Diagnosis and Natural Course of Membranous Nephropathy

By Richard J. Glassock

Membranous nephropathy is a relatively common glomerular disease found to underlie both nonnephrotic and nephrotic proteinuria. In adults, about 75% of cases are primary (idiopathic) and 25% are secondary to a wide variety of causes, including neoplasia, infections, autoimmunity, and drugs. Presenting features are not distinctive enough to permit a diagnosis without a renal biopsy examination. Serologic studies are normal in the idiopathic disorder. The morphologic features are characteristic and include gradual thickening of the capillary wall caused by the in situ deposition of immune complexes accompanied by new basement membrane synthesis. The natural history of the untreated disorder is variable. Spontaneous remissions (complete and partial) of proteinuria, usually accompanied by stable renal function, eventually occur in 40% to 50% of patients and the remainder slowly progress to end-stage renal disease (ESRD) or die of complications or from unrelated disease after 5 to 15 years. Factors associated with a progressive course include older age at onset, male gender, persisting hypertension, hyperlipidemia and/or hypoalbuminemia, reduced renal function at discovery, persisting nephrotic range glomerular proteinuria, concomitant tubular proteinuria, and advanced glomerular damage with chronic tubulointerstitial fibrosis.

MEMBRANOUS nephropathy (MN), also known as membranous glomerulonephritis, is a common glomerular lesion frequently found to underlie the nephrotic syndrome or persistent nonnephrotic proteinuria.[1,2] In adults it is most often a primary glomerular disease (idiopathic MN), whereas in children it most often is associated with some underlying disease (secondary MN).[2] The glomerular lesions detected by light, immunofluorescence, and electron microscopy are quite characteristic. Similar lesions can be induced experimentally in animals. The pathogenesis of the lesion in animals involves in situ formation of immune complexes in the subepithelial space,[3] but the pathogenesis of the primary glomerular lesion in humans remains uncertain.[4] Untreated, the long-term outcome of the disease is variable but spontaneous remission or progression to end-stage renal disease (ESRD) both occur.[5] This article describes the clinical presentation, diagnosis, renal biopsy findings, and the natural history of the untreated disorder. Other articles in this issue deal with treatment of the disorder, including de novo and recurrent disease in renal transplants, and outline the management of complicating events, such as thrombosis and hyperlipidemia.

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CLINICAL PRESENTATION

MN is typically a disease of older adults.[1,2] In most series, the average age of discovery is in the fifth to sixth decade of life and over 80% of patients are over the age of 40 years at the time of presentation. MN is the most common cause of idiopathic nephrotic syndrome in adults, but is quite uncommon in children. Among adults with nephrotic syndrome with a lesion of MN on renal biopsy examination approximately 75% will have the primary form (idiopathic MN) of the disorder and about 25% will have an underlying disease (secondary MN) such as neoplasia, autoimmunity, infections, or drug hypersensitivity (see Table 1).[1,2,6] Many of these disorders can be occult at the time of presentation of the disorder and require an intensive serologic and/or imaging-based search. In children the opposite is true because over 75% of cases are caused by an underlying disease, particularly autoimmunity and infections (eg, hepatitis B viral infection). Men are affected predominantly with the primary idiopathic form of MN. The male: female ratio is about 2:1 in most series of adult cases. Young women with a renal biopsy examination revealing MN always should be suspected of having a secondary form of MN, particularly systemic lupus erythematosus (SLE). Patients of any race or ethnic group can be affected.[1]

The overall incidence of MN of any cause varies according to geographic region, in large part owing to the frequency of endemic infections (particularly hepatitis B), but the occurrence of the primary disease is similar across geographic regions. The presence of disease susceptibility genes within a population may account for some of the reported

