Membranous Glomerulonephritis

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Membranous glomerulonephritis (MGN) is the most common primary cause of the nephrotic syndrome, accounting for about 20% of cases in most series. It is characterized by basement membrane thickening and subepithelial immune deposits without cellular proliferation or infiltration. Although it is not entirely applicable to the human disease, the Heymann nephritis model in the rat has afforded insight into its pathogenesis. MGN is a classic instance of immune complex deposition disease and complement activation. Although a consensus is slowly emerging on its natural history and treatment, these issues remain controversial.

Etiology and Incidence

MGN is idiopathic in the majority of cases; approximately 25% of adults and 80% of children have an identifiable immunological stimulus (secondary MGN). Idiopathic disease has a male and adult predominance. The peak incidence is between 30 and 50 yr, and MGN is particularly likely in patients over 50 yr of age who present with nephrotic syndrome. Secondary causes of MGN are listed in Table 1. Worldwide, malaria and schistosomiasis are undoubtedly the most common causes. In the United States, the most important causes of secondary MGN are systemic lupus erythematosus (SLE), neoplasia, hepatitis B infection, and drugs. Secondary causes of MGN may be occult. For example, patients with MGN as a result of SLE are often young women with isolated renal disease and, sometimes, no serological evidence of SLE for the first years of their illness. Neoplasia underlying MGN may also be unrecognized. MGN is associated with cancer in 6 to 11% of cases, and in 10.3% in a recent series (1). In 40 to 45% of patients, nephrotic syndrome as a result of MGN presents before the diagnosis of tumor, and in another 40%, the presentations are simultaneous. Those solid tumors most commonly implicated include lung, gastrointestinal tract, kidney, and breast; hematological malignancies are also associated. A causal relationship is evident: complete remission of proteinuria may follow successful treatment of tumor, and recurrence of proteinuria may herald tumor recurrence. An immune complex pathogenesis involving tumor antigens is suspected; for example, carcinoembryonic antigen has been eluted from glomerular deposits. Chronic hepatitis B infection may also be unrecognized at presentation of MGN. In children in endemic areas, such as East Asia, hepatitis B is acquired by vertical transmission during pregnancy; children may be asymptomatic and without clinical or laboratory evidence of hepatitis. The e antigen, unlike surface and core antigens, is small enough to pass through the glomerular basement membrane (GBM) and appears to be the pathogenic antigen in hepatitis B-associated MGN (2). As in SLE, MGN may be suspected by the presence of mesangial and subendothelial deposits as well as hypocomplementemia (3); these findings suggest a continuum with membranoproliferative glomerulonephritis (MPGN), which may also occur as a result of hepatitis B infection. Children with hepatitis B-associated MGN typically have spontaneous remission, often coinciding with development of anti-e antibodies. MGN may complicate rheumatoid arthritis, but more commonly it is a consequence of treatment with penicillamine or gold. As in other forms of secondary MGN, mesangial deposits are more common than idiopathic MGN. MGN may develop slowly with these agents (6 months to 4 yr); complete remission after drug withdrawal is the rule but may also require several years. Nonsteroidal anti-inflammatory drugs (NSAID) may be a much more common cause of MGN than has been recognized. In a recent series, 10% of early (stage I) MGN occurred as a result of NSAID use, often NSAID that were over-the-counter (OTC) preparations. Diverse NSAID classes were represented. The onset of symptoms was rapid, as was resolution after drug withdrawal (10 to 40 wk), and there were no recurrences. Some cases previously attributed to minimal change disease (MCD) may in fact have had MGN. Because OTC medications are frequently under-reported by patients, NSAID represent yet another occult cause of secondary MGN (4).

Pathology

The hallmark of MGN is subepithelial deposition of immunoglobulin G (IgG) together with (in idiopathic MGN) normal cellularity of the glomerular tuft. Stages of disease were classified by Ehrenreich and Churg (5) (Figure 1). Early lesions (stage I) include few and scattered immune deposits and the GBM is not yet thickened; on light microscopy, this lesion is indistinguishable from MCD and immunofluorescence and electron microscopy (EM) are indispensable for diagnosis. In stage II, deposits are more uniform and numerous and "spikes" of normal basement membrane material extend up between the deposits (Figures 2 and 3). The GBM is uniformly thickened. In stage III, deposits are entirely incorporated within and surrounded by GBM but remain separated by normal basement
membrane material. In stages II and III, silver staining (which stains GBM but not immune deposits) demonstrates “spikes” corresponding to GBM interposed between deposits. These spikes are absent in stage I (when there are few, scattered deposits) and stage IV, when deposits have been resorbed. EM shows rarefaction of deposits in stage IV, corresponding to resorption. The GBM is markedly but irregularly thickened. Interstitial fibrosis and tubular atrophy occur in advanced disease and, as in other glomerular diseases, offer a better clue to prognosis than the histological stage of MGN. Immunofluorescence staining in stages II and III reveals granular IgG uniformly in all glomerular capillary walls. Complement (C3 and C5b-C9) is present in 75% of cases. Prominent deposits of IgM and IgA are features of SLE, but small amounts may be detected in 30% of idiopathic cases.

