant* 2004;19:3160.
251. De S, Al-Nabhani D, Thorner P, et al. Remission of resistant MPGN type I with mycophenolate mofetil and steroids. *Pediatr Nephrol* 2009;24:597–600.
252. Perez-Saez MJ, Toledo K, Navarro MD, et al. Recurrent membranoproliferative glomerulonephritis after second renal graft treated with plasmapheresis and Rituximab. *Transplant Proc* 2011;43:4005–4009.
253. Kasai N, Parbtani A, Cameron JS, et al. Platelet aggregating immune complexes and intraplatelet serotonin in idiopathic glomerulonephritis and systemic lupus. *Clin Exp Immunol* 1981;43:64.
254. Donadio JV Jr, Anderson CF, Mitchell C III, et al. Membranoproliferative glomerulonephritis: A prospective clinical trial of platelet-inhibitor therapy. *N Engl J Med* 1984;310:1421.
255. Zauner I, Bohler J, Braun N, et al. Effect of aspirin and dipyridamole on proteinuria in idiopathic membranoproliferative glomerulonephritis: A multicentre prospective clinical trial. *Nephrol Dial Transplant* 1994;9:619.
256. Zimmerman SW, Moorthy AV, Dreher WH, et al. Prospective trial of warfarin and dipyridamole in patients with membranoproliferative glomerulonephritis. *Am J Med* 1983;75:920.
257. Harmankaya O, Basturk T, Ozturk Y, et al. Effect of acetylsalicylic acid and dipyridamole in primary membranoproliferative glomerulonephritis type I. *Int Urol Nephrol* 2001;33:583.
258. Chapman SJ, Cameron JS, Chantler C, et al. Treatment of mesangiocapillary glomerulonephritis in children with combined immunosuppression and anticoagulation. *Arch Dis Child* 1980;55:446.
259. Dillon JJ, Hladunewich M, Haley WE, et al. Rituximab therapy for type 1 membranoproliferative glomerulonephritis. *Clin Nephrol* 2012;77:290–295.
260. Radhakrishnan S, Lunn A, Kirschfink M, et al. Eculizumab and refractory membranoproliferative glomerulonephritis. *N Engl J Med* 2012;366:1165–1166.
261. Kong WY, Swaminathan R, Irish A. Our experience with rituximab therapy for adult onset primary glomerulonephritis and review of literature. *Int Urol Nephrol* 2013;45:795–802.
262. Amemiya S, Ito H, Kato H, et al. A case of membranous proliferative glomerulonephritis type III (Burkholder) with the deposition of both HBeAg and HBsAg. *Int J Pediatr Nephrol* 1983;4:267.
263. Jackson EC, McAdams AJ, Strife CF, et al. Differences between membranoproliferative glomerulonephritis types I and III in clinical presentation, glomerular morphology, and complement perturbation. *Am J Kidney Dis* 1987;9:115.
264. Strife CF, Jackson EC, McAdams AJ. Type III membranoproliferative glomerulonephritis: Long-term clinical and morphologic evaluation. *Clin Nephrol* 1984;21:323.
265. West CD, McAdams AJ. Glomerular paramesangial deposits: association with hypocomplementemia in membranoproliferative glomerulonephritis types I and III. *Am J Kidney Dis* 1998;31:427.
266. West CD, McAdams AJ. Membranoproliferative glomerulonephritis type III. Association of glomerular deposits with circulating nephritic factor-stabilized convertase. *Am J Kidney Dis* 1998;32:56.
267. Sun IO, Hong YA, et al. Type III membranoproliferative glomerulonephritis in a patient with primary Sjögren's syndrome. *Clin Nephrol* 2013;79:171–174.
268. de Chadarevian JP, Lischner HW, Karmazin N, et al. Pulmonary hypertension and HIV infection: new observations and review of the syndrome. *Mod Pathol* 1994;7:685.
269. Iitaka K, Moriya S, Nakamura S, et al. Long-term follow-up of type III membranoproliferative glomerulonephritis in children. *Pediatr Nephrol* 2002;17:373.
270. Morales JM, Martinez MA, Munoz de Bustillo E, et al. Recurrent type III membranoproliferative glomerulonephritis after kidney transplantation. *Transplantation* 1997;63:1186.