Table 1. Causes and Diseases Associated With MN

- Primary (Idiopathic) MN
- Secondary MN autoimmune diseases
  - SLE
  - Rheumatoid arthritis
  - Mixed connective tissue disease
  - Dermatomyositis
  - Ankylosing spondylitis
  - Systemic sclerosis
  - Myasthenia gravis
  - Bullous pemphigoid
  - Hyperthyroidism (Grave's disease)
  - Hashimoto's thyroiditis
- Infectious diseases
  - Hepatitis B*
  - Hepatitis C
  - Malaria
  - Schisotomiasis
  - Filariasis
  - Syphillis
  - Leprosy
  - Hydatid disease
  - Enterococcal endocarditis
- Neoplasia
  - Carcinomas
    - Lung*
    - Breast*
    - Colon/rectum*
    - Esophagus
    - Stomach*
    - Bladder
    - Cervix
    - Kidney
    - Ovary
    - Prostate
    - Pharynx
  - Other
    - Hodgkin's disease
    - Non-Hodgkin's lymphoma
    - Sarcomas
    - Chronic lymphocytic leukemia
  - Other (Cont'd)
    - Mesothelioma
    - Pheochromocytoma
    - Wilm's tumor
    - Liver cell adenoma
    - Angiolymphatic hyperplasia
    - Schwannoma
    - Neuroblastoma
- Drugs
  - Gold*
  - Mercury (organic, inorganic, elemental)
  - Penicillamine
  - Bucillamine
  - Captopril
  - Probenicid
  - Trimethadione
  - Diclofenac*
  - Fenoprofen*
  - Ketoprofen*
  - Sulindac
  - Lithium
  - Formaldehyde
  - Volatile hydrocarbons
- Miscellaneous
  - Dermatitis herpetiformis
  - Sjogren's syndrome
  - Sarcoidosis*
  - Thyroid diseases*
  - Diabetes mellitus*
  - Temporal arteritis
  - Crohn's disease
  - Sickle cell disease
  - Kimura's disease
  - Multiple sclerosis
  - Weber-Christian disease
  - Primary biliary cirrhosis
  - Gullian-Barre syndrome
  - Myelodysplasia
  - Urticarial vasculitis
  - Hemolytic-uremia syndrome

* Most common causes.

differences in incidence in various areas of the world. In Victoria, Australia, between 1995 and 1997 the incidence of a lesion of MN discovered by renal biopsy examination was 13.27 per million person-years, and a lesion of MN represented 10.6% of all renal biopsy examinations revealing glomerulonephritis.[7] In an extensive epidemiologic study from the United Kingdom the annual incidence of MN was about 11 cases per million population per year.[8] About 20% of newly diagnosed cases of proteinuric glomerular disease are accounted for by MN. Among adults with nephrotic range proteinuria, MN is found by renal biopsy examination in about 25% to 40% of cases. In African Americans a lesion of focal and segmental glomerulosclerosis is found more frequently than MN in patients presenting with apparent idiopathic nephrotic syndrome.

The typical presenting feature of idiopathic MN in adults is nephrotic syndrome (80%) or persisting nonnephrotic proteinuria (20%).[1,2] The onset of clinical abnormalities usually is insidious and discovery of disease often is a result of a routine urinalysis showing abnormal proteinuria or the on-