Histologic stage is not correlated with the magnitude of proteinuria. Advanced stage is, however, associated with reduction of GFR. Histological progression can occur without clinical progression, and clinical remission can occur in the absence of histological regression. Mesangial or subendothelial deposits or both are characteristic of secondary forms of MGN, such as SLE, hepatitis B, and gold- and penicillamine-associated disease. When mesangial deposits occur in idiopathic MGN, they may confer a more favorable prognosis (6). SLE is also characterized by prominent immunoglobulins of all classes, tubuloreticular inclusions, and tubular basement membrane deposits; none of these is entirely specific to SLE, with the exception of tubular basement membrane deposits (7). Concomitant renal diseases may be present in MGN, including IgA nephropathy, focal glomerulosclerosis (FGS), diabetic nephropathy, crescentic glomerulonephritis (GN), and tubulointerstitial nephritis. FGS could be a consequence of prior injury as a result of MGN. In some diabetic patients, MGN may be mediated by porcine insulin immune deposits and may improve when human insulin is substituted. Why crescentic GN complicates the course of MGN is unknown.

Pathogenesis

Understanding of MGN has been advanced by the Heymann nephritis model, which it closely resembles. Active Heymann nephritis is induced in the rat by immunization with crude proximal tubular brush border extract and passive Heymann nephritis is induced by injecting antibodies to this extract. Farquhar et al. have recently reviewed the antigenic determinants of the Heymann nephritis model (8). Brush border and glomerular epithelial cell (GEC) share an antigen, which has been named megalin (formerly gp330). Megalin is a member of the low-density lipoprotein receptor family and binds similar ligands. It also has calcium-sensing and regulatory properties and may mediate uptake of filtered calcium in the proximal tubule. Immune complexes involving megalin form in situ in clathrin-coated pits (specialized cell membrane structures) of the glomerular epithelial cell. Over several days, these complexes become highly crosslinked and enlarge, are shed from the GEC, and become strongly (perhaps covalently) bound to GBM. A related protein, called receptor-associated protein (RAP), binds to megalin and may serve as its intracellular chaperone. RAP is a second major antigen in Heymann nephritis. How these immune deposits mediate proteinuria is not known, but the process requires complement activation, in particular, the terminal complement complex (C5b-C9, also called the membrane attack complex, or MAC). Insertion of the MAC into the GEC membrane induces lytic damage; charge- and size-selective barriers to albumin filtration are impaired in humans with MGN and in the Heymann nephritis model. Glomerular epithelial cells transport the MAC through the cell and into the urinary space (9).

Despite striking similarities between Heymann nephritis and human MGN—subepithelial immune deposits, binding of immune deposits to the GBM, terminal complement activation,
heavy proteinuria—the analogy of the rat model to the human disease remains incomplete. Although megalin has been found in human proximal tubules, it has not been found in human glomeruli. The target antigen(s) in human MGN has not been identified. Although an antigen similar to megalin may mediate human MGN, it is more likely that a different antigen(s) is responsible. These antigens may be of renal (as in Heymann nephritis) or nonrenal origin. It may be that both Heymann nephritis and MGN manifest the pathophysiology common to immune deposits in the subepithelial space; a lesion resembling MGN has been demonstrated experimentally with cationized ferritin, which passes the GBM (10). A variety of nonrenal antigens has been identified in secondary MGN, including hepatitis B e antigen (and possibly core and surface antigens), double-stranded DNA (in SLE), carcinoembryonic antigen (colon cancer), thyroglobulin (Hashimoto’s thyroiditis), and porcine insulin (diabetes). In these conditions, passive trapping of circulating immune complexes rather than in situ immune complex formation has been suggested, but the issue remains moot.

**Clinical Features**

The hallmark of MGN is the nephrotic syndrome. More than 80% of patients have heavy proteinuria at presentation (11). Hypertension is usually found after renal insufficiency has occurred, but is present in 30% at presentation. The kidneys are often large, even after renal insufficiency has supervened. Microscopic hematuria occurs in 50% of the patients, even though inflammatory lesions are not seen histologically. Gross hematuria and red blood cell casts are rare.