271. Ramesh Prasad GV, Shamy F, Zaltzman JS. Recurrence of type III membranoproliferative glomerulonephritis after renal transplantation. *Clin Nephrol* 2004;61:80.
272. Vernon KA, Cook HT. Complement in glomerular disease. *Adv Chronic Kidney Dis* 2012;19:84–92.
273. Couser WG. Basic and translational concepts of immune-mediated glomerular diseases. *J Am Soc Nephrol* 2012;23:381–399.
274. Fervenza FC, Sethi S, Glassock RJ. Idiopathic membranoproliferative glomerulonephritis: does it exist? *Nephrol Dial Transplant* 2012;27:4288–4294.
275. West C. Complement and glomerular diseases. In: Volonakis JE, Frank MM, eds. *The Human Complement System in Health and Sisease*. New York: M. Dekker, Inc., 1998:571.
276. Horigome I, Seino J, Sudo K, et al. Terminal complement complex in plasma from patients with systemic lupus erythematosus and other glomerular diseases. *Clin Exp Immunol* 1987;70:417.
277. Clardy CW, Forristal J, Strife CF, et al. Serum terminal complement component levels in hypocomplementemic glomerulonephritides. *Clin Immunol Immunopathol* 1989;50:307.
278. Peters DK, Martin A, Weinstein A, et al. Complement studies in membranoproliferative glomerulonephritis. *Clin Exp Immunol* 1972;11:311.
279. Ruddy S, Carpenter CB, Chin KW, et al. Human complement metabolism: An analysis of 144 studies. *Medicine (Baltimore)* 1975;54:165.
280. Charlesworth JA, Williams DG, Sherington E, et al. Metabolic studies of the third component of complement and the glycine-rich beta glycoprotein in patients with hypocomplementemia. *J Clin Invest* 1974;53:1578.
281. Vallota EH, Forristal J, Spitzer RE, et al. Continuing C3 breakdown after bilateral nephrectomy in patients with membranoproliferative glomerulonephritis. *J Clin Invest* 1971;50:522.
282. West CD, Winter S, Forristal J, et al. Evidence for in vivo breakdown of beta-1c-globulin in hypocomplementemic glomerulonephritis. *J Clin Invest* 1967;46:539.
283. Spitzer RE, Vallota EH, Forristal J, et al. Serum C3 lytic system in patients with glomerulonephritis. *Science* 1969;164:436.
284. Williams DG, Bartlett A, Duffus P. Identification of nephritic factor as an immunoglobulin. *Clin Exp Immunol* 1978;33:425.
285. Davis AE, Gelfand EW, Schur PH, et al. IgG subclass studies of C3 nephritic factor. *Clin Immunol Immunopathol* 1978;11:98.
286. Davis AE, Ziegler JB, Gelfand EW, et al. Heterogeneity of nephritic factor and its identification as an immunoglobulin. *Proc Natl Acad Sci U S A* 1977;74:3980.
287. Whaley K, Ward D, Ruddy S. Modulation of the properdin amplification loop in membranoproliferative and other forms of glomerulonephritis. *Clin Exp Immunol* 1979;35:101.

288. Daha MR, Fearon DT, Austen KF. C3 nephritic factor (C3NeF): Stabilization of fluid phase and cell bound alternative pathway convertase. *J Immunol* 1976;116:1.
289. Spitzer RE, Stitzel AE, Tsokos GC. Production of IgG and IgM autoantibody to the alternative pathway C3 convertase in normal individuals and patients with membranoproliferative glomerulonephritis. *Clin Immunol Immunopathol* 1990;57:10.
290. Strife CF, Leahy AE, West CD. Antibody to acryptic, solid phase C1q antigen in membranoproliferative nephritis. *Kidney Int* 1989;35:836.
291. Walport MJ, Davies KA, Botto M, et al. C3 nephritic factor and SLE. Report of four cases and review of the literature [Review]. *Q J Med* 1994;87:609.
292. Paixao-Cavalcante D, Lopez-Trascasa M, Skattum L, et al. Sensitive and specific assays for C3 nephritic factor clarify mechanisms underlying complement dysregulation. *Kidney Int* 2012;82:1084–1092.