set of peripheral edema caused by the nephrotic syndrome. An abrupt onset of disease is more suggestive of a secondary form of MN (eg, caused by infections or drugs). The proteinuria in MN usually is nonselective (immunoglobulin [Ig]G/transferrin clearance ratio ≥ 0.2), but exceptions to this generalization have been observed. Microscopic hematuria is not uncommon (about 30%), but gross hematuria is rare (<5%). The daily excretion of protein can vary widely, from barely above normal to massive (>20 g/d), but among patients with nephrotic range proteinuria (>3.5 g/d in an adult), over 75% initially excrete between 3.5 and 10 grams of protein daily.[1,2] Daily protein excretion rates can vary owing to the influence of exercise, diet (protein intake), and medications (particularly angiotensin inhibitors and nonsteroidal anti-inflammatory agents). Peripheral edema, caused by primary renal salt retention, can be an early manifestation in the presence of nephrotic range proteinuria. Massive anasarca can be a consequence of very heavy proteinuria and profound hypoalbuminemia. Hypertension is common, but seldom severe. Thromboembolic complications, such as deep venous thrombosis, renal vein thrombosis (RVT), and pulmonary embolism may develop, most frequently among patients with persistent nephrotic syndrome accompanied by hypoalbuminemia (<2.5 g/dL).[1,2] For poorly understood reasons, MN is the most common disorder predisposing to RVT. The frequency of RVT in MN varies widely, according to published reports, from about 5% to 50% depending on the series and the methods of detection. At present, spiral computed tomography, Doppler ultrasound, and magnetic resonance imaging are the most useful noninvasive methods of detecting RVT. Venous angiography is the gold standard. Whether screening for RVT by noninvasive imaging is appropriate in all cases of MN is unknown. Chronic unilateral or bilateral RVT does not appear to hasten progression to end-stage renal disease (ESRD), but it does contribute to the persistence of proteinuria and does increase the risk for a pulmonary embolus. Patients with MN who have already had a thromboembolic event (deep vein or arterial thrombosis, pulmonary embolus) probably do not need any investigation because they will be treated with long-term anticoagulants in any case. If the clinical findings suggest an RVT (disparity in kidney size, scalloping of the ureters, flank pain) in a patient who has not experienced a thromboembolic event, a search for RVT may be worthwhile because if an RVT (unilateral or bilateral) is discovered, long-term anticoagulation would be indicated (for as long as the nephrotic syndrome is present). The use of plasma markers of thrombosis (eg, thromboglobulin levels, fibrinopeptide levels) in detection of RVT in MN is not established. Theoretically, a regimen of prophylactic anticoagulants (Warfarin) might be indicated in a patient with MN and persistent hypoalbuminemia (<2.5 g/dL) because decision-analysis simulations have suggested that the benefits of such an approach outweigh the risk (primary bleeding). If prophylactic anticoagulants are to be administered, there would be little to be gained by searching for an occult RVT.[1,2] Hyperlipidemia is common, with increased levels of low-density lipoprotein cholesterol and triglycerides and normal or low levels of total high-density lipoprotein cholesterol. The plasma levels of high-density lipoprotein 3 may be increased while the levels of high-density lipoprotein 2 are reduced.[1] Renal function is most frequently normal or slightly reduced at the time of discovery, but patients can present with more advanced disease associated with impaired glomerular filtration rate, as estimated from serum creatinine values. Serum complement values (C3, C4, and C'H50) almost always are normal in patients with primary disease, but they may be reduced mildly in MN associated with SLE. Other serology test results usually are negative in primary disease. Hepatitis B surface antigen is positive in hepatitis B infection–related cases and hepatitis C antibody may be positive in those with hepatitis C–related disease. A positive fluorescent antinuclear antibody (FANA) test may be indicative of underlying SLE, but in older patients (>60 y) this is most often a false-positive, especially if the abnormal test is in low titer and the anti-DNA antibody test is negative. Younger women with low-titer FANA strongly should be suspected of having underlying SLE and undergo an appropriate serologic evaluation. Cryoglobulins are negative except in hepatitis C–related disease. Rarely, MN may follow an acute streptococcal infection.

DIAGNOSIS

The diagnosis of MN strongly should be suspected in any adult over the age of 40 years who presents with the insidious onset of the nephrotic

syndrome or persistent nonnephrotic proteinuria, regardless of the level of renal function. The urine sediment does not offer much help in diagnosis, although a bland sediment or mild microhematuria would be compatible with MN. In the primary form of MN (idiopathic MN) all serologies including FANA, serum complement, viral antibodies, and antigens should be negative or normal; however, older patients may display a weakly reactive FANA. Renal size usually is normal or at the upper limit of normal bilaterally by ultrasound. If an RVT has preceded the discovery of MN, there may be disparities in renal size or scalloping of the ureters because of the development of a collateral circulation. Thromboembolic manifestations (such as a pulmonary embolus) may precede the recognition of MN or occur subsequent to the diagnosis.