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**Figure 1.** Schematic drawing of the four stages of membranous glomerulonephritis. See text for explanation. Ep, epithelial cell; En, endothelial cell; P, foot process; BM, basement membrane; D, deposit; Sp, spike. (Reproduced by permission of the New England Journal of Medicine)
Laboratory studies show normal complement values in idiopathic MGN; hypocomplementemia suggests SLE or, sometimes, hepatitis B infection. Antinuclear antibodies, rheumatoid factor, and cryoglobulins are absent in idiopathic MGN. Urinary excretion of the C5b-C9 terminal complement complex is elevated in some patients and can be correlated with disease activity and prognosis (12,13). Specific human leukocyte antigen (HLA) phenotypes have been associated with idiopathic MGN, including DRw3 (common in diabetes and dermatitis herpetiformis), B8, and B18. There is marked geographic variation in the HLA associations of MGN.

Abrupt deterioration of renal function sometimes supervenes in MGN. Probably the most common cause is prerenal azotemia as a result of overly aggressive diuresis; peripheral edema may be the price of preserved intravascular volume. Prerenal azotemia responds to increased salt and water intake and reduction of diuretic dose. Occasionally nephrotic patients develop acute tubular necrosis, either spontaneously or after diuresis, that may be irreversible. Renal interstitial edema (nephrosarca) as a result of reduced plasma oncotic pressure theoretically could complicate MGN but has not been specifically reported. Nephrosarca should be suspected in patients whose renal insufficiency improves after diuresis. Allergic interstitial nephritis has complicated treatment with sulfas-containing diuretics such as furosemide and thiazides, often in the absence of fever, rash, or eosinophilia. Rarely, patients with MGN have tubulointerstitial nephritis because of anti-tubular basement membrane antibodies. These patients, almost invariably male children, have progressed to ESRD (14). Crescentic GN, more often associated with immune complex deposition rather than with anti-GBM antibodies, occasionally supervenes in MGN. Its pathogenesis is unknown. The majority of patients have gone on to death or to dialysis and those patients with anti-GBM antibodies have had worse outcomes (15). Finally, renal vein thrombosis is a manifestation of the hypercoagulable state characteristic of the nephrotic syndrome. This complication has been particularly associated with MGN, as well as MPGN, SLE, and amyloidosis. Its incidence has ranged from 5 to 50% in different studies, depending on, among other things, how systematically it is sought. A clue to renal vein thrombosis is the presence, on histopathologic examination, of glomerular infiltration with margined polymorphonuclear cells and interstitial edema. The majority of patients with renal vein thrombosis have unilateral or bilateral branch vein (subtotal) occlusions; they are asymptomatic with stable renal function or present with pulmonary emboli. A small minority present with acute and total renal venous occlusion and renal infarction; these patients, who are usually younger, have flank pain, gross hematuria, markedly elevated serum lactate dehydrogenase (LDH), and—possibly—renal functional deterioration or increased proteinuria or both that improves after anticoagulation treatment.
may have renal vein thrombosis but it rarely has consequences for renal function. The definitive test for renal vein thrombosis is renal vein contrast angiography, although noninvasive screening can be accomplished with Doppler ultrasound or magnetic resonance imaging.

There are three possible approaches to screening for renal vein thrombosis in patients with idiopathic MGN and the nephrotic syndrome: (1) routine screening in all patients, with long-term anticoagulation in those with renal vein thrombosis; (2) investigation for renal vein thrombosis only after a thromboembolic event such as pulmonary embolus; and (3) routine anticoagulation in all patients. If anticoagulation treatment is based on screening, screening should be repeated periodically if the results are initially negative; however, there is no consensus on how frequently screening should be performed. A recent decision analysis indicated that the risk of fatal pulmonary emboli in idiopathic MGN exceeded the risk of fatal bleeding because of anticoagulation (16). This conclusion was robust for plausible ranges of relevant clinical parameters, including duration of nephrotic syndrome, incidence of thromboembolic events, and mortality rate of patients with pulmonary emboli. The authors suggested that prophylactic anticoagulation be considered in all patients with idiopathic MGN and nephrotic syndrome in whom there is no contraindication.

**Diagnosis and Differential Diagnosis**

The diagnosis of MGN requires renal biopsy and histopathological examination by light, immunofluorescence, and electron microscopy. Renal biopsy may be deferred in patients in whom immunosuppressive treatment is not a reasonable option, including those with advanced renal failure, those with subnephrotic proteinuria (in whom the prognosis is excellent and specific treatment is not offered), and elderly patients in whom the risks of therapy are felt to be prohibitive. The argument that a course of steroids may be undertaken initially in adults in preference to renal biopsy has less force now than it used to have. Idiopathic MGN probably does not respond to glucocorticoids (see below), and focal glomerulosclerosis (another diagnostic possibility) is now thought to require a longer course of oral steroids than the standard treatment given for MCD.