293. Ohi H, Yasugi T. Occurrence of C3 nephritic factor and C4 nephritic factor in membranoproliferative glomerulonephritis (MPGN). *Clin Exp Immunol* 1994;95:316.
294. Zhang Y, Meyer NC, Wang K, et al. Causes of alternative pathway dysregulation in dense deposit disease. *Clin J Am Soc Nephrol* 2012;7:265–274.
295. Tanuma Y, Ohi H, Hatano M. Two types of C3 nephritic factor: properdin-dependent C3NeF and properdin-independent C3NeF. *Clin Immunol Immunopathol* 1990;56:226.
296. Miller EC, Chase NM, Densen P, et al. Autoantibody stabilization of clinical pathway C3 convertase leading to C3 deficiency and Neisserial sepsis: C4 nephritic factor revised. *Clin Immunol* 2012;145:241–250.
297. Ohi H, Watanabe S, Fujita T, et al. Significance of C3 nephritic factor (C3NeF) in non-hypocomplementemic serum with membranoproliferative glomerulonephritis (MPGN). *Clin Exp Immunol* 1992;89:479.
298. Fremeaux-Bacchi V, Weiss L, Brun P, et al. Selective disappearance of C3NeF IgG autoantibody in the plasma of a patient with membranoproliferative glomerulonephritis following renal transplantation. *Nephrol Dial Transplant* 1994;9:811.
299. Couser WG. Mechanisms of immune glomerular injury. In: Coffman TM, et al., eds. *Schrier's Diseases of the Kidney*, 9th ed. Philadelphia: Lippincott Williams & Wilkins, 2013:1260–1276.
300. Pettigrew HD, Teuber SS, Gershwin E. Clinical significance of complement deficiencies. *Ann N Y Acad Sci* 2009;1173:108–123.
301. Vaziri-Sani F, Holmberg L, Sjoholm AG, et al. Phenotypic expression of factor H mutations in patients with atypical hemolytic uremic syndrome. *Kidney Int* 2006;69:981–988.
302. Leroy V, Frémeaux-Bacchi V, Peuchmaur M, et al. Membranoproliferative glomerulonephritis with C3NeF and genetic complement dysregulation. *Pediatr Nephrol* 2011;26:419–424.
303. Pickering RJ, Michael AF, Herdman RC. The complement system in chronic glomerulonephritis: three newly associated observations. *J Pediatr* 1971;78:30.
304. Welch TR, Kleesattel A, Beischel L. Inhibition of immune complex solubilization by sera of patients with membranoproliferative glomerulonephritis. *Clin Exp Immunol* 1988;72:103.
305. Verroust PJ, Wilson CB, Dixon FJ. Lack of nephritogenicity of systemic activation of the alternate complement pathway. *Kidney Int* 1974;6:157.
306. Simpson IJ, Moran J, Evans DJ, et al. Prolonged complement activation in mice. *Kidney Int* 1978;13:467.
307. Angus KW, Gardiner AC, Mitchell B, et al. Mesangiocapillary glomerulonephritis in lambs: The ultrastructure and immunopathology of diffuse glomerulonephritis in newly born Finnish lambs. *J Pathol* 1980;131:65.
308. Amertunga R, Winkelstein JA, Brody L, et al. Molecular analysis of the third component of canine complement (C3) and identification of the mutation responsible for hereditary canine C3 deficiency. *J Immunol* 1998;160:2824.
309. Muhlfeld AS, Segerer S, Hudkins K, et al. Deletion of the fcgamma receptor IIb in thymic stromal lymphopoietin transgenic mice aggravates membranoproliferative glomerulonephritis. *Am J Pathol* 2003;163:1127.
310. Rostoker G, Wirquin V, Terzidis H, et al. Mucosal immunity in primary glomerulonephritis. III. Study of intestinal permeability. *Nephron* 1993;63:286.
311. Maripuri S, Grande JP, Osborn TG, et al. Renal involvement in primary Sjogren's syndrome: a clinicopathologic study. *Clin J Am Soc Nephrol* 2009;4:1423–1431.
312. Kiryluk K, Preddie D, D'Agati VD, et al. A young man with Propionibacterium acnes-induced shunt nephritis. *Kidney Int* 2008;73:1434–1440.