Many other glomerular lesions can present in a fashion resembling MN. These prominently include minimal change disease, focal and segmental glomerulosclerosis, amyloidosis, monoclonal immunoglobulin deposition diseases, and diabetic glomerulosclerosis.[1,2] However, renal biopsy examination and careful study of the specimen by light, immunofluorescence, and electron microscopy readily separates MN from the other lesions that can produce similar clinical manifestations and that can develop in patients of similar age. Once renal biopsy examination has established the presence of MN, it always is worthwhile to rereview the case from the perspective of a possible secondary form of MN (see Table 1), and to conduct appropriate investigations to ensure that they are not likely to be present, unless an underlying disease known to provoke MN is already evident from the clinical examination. As outlined later, the renal biopsy finding may offer some clues to the presence of an underlying disease (such as SLE). In adults, the main causes of secondary MN are neoplasia (usually carcinoma), autoimmune disease (most commonly SLE), chronic infections (chiefly viral hepatitis), and exposure to drugs (see Table 1 for details). A possible underlying neoplastic disease (especially carcinoma) should be suspected in all patients over the age of 60 years at the time of presentation with MN.[6] A search for possible secondary forms of MN might consist of a chest radiograph (or better yet a chest computed tomography), mammography in women, stools for occult blood (and a colonoscopy if patient is >50 y), a careful thyroid examination, a prostate-specific antigen and digital rectal examination in men, serologic studies for hepatitis B and C, a FANA and anti-DNA antibody, a careful history of drug or medication exposure, and a repeat physical examination searching for suspicious masses, skin lesions, or adenopathy. If these tests do not reveal an underlying disease, it is most likely that the primary or idiopathic form of MN is present. Unfortunately, at present there are no laboratory tests that will permit a direct diagnosis of idiopathic MN (a rule-in test) to be made without excluding other possible causes (rule-out testing).

RENAL BIOPSY EXAMINATION

As mentioned earlier, the pathologic findings in the renal biopsy examination are characteristic in MN.[1,2,9] By light microscopy, the glomeruli are of normal size and not hypercellular. In early stages, the peripheral capillary walls are thin and delicate by conventional stains (periodic acid-Schiff and periodic acid-Schiff–silver methenamine), but small red-orange deposits on the outer aspect of the capillary wall may be detected by trichrome staining. These deposits contain IgG (see later) and almost certainly represent the in situ formation of immune complexes. In the primary disease, the mesangium is free of deposits, but in secondary disease caused by SLE mesangial deposits, subendothelial deposits may be observed. In later stages, conventional stains reveal some thickening of the peripheral capillary walls and the presence of spike-like projections of basement membrane material outward toward the visceral epithelial cell processes. Later, the capillary wall is definitely thickened as the spike-like projections encircle the subepithelial deposits. Still later, the capillary wall may be thickened markedly with a Swiss-cheese appearance owing to the incorporation of the deposits into lacunae within the thickened basement membrane. Varying degrees of focal and segmental sclerosis and mesangial prominence may develop at these later stages. Crescents usually are not seen unless some superimposed disease process complicates the picture (eg, antiglomerular basement membrane antibody or antineutrophil cytoplasmic antibody–associated disease). Varying degrees of tubulointerstitial fibrosis, focal cellular infiltration, and tubular atrophy can be seen as the disease progresses. The vasculature usually is not affected unless hypertension or diabetes is concomitantly present.

Immunofluorescence microscopy reveals characteristic finding and this procedure serves as the backbone for the proper recognition of MN in renal biopsy specimens. All glomeruli reveal uniform deposition of IgG along the outer aspect of the capillary walls. In early stages these deposits are discrete and of small size, giving rise to a string-of-beads appearance. In later stages, the deposits may coalesce producing a lumpy-bumpy pattern. As the disease remits, the deposits may become only weakly positive for IgG. In the primary disease, the mesangium should be free of Ig deposits. Complement C3 and C3 degradation products also are present in the deposits, particularly if they are being formed actively.[10] IgA, IgE, and IgM often are absent, except in SLE-related MN. C1q deposits are weak in the primary form of MN, but are quite prominent in SlE-related MN. The presence of IgG, IgA, IgE, IgM, and C3 (full-house) in the deposits is often an indication of underlying SLE. Special staining with reagents detecting the C5b-C9 membrane attack complex are positive whereas active formation of deposits is underway. Antigens related to neoplastic diseases or viral agents (hepatitis B/C) may be detected in the glomerular lesions in the secondary forms of MN.