The differential diagnosis of MGN involves first distinguishing it from other categories of glomerulonephritis on histopathological examination and then determining whether it is primary or secondary. Stage I MGN shows no GBM thickening and no spikes on silver stain and may be indistinguishable from MCD; immunofluorescence (showing immunoglobulin and complement) and electron microscopy (showing subepithelial
deposits) are indispensable for diagnosis. Advanced MGN can sometimes be confused with MPGN: reticulation of the GBM in MGN may simulate double contours (tram tracks) on silver staining of light microscopic sections. Again, electron microscopy will resolve this difficulty.

Secondary causes of MGN should be apparent from clinical presentation and the histopathological features, but 10 to 25% of patients with suspected idiopathic MGN eventually prove to have a secondary cause (17). Patients with SLE usually have typical clinical and serological manifestations; however, MGN may be the first manifestation of SLE, especially in young women, and may precede serological abnormalities by several years. Prominent IgA and subendothelial and mesangial deposits suggest the diagnosis, but only tubular basement deposits are specific (7). Watchful waiting is a tenable strategy, because the prognosis of MGN in SLE in the absence of inflammatory (nephritic) lesions is very good (18); treatment for idiopathic MGN is also acceptable, because it is similar to that for SLE. Hepatitis B infection may also be occult: serum transaminase levels may be normal and there may be no history of clinical hepatitis. The presence of mesangial deposits and serological screening should confirm this diagnosis. Relevant drugs should be evident on medication review; the recent description of MGN as a result of NSAID use makes a careful inquiry for OTC drugs mandatory. Finally, there is some question how extensively to investigate occult cancer. Complete blood count and chest radiograph are obtained routinely, and renal ultrasound can be obtained at the time of renal biopsy. Mammography, stool testing for occult blood, and flexible sigmoidoscopy are recommended for routine screening of healthy adults over the age of 50 and should probably be performed in patients with MGN over the age of 40; colonoscopy should be strongly considered. More extensive testing is required for patients in whom there are features suggestive of malignancy, and continued careful observation is necessary in older patients in whom cancer may not have been detected by initial screening.

Natural History

Reports of the natural history of MGN have yielded different results because of variations in patient population, geography, duration of follow-up, and end points. Idiopathic MGN is a relatively benign form of chronic glomerulonephritis. Non-nephrotic patients have an excellent prognosis, with less than 5% progressing to chronic renal failure. At 10 to 15 yr, up to one half of nephrotic patients have had complete or partial remission of the nephrotic syndrome—20 to 40% eventually undergo complete remission—and one third to one half have chronic renal failure or ESRD. Few patients have persistent nephrotic syndrome with normal renal function or mild renal insufficiency (19). Although several recent studies have claimed that the prognosis is more benign than previously believed, there is little data to suggest that the rough proportions indicated above have changed. An extensive review of the published experience reported ESRD in 14% at 5 yr, 35% at 10 yr, and 41% at 15 yr (20). Donadio and colleagues studied 140 patients (83% nephrotic) for a mean of 6.2 yr; at last follow-up, 20% had ESRD and 16% had renal insufficiency; 51% had complete or partial remission of the nephrotic syndrome (11). Ponticelli and colleagues followed-up 39 nephrotic patients (the control group of a treatment study) for 10 yr; 40% had ESRD and 47% had complete or partial remission of the nephrotic syndrome (21). Schiepatti and colleagues (22) studied 100 consecutive patients (63% nephrotic) for a mean of 52 months; at 8 yr, 27% had developed ESRD; upwards of 60% of patients had partial or complete remission of proteinuria, but some of these patients did not have nephrotic syndrome at baseline. Although these authors believed that the benign prognosis of MGN did not justify immunosuppressive treatment, their results are comparable to those of most other studies when allowance is made for the inclusion of a substantial number of non-nephrotic patients with excellent prognosis. The prognosis of MGN with nephrotic syndrome appears “benign” with relatively brief follow-up and in comparison with more aggressive diseases such as diabetic glomerulosclerosis, but a 35 to 40% incidence of ESRD at 10 to 15 yr is not trivial.