313. Fabrizi F, Dixit V, Martin P, et al. The evidence-based epidemiology of HCV-associated kidney disease. *Int J Artif Organs* 2012;35:621–628.
314. Lhotta K, Wurnzer R, Konig P. Glomerular deposition of mannose-binding lectin in human glomerulonephritis. *Nephrol Dial Transplant* 1999;14:881.
315. Fornasieri A, Tazzari S, Li M, et al. Electron microscopy study of genesis and dynamics of immunodeposition in IgMk-IgG cryoglobulin-induced glomerulonephritis in mice. *Am J Kidney Dis* 1998;31:435.
316. Waldo FB, West CD. Quantitation of (C1INH)2 C1r-C1s complexes in glomerulonephritis as an indicator of C1 activation. *Clin Immunol Immunopathol* 1987;42:239.
317. Tani Y, Kida H, Abe T, et al. B-lymphocyte subset patterns and their significance in idiopathic glomerulonephritis. *Clin Exp Immunol* 1982;48:201.
318. McGinley E, Martin W, Henderson N, et al. Defective splenic reticuloendothelial function in idiopathic membranous nephropathy. *Clin Exp Immunol* 1984;56:295.
319. Milner LS, Houser MT, Kolbeck PC, et al. Glomerular injury in end-stage liver disease: role of circulating IgG and IgM immune complexes. *Pediatr Nephrol* 1993;7:6.
320. Tanuma Y, Ohi H, Hatano M. Accelerated decay of the cell bound C4b2a complex by serum of patients with membranoproliferative glomerulonephritis and acute poststreptococcal glomerulonephritis. *Clin Immunol Immunopathol* 1992;62:270.
321. Banas MC, Banas B, Hudkins KL, et al. TLR4 links podocytes with the innate immune system to mediate glomerular injury. *J Am Soc Nephrol* 2008;19:704–713.
322. Lin M, Han Liu W, Li RX, et al. The TLR4 antagonist CRX-526 protects against advanced diabetic nephropathy. *Kidney Int* 2013;83:887–900.
323. Brando B, Busnach G, Bertoli S, et al. T-suppressor cell abnormalities in type I membranoproliferative glomerulonephritis. *Proc Eur Dial Transplant Assoc* 1983;19:669.
324. Fornasieri A, Sinico R, Fiorini G, et al. T-lymphocyte subsets in primary and secondary glomerulonephritis. *Proc Eur Dial Transplant Assoc* 1983;19:635.
325. Hotta O, Yusa N, Furuta T, et al. Membranoproliferative glomerulonephritis in the aged and its possible causal relationship with $CD8^+CD57^+$ lymphocytes. *Clin Nephrol* 1998;49:138.
326. Ostendorf T, Eitner F, Floege J. The PDGF family in renal fibrosis. *Pediatr Nephrol* 2012;27:1041–1050.
327. Lopez-Hernandez FJ, Lopez-Novoa JM. Role of TGF-β in chronic kidney disease: an integration of tubular, glomerular and vascular effects. *Cell Tissue Res* 2012;347:141–154.
328. Miller K, Dresner IG, Michael AF. Localization of platelet antigens in human kidney disease. *Kidney Int* 1980;18:472.
329. Duffus P, Parbtani A, Frampton G, et al. Glomerular localization of platelet related antigens, platelet factor 4 and beta-thromboglobulin in glomerulonephritis. *Clin Nephrol* 1982;17:288.
330. Nishi Y, Namikoshi T, Sasaki T, et al. Histopathological manifestations of membranoproliferative glomerulonephritis and glomerular expression of plasmalemmal vescle-associated protein-1 in a patient with polycythemia vera. *Clin Nephrol* 2010;5:393–398.
331. Parbtani A, Frampton G, Cameron JS. Platelet and plasma serotonin concentrations in glomerulonephritis II. *Clin Nephrol* 1980;14:112.
332. George CR, Slichter SJ, Quadracci LJ, et al. A kinetic evaluation of hemostasis in renal disease. *N Engl J Med* 1974;291:1111.
333. Rashid HU, Papiha SS, Agroyannis B, et al. The associations of HLA and other genetic markers with glomerulonephritis. *Hum Genet* 1983;63:38.