Adverse prognostic factors include male sex, age above 50 yr, heavy proteinuria (above 10 g daily), hypertension at presentation, and, most importantly, baseline renal insufficiency and interstitial fibrosis and tubular atrophy on kidney biopsy. Complete remission, whether spontaneous or induced by treatment, is a good prognostic sign. According to Passerini and colleagues, progression to renal failure did not occur after complete remission; relapse of proteinuria occurred in half but, because of subsequent remissions, 73% of patients were in complete remission at final follow-up (23). Relapse of proteinuria after remission was previously thought to be rare, but in recent studies it has occurred in 29 to 35% of patients, whether remission occurred spontaneously or after treatment (24). Most patients who progress to renal failure have a decrease in GFR after 2 or 3 yr and virtually all within 5 yr; therefore, persistence of normal renal function at 3 yr is also a favorable prognostic sign. Stage I disease carries a better prognosis than more advanced disease, and spontaneous remission is more likely; however, there seems to be no difference in prognosis between stages II, III, and IV. A subset of patients, males with proteinuria and baseline renal insufficiency, has been reported in whom progression to ESRD is very rapid, within 2.5 yr (11). However, only slow and steady progression to renal failure has been observed in other studies. Pei and colleagues have refined the idea that magnitude of proteinuria at presentation is a reliable prognostic factor; they claim that proteinuria has better predictive power when its duration is taken into account. They examined systematically prognostic factors in a group of 184 patients followed up for a mean of 5.8 yr. As a whole, the group had a 26% risk of chronic renal failure, but risk increased to 66% for patients with proteinuria above 8 g/day for 6 or more months, 55% with proteinuria above 6 g/day for 9 or more months, and 47% for proteinuria above 4 g/day for 18 or more months. Negative predictive values (probability of maintaining renal function if these criteria were not met) were 88%, 85%, and 80%, respectively. Thus, heavy proteinuria was not an adverse risk factor if not sustained. The model could be
further improved by including creatinine clearance and rate of change of creatinine clearance (25).

Because virtually all patients with SLE and MGN are treated with steroids or cytotoxic drugs or both, the natural history of this entity is unknown. The prognosis of MGN as a result of SLE depends on the presence of coexisting active inflammatory lesions; 10-yr patient or kidney survival rates were 72% in pure MGN (World Health Organization [WHO] class Va and Vb), 48% in MGN with focal proliferative glomerulonephritis (WHO class Vc), and 20% in MGN with diffuse proliferative glomerulonephritis (class Vd) (18). MGN resulting from SLE is less likely to undergo spontaneous remission and more likely to relapse than idiopathic MGN. Hepatitis B-associated MGN typically remits in children and has a less favorable prognosis in adults. Drug-induced MGN remits after the offending agent is stopped.

Treatment

On the basis of retrospective studies, glucocorticoids appeared to have a favorable impact on idiopathic MGN. An early prospective trial, the American Collaborative Study, concluded that a brief (2-month) course of high-dose, alternate-day glucocorticoid therapy was effective in slowing progression of renal failure over a 2-yr follow-up period (26). The treated group had more remissions but also more relapses, so that there was no significant effect on proteinuria (a finding that casts some doubt on the efficacy of steroids in protecting renal function). The major defect of the study was an unusually severe course in the control group: ten of 38 patients went on to renal failure or death within a 2-yr period. The appearance of benefit in steroid-treated patients may, therefore, have been the consequence of an oddly selected control group. Two more recent studies have failed to confirm a benefit of glucocorticoid therapy. A Canadian study used a lower dose (45 mg/m², every other day) for a longer duration (6 months) and had a longer follow-up period (48 months) (27). Patients who had previously received steroids were not excluded, so it is possible that the study was weighted with steroid nonresponders. There was no difference between treated and control patients in frequency of remissions, rate of change of creatinine clearance, or progression to renal failure. As compared with the American Collaborative trial, these patients had a longer duration of disease and perhaps a greater representation of advanced (stage III and IV) disease, which could have made them less steroid-responsive. However, a British trial, adopting the same treatment protocol as the American trial in 103 patients with follow-up of 3 yr, also could find no benefit of steroid treatment on progression of renal failure (28). There was a transient effect on proteinuria at 3 to 6 months, which was not sustained. These prospective trials may not rule out a small (less than 10%) subgroup with remitting and relapsing disease whose proteinuria is steroid-responsive (29). The authors of a recent meta-analysis concluded that steroid therapy has been of no benefit in inducing remission of nephrotic syndrome or in preventing progressive renal failure; they called for an end to steroid treatment of MGN (20). I concur that the benefit of steroids is doubtful, although it is possible that intravenous pulse methylprednisolone may have greater efficacy than oral steroids (see below). One point in favor of oral glucocorticoid treatment of idiopathic MGN is that adverse effects have been rare in the major trials.

In contrast to steroid therapy, there is convincing evidence that cytotoxic therapy with cyclophosphamide or chlorambucil has benefit in idiopathic MGN. Ponticelli and colleagues designed a somewhat complex protocol whose purpose was to minimize adverse effects from steroids and cytotoxic drugs (30). They administered glucocorticoids and chlorambucil in alternate months for 6 months; the month of glucocorticoid treatment began with intravenous methylprednisolone, 1 g daily for 3 days, followed by 0.4 mg/kg daily by mouth (a regimen intended to be less toxic than oral doses of 1 mg/kg daily or 2 mg/kg every other day); the chlorambucil dose was 0.2 mg/kg daily, or lower in the event of leukopenia. Their population had nephrotic syndrome, with well-preserved renal function and a duration of disease of only 5 months; most had histological stage I or II disease. At 10 yr, only 8% of treated patients had ESRD as compared with 40% of controls; 88% had experienced complete or partial remission as compared with 47% of controls. Only at 90 months of follow-up did the plasma creatinine fall significantly from baseline in the treated group. Four patients had to stop therapy because of adverse events, which were reversible (21). These excellent results are superior to any others in the literature, possibly because of early initiation of treatment or the early stage of disease or both. Both proteinuria and renal function benefited from these therapies, in contrast to the results from the American Collaborative Study. However, the incidence of major adverse events was higher than with steroids alone.

Other studies of cytotoxic treatment have confirmed a benefit on remission of nephrotic syndrome but not on renal function. Two recent meta-analyses have concluded that cytotoxic treatment of idiopathic MGN does increase the probability of complete or of complete and partial remission, but they were unable to show that such treatment improved renal function or renal survival. (20,31) This result is difficult to reconcile with the observation that remission, whether spontaneous or induced by treatment, predicts improved renal function and survival. (23) It seems likely that cytotoxic therapy does benefit renal function; but many studies have failed to prove this point, for the following reasons: (1) Alternative cytotoxic regimens have been used. Cyclophosphamide was substituted for chlorambucil in the Ponticelli protocol and has been used, perhaps, in less aggressive doses (cyclophosphamide, 1 to 2 mg/kg or 1.5 mg/kg or 100 mg daily). Some trials have used concurrent steroids and some have not. Few have used pulse methylprednisolone. (2) Duration of follow-up has been inadequate in most studies, in some cases for no more than 1 or 2 yr. (3) Some trials have included a large proportion of non-nephrotic patients whose good prognosis makes it difficult to show any benefit of treatment on preservation of renal function. (4) Patients in some trials may have had longer duration of disease and/or more advanced histological stage, making response less likely or complete. Indeed, many trials of cytotoxic treatment have specifically targeted patients with renal
insufficiency, on the basis that potentially toxic therapy ought to be reserved for patients whose need for it is unequivocal. Of these studies, the only prospective controlled trial of cytotoxic treatment in patients with renal insufficiency (serum creatinine concentration, 2.3 to 2.7 mg/dl) compared prednisone alone to prednisone with monthly intravenous cyclophosphamide; no benefit of either regimen on progression of renal insufficiency was found (32). However, intravenous pulse cyclophosphamide is likely to be an inferior agent in this setting. In a recent controlled study, patients with renal insufficiency (creatinine concentration, 2.5 to 2.9 mg/dl) were treated either with alternating steroids and chlorambucil, as described by Ponticelli and colleagues, or with alternating steroids and pulse intravenous cyclophosphamide (33). The chlorambucil-treated group showed improvement in serum creatinine concentration (2.9 to 2.1 mg/dl), whereas the cyclophosphamide-treated group showed progressive deterioration (2.5 to 3.4 mg/dl). In uncontrolled studies of patients with renal insufficiency, cytotoxic treatment has had variable success. In one study of patients with rising serum creatinine concentrations (1.6 to 2.2 mg/dl), prolonged (1 yr) and relatively low-dose (100 mg/day) cyclophosphamide therapy with concurrent oral steroids reduced serum creatinine concentration and induced sustained reduction of proteinuria in all 11 patients (34). However, in another study of 21 patients with renal insufficiency, treated with alternating monthly cycles of chlorambucil and corticosteroids, six patients had advanced renal insufficiency or were on dialysis, three died, 11 had stable or improved renal function, two were in complete remission, and four were in partial remission (35). The incidence of drug-related adverse effects was over 50%. Thus, treatment of patients who have renal insufficiency is likely to achieve less therapeutic benefit at the cost of increased adverse events. “Salvage” of patients with renal insufficiency cannot be expected to produce the success achieved in early disease with normal renal function. An important question is whether patients with renal insufficiency have intrinsically more aggressive disease that would not respond well to cytotoxic therapy even if it was initiated early.