334. Welch TR, Beischel L, Balakrishnan K, et al. Major histocompatibility complex extended haplotypes in membranoproliferative glomerulonephritis. *N Engl J Med* 1986;314:1476.
335. Wank R, Schendel DJ, O'Neill GJ, et al. Rare variant of complement C4 is seen in high frequency in patients with primary glomerulonephritis. *Lancet* 1984;1:872.
336. Welch TR, Berry A. C3 alleles in diseases associated with C3 activation. *Dis Markers* 1987;5:81.
337. Bishof NA, Welch TR, Beischel LD, et al. DP polymorphism in HLA-A1, -B8, -DR3 extended haplotypes associated with membranoproliferative glomerulonephritis and systemic lupus erythematosus. *Pediatr Nephrol* 1993;7:243.

338. Bakkaloglu A, Soylemezoglu O, Tinaztepe K, et al. Familial membranoproliferative glomerulonephritis. *Nephrol Dial Transplant* 1995;10:21.
339. Bilge I, Sirin A, Agachan B, et al. Is paraoxonase 192 gene polymorphism a risk factor for membranoproliferative glomerulonephritis in children? *Cell Biochem Funct* 2007;25:159–165.
340. Malik TH, Lavin PJ, Goicoechea de JE, et al. A hybrid CFHR3-1 gene causes familial C3 glomerulopathy. *J Am Soc Nephrol* 2012;23: 1155–1160.
341. Vernon KA, Pickering MC, Cook HT. Experimental models of membranoproliferative glomerulonephritis, including dense deposits disease. *Contrib Nephrol* 2011;169:198–210.
342. Reusch C, Hoerauf A, Lechner J, et al. A new familial glomerulonephropathy in Bernese mountain dogs. *Vet Rec* 1994;134:411.
343. Sabnis SG, Gunson DE, Antonovych TT. Some unusual features of mesangioproliferative glomerulonephritis in horses. *Vet Pathol* 1984;21:374.
344. Young GB, Sales DI, Waddington D, et al. Genetic aspects of mesangiocapillary glomerulonephritis in Finnish sheep. *Br Vet J* 1981;137:368.
345. Maggio-Price L, Russell R, Wolf NS, et al. Clinicopathologic features of young and old sphha/sphha mice: mutants with congenital hemolytic anemia. *Am J Pathol* 1988;132:461.
346. Taneda S, Segerer S, Hudkins KL, et al. Cryoglobulinemic glomerulonephritis in thymic stromal lymphopoietin transgenic mice. *Am J Pathol* 2001;159:2355–2369.
347. Guo S, Wietecha TA, Hudkins KL, et al. Macrophages are essential contributors to kidney injury in murine cryoglobulinemic membranoproliferative glomerulonephritis. *Kidney Int* 2011;80:945–958.
348. Kikuchi S, Pastore Y, Fossati-Jimack L, et al. A transgenic mouse model of autoimmune glomerulonephritis and necrotizing arteritis associated with cryoglobulinemia. *J Immunol* 2002;169:4644–4650.
349. Isaacs KL, Millet F. Antigen size and charge in immune complex glomerulonephritis II. *Am J Pathol* 1983;111:298.
350. Noble B, Olson KA, Milgrom M, et al. Tissue deposition of immune complexes in mice receiving daily injections of bovine serum albumin. *Clin Exp Immunol* 1980;42:255.
351. Kuriyama T. Chronic glomerulonephritis induced by prolonged immunization in the rabbit. *Lab Invest* 1973;28:224.
352. Morales JM, Kamar N, Rostaing L. Hepatitis C and renal disease: epidemiology, diagnosis, pathogenesis and therapy. *Contrib Nephrol* 2012;176:10–23.
353. Fabrizi F, Martin P, Dixit V, et al. Hepatitis C virus infection and kidney disease: a meta-analysis. *Clin J Am Soc Nephrol* 2012;7:549–557.
354. Baid S, Cosimi AB, Tolkoff-Rubin N, et al. Renal disease associated with hepatitis C infection after kidney and liver transplantation. *Transplantation* 2000;70:255.