Whether pulse methylprednisolone confers any independent benefit is unclear. In one uncontrolled series of patients with advancing renal insufficiency, pulse methylprednisolone, 1 g daily for 5 days followed by a tapering course of oral prednisolone, reduced serum creatinine concentration by a mean of 46%, and the effect was sustained in 10 of 15 patients; proteinuria was not reduced (36). In a recent study of patients with nephrotic syndrome and normal renal function, one group received monthly alternating chlorambucil and steroids as described above; the other received steroids alone (pulse methylprednisolone for 3 days followed by steroid 0.4 mg/kg daily during months 1, 3, and 5, with no therapy in months 2, 4, and 6) (37). The group receiving combined chlorambucil and steroids had a higher rate of remission of nephrotic syndrome, although this difference (62% versus 42%, \( P = 0.102 \)) was not statistically significant in the fourth year after treatment. The high rate of remission with steroids alone suggests that pulse methylprednisolone may be superior to prior oral steroid regimens. However, it is unlikely that pulse steroid therapy is as good as combined cytotoxic and steroid therapy. Failure to show a significant difference at 4 yr was presumably a result of the small sample size (type II error). Nevertheless, pulse methylprednisolone may be worth considering in patients with a relapsing and remitting course or with acute renal deterioration (e.g., as a result of crescentic GN).

There are three approaches to cytotoxic therapy of idiopathic MGN. The first is to treat all patients with nephrotic syndrome at presentation. Exceptions are made for patients over the age of 65, who are at increased risk of adverse events, and patients with serum creatinine levels over 3 mg/dl, in whom the risk of therapy exceeds expected benefit. The advantage of this approach is that treatment is begun early, minimizing the risk of progressive renal failure; in addition, remission of the nephrotic syndrome will occur sooner, lessening the risk of atherosclerotic and thromboembolic complications. The disadvantages of this approach are that the long-term risk of cancer, even when cytotoxic therapy is given in moderate doses for limited duration, is unknown; and that some patients destined for spontaneous remission will be subjected needlessly to this potential toxicity. The second approach is to treat only those patients with renal insufficiency, severe and intractable nephrotic syndrome, or thromboembolic events. This approach restricts potentially toxic therapy to those who clearly need it. However, delay in instituting treatment could allow irreversible structural damage and eventual renal failure in patients whose progression to renal failure could have been averted. At the present time, both of these approaches are considered risky. A third approach, intermediate between them and currently favored, is to stratify patients on presentation as to their risk of renal failure (17,38). A very low risk population is defined by: non-nephrotic proteinuria and normal renal function; or an age of 2 to 16 yr and normal renal function. In these populations, remission is expected and no therapy will be needed. A low risk population is defined by: young age, female gender, normotension, normal renal function, mild to moderate proteinuria (less than 5 g daily), stage I histopathology, and absence of glomerular sclerosis or interstitial fibrosis. Urinary excretion of the terminal complement complex (MAC) (13) or of β2-microglobulin (a marker of tubulointerstitial damage) (39) may also have prognostic value, but is of unproven utility and is not widely available. If these factors indicate a favorable prognosis, cytotoxic therapy is deferred in the hope of spontaneous remission (after which progression to renal failure is unlikely). The majority of these patients will have spontaneous remission, but some will subsequently show evidence of increased risk. The high risk population is defined by: age over 50, male gender, hypertension, decreased renal function, proteinuria greater than 10 g daily, and renal biopsy evidence of glomerular sclerosis or interstitial fibrosis. These patients receive cytotoxic therapy, as do patients with severe and intractable nephrotic syndrome or with thromboembolic events. Patients with proteinuria between 3.5 and 10 g daily but who are not at high risk (e.g., younger men or older women with normal renal function and no interstitial fibrosis) are followed up closely without cytotoxic treatment. Hebert suggested that patients not treated with cytotoxic agents receive appropriate conservative
care: aggressive blood pressure control, angiotensin-converting enzyme inhibitors, and dietary protein restriction (38). Decline of creatinine clearance rate is an indication for cytotoxic therapy. Persistent proteinuria—≥8 g daily for 6 months, ≥ 6 g daily for 9 months, ≥ 4 g daily for 18 months—increases the risk of progressive renal failure and also justifies such treatment.

Although this approach is rational, it is not necessarily right. It may be that delaying treatment in a subgroup of patients until they are ascertained to be at high risk forfeits their best chance for cure, and that the risks of limited cytotoxic treatment are negligible. This issue could only be resolved by a prospective trial, which hardly seems feasible. The risk of cytotoxic treatment is long-term and relatively small. The difference in outcome between treating most nephrotic patients at presentation and treating them only if at increased risk is also likely to be small. Hence such a trial would require a very large sample size and very long follow-up. Also, the advantage of risk stratification depends on the accuracy of risk assessment, which is almost certain to improve during the course of a long trial, rendering the study’s original methods of risk assessment obsolete. Thus a controlled trial is not likely to settle the issue of treatment of idiopathic MGN. Pei and colleagues (25) point out that clinicians have to weigh the unknown risks of cytotoxic treatment against the increasingly well-defined risks of MGN. But even a 10 to 15% risk of progressive renal failure (the negative predictive value achieved in their study) may seem high if the long-term risk of cytotoxic drugs is minimal.

There are several protocols for cytotoxic therapy. The Milan protocol (Ponticelli et al.) (29), consisting of 6 alternating months of chlorambucil and steroid, represents a standard of safety and efficacy that should be modified with caution. Nevertheless, the suggested dose of chlorambucil (0.2 mg/kg per day) may be too high, especially in patients with renal insufficiency, and a reduced dose of 0.15 mg/kg per day may be preferable. Some authors eschew use of pulse methylprednisolone and recommend low-dose oral prednisone (15 to 20 mg daily or 30 to 40 mg every other day) concomitant with cytotoxic therapy to minimize leukopenia (38). It is not known whether chlorambucil or cyclophosphamide is superior. Oral cyclophosphamide has been recommended in doses between 1.0 mg/kg and 2.5 mg/kg for 3 to a maximum of 6 months; some authors have used it for upwards of 2 yr (40), but this seems risky. Intravenous pulse cyclophosphamide is apparently inferior. The cytotoxic dose should be reduced if the white blood cell count falls below 5000/cm3 (3,38). Patients with creatinine concentrations above 3 mg/dl are not treated with cytotoxic drugs; the risk of harm exceeds the likelihood of benefit. Patients over the age of 65 have increased risk of adverse effects of cytotoxic therapy and should be treated only if they have severe nephrotic syndrome or incipient renal failure (41).

The role of cyclosporin A in patients with renal insufficiency is in evolution. As in MCD, a short (12-wk) course of cyclosporine reduced proteinuria, but the effect was not sustained when the drug was withdrawn (42). In a placebo-controlled prospective trial of patients with progressive renal insufficiency, a 1-yr course of cyclosporine slowed the rate of fall of creatinine clearance in a subsequent 21-month observation period; proteinuria was also reduced (43). However, there is concern whether immune deposition continues during cyclosporine treatment and whether cyclosporine itself, even in low doses, causes interstitial fibrosis and renal failure. In patients who fail to respond to cytotoxic treatment, or who have a relapsing and remitting course, cyclosporine or pulse methylprednisolone treatment may be considered. Conservative therapy to reduce proteinuria and ameliorate the nephrotic syndrome includes dietary protein restriction, angiotensin-converting enzyme inhibitors, and NSAID; reduction of proteinuria may ameliorate the course of progressive renal failure (44).

Secondary MGN often resolves after the underlying disease is reversed (malignancy, drug discontinuation, spontaneous or interferon-induced remission of hepatitis B). It is most important to rule out underlying diseases such as cancer and hepatitis before treating apparently idiopathic MGN with immunosuppression: cytotoxic therapy impairs host responses to malignancy, and withdrawal of steroid therapy enhances viral replication in hepatitis B (45). Indeed, the possibility that a secondary cause of MGN has been missed is an argument in favor of delaying cytotoxic treatment of idiopathic MGN. MGN resulting from SLE has almost invariably been treated with steroids and often with cytotoxic agents. In patients with coexisting inflammatory lesions, whether the lesions are focal or diffuse, combined steroid and cytotoxic therapy is appropriate. The benign prognosis of pure membranous nephropathy as a result of SLE may justify conservative treatment and observation.

Conclusions
MGN is a prototypical immune complex nephropathy. Although much of its pathogenesis, causes, course, and treatment have been elucidated, the relevant antigen or antigens of idiopathic MGN remain unknown. Promising strategies to monitor the progress of MGN have, nevertheless, emerged from animal models. Although steroid therapy, at least by the oral route, has been disappointing, a consensus is emerging that cytotoxic therapy has significant benefit in a subset of patients. A rational approach to therapy is risk stratification. Nevertheless, it remains unknown whether this approach is superior to early treatment of all (or most) patients with nephrotic syndrome. There are only two ways to resolve this problem. One, a controlled prospective trial, is unlikely to be definitive. Despite its uncertain timeline, the alternative is far more attractive: more understanding of the pathogenesis of this disease followed by specific treatment.

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