355. Roithinger FX, Allinger S, Kirchgatterer A, et al. A lethal course of chronic hepatitis C, glomerulonephritis, and pulmonary vasculitis unresponsive to interferon treatment. *Am J Gastroenterol* 1995;90:1006.
356. Szymanski IO, Pullman JM, Underwood JM. Electron microscopic and immunochemical studies in a patient with hepatitis C virus infection and mixed cryoglobulinemia type II. *Am J Clin Pathol* 1994; 102:278.
357. Cao Y, Zhang Y, Wang S, et al. Detection of the hepatitis C virus antigen in kidney tissue from infected patients with various glomerulonephritis. *Nephrol Dial Transplant* 2009;24:2745–2751.
358. Rodriguez-Inigo E, Casqueiro M, Bartolome J, et al. Hepatitis C virus RNA in kidney biopsies from infected patients with renal diseases. *J Viral Hepat* 2000;7:23.
359. Sanonno D, Lauletta G, Montrone M, et al. Hepatitis C virus RNA and core protein in kidney glomerular and tubular structures isolated with laser capture microdissection. *Clin Exp Immunol* 2005;140:498.
360. Dolganiuc A, Oak S, Kodys K, et al. Hepatitis C core and nonstructural 3 proteins trigger toll-like receptor 2-mediated pathways and inflammatory activation. *Gastroenterology* 2004;27:1513.
361. Wörnle M, Schmid H, Banas B, et al. Novel role of toll-like receptor 3 in hepatitis C-associated glomerulonephritis. *Am J Pathol* 2006;168: 370–385.
362. Merkle M, Ribeiro A, Wörnle M. TLR3-dependent regulation of cytokines in human mesangial cells: a novel role for IP-10 and TNF-alpha in hepatitis C-associated glomerulonephritis. *Am J Physiol Renal Physiol* 2011;301:F57–F69.
363. Abou-Zeid AA, El-Sayegh HK. Toll-like receptor 3 gene expression in Egyptian patients with glomerulonephritis and hepatitis C virus infection. *Scand J Clin Lab Invest* 2011;71:456–461.
364. Sureshkumar KK, Thai NL, Marcus RJ. Kidney transplantation in hepatitis C-positive recipients: does type of induction influence outcomes? *Transplant Proc* 2012;44:1262–1264.
365. Roth D, Cirocco R, Zucker K, et al. De novo membranoproliferative glomerulonephritis in hepatitis C virus-infected renal allograft recipients. *Transplantation* 1995;59:1676.
366. Morales JM, Marcén R, Andres A, et al. Renal transplantation in patients with hepatitis C virus antibody. A long national experience. *NDT Plus* 2010;3(Suppl 2):ii41–ii46.
367. Raz E, Michaeli J, Brezis M, et al. Improvement of immune-complex nephritis associated with hepatitis B surface antigen excess. *Am J Nephrol* 1989;9:162.
368. Lai KN, Ho RT, Tam JS, et al. Detection of hepatitis B virus DNA and RNA in kidneys of HBV related glomerulonephritis. *Kidney Int* 1996;50:1965.
369. Thursz MR, Kwiatkowski D, Allsopp CE, et al. Association between an MHC class II allele and clearance of hepatitis B virus in the Gambia. *N Engl J Med* 1995;332:1065.
370. Zheng X, Wei R, Tang L, et al. Meta-analysis of combined therapy for adult hepatitis B virus-associated glomerulonephritis. *World J Gastroenterol* 2012;18:821–832.
371. Elewa U, Sandri AM, Kim WR, et al. Treatment of hepatitis B virus-associated nephropathy. *Nephron Clin Pract* 2011;119:c41–c49.
372. Nasr SH, Satoskar A, Markowitz GS, et al. Proliferative glomerulonephritis with monoclonal IgG deposits. *J Am Soc Nephrol* 2009;20:2055–2062.
373. Moulin B, Ronco PM, Mougenot B, et al. Glomerulonephritis in chronic lymphocytic leukemia and related B-cell lymphomas. *Kidney Int* 1992;42:127.
374. Guiard E, Karras A, Plaisier E, et al. Patterns of noncryoglobulinemic glomerulonephritis with monoclonal Ig deposits: correlation with IgG subclass and response to rituximab. *Clin J Am Soc Nephrol* 2011;6:1609–1616.