By electron microscopy, characteristic morphologic features are present. Electron dense deposits, of varying size, are seen in the subepithelial space beneath visceral epithelial foot processes. Initially these deposits are small and discrete, but they enlarge and coalesce in later stages, associated with formation of new basement membrane–like material projecting outward between the deposits (spikes). As the new basement membrane material encircles the deposits, domes are formed and the deposits may become less electron dense or actually appear electron lucent. Electron-dense deposits appear to represent newly formed deposits whereas electron lucent deposits appear to represent old deposits in the process of degradation and resorption. The visceral epithelial cells undergo fusion and effacement and the slit-pore membrane is obliterated. Protein reabsorption vacuoles can be seen in the enlarged podocytes. In the primary disease, the mesangium is free of electron-dense deposits. In the later stages, the basement membrane is thickened greatly and distorted on its subepithelial aspect. Electron-lucent areas can be seen within the thickened basement membrane representing older, partially resorbed deposits. The changes in the tubulointerstitial area and the vasculature are reflective of the changes seen by light microscopy. In SLE-related MN, tubuloreticular inclusions may be seen in endothelial cells. If a renal vein thrombosis has complicated the picture, margination of leukocytes in the glomerular capillaries may be seen; otherwise there are no pathologic features that can be relied on to indicate the presence or absence of unilateral or bilateral renal vein thrombosis

Thus, renal biopsy allows for easy identification of MN. Sample size is usually not a problem (as it is for many other glomerular diseases) because a single glomerulus showing the typical features of MN is enough to establish firmly the pathologic diagnosis. In early stages, it may be difficult to establish the presence of MN by light microscopy alone. Both immunofluorescence and electron microscopy are equally helpful in establishing the correct morphologic diagnosis. However, except for features suggestive of SLE, renal biopsy examination is not very helpful in separating the primary and secondary forms of MN. A focused clinical and laboratory examination, as outlined earlier, is needed to exclude the common causes of secondary MN, unless an underlying disease, such as a carcinoma or an infection, is already evident at the time of presentation.

NATURAL, UNMODIFIED HISTORY AND PROGNOSIS

The natural, unmodified course of idiopathic MN is quite variable.[1,5] In the absence of specific treatment (eg, steroids, alkylating agents, cyclosporine, and so forth), the disorder may pursue one or more of the following pathways: (1) a complete and lasting remission of all clinical manifestations, including abnormal proteinuria, with stable normal renal function; (2) a complete remission of proteinuria followed by one or more relapses, but with continued stable renal function; (3) a partial remission of nephrotic range proteinuria, followed by stable or slowly progressive deterioration of renal function; (4) persistence of nonnephrotic proteinuria with or without progressive deterioration of renal function; (5) persistence of nephrotic range proteiniuria accompanied by slowly progressive deterioration of renal function; (6) persistence of nephrotic range proteinuria and the development of superimposed acute or rapidly progressive renal failure (often caused by the development of a com-

plication such as acute hypersensitivity interstitial nephritis or crescentic glomerulonephritis). The literature is replete with retrospective examination of natural history of MN, but at least some of these studies have several flaws.[1,2,5,11-21]

First, they may have represented a selection of less severely affected patients because more symptomatic patients are likely to receive some form of treatment. Second, measures to counteract factors contributing to progression (hypertension, hyperlipidemia) were treated to a variable extent. Third, some series included children and young adults who have an intrinsically more favorable course with a higher likelihood of spontaneous remission. Fourth, series that included a higher proportion of women may be biased toward a more favorable outcome. Fifth, series that included patients with nonnephrotic proteinuria also would be biased with respect to a more favorable outcome in terms of progressive renal insufficiency. Prospective controlled trials, which include an untreated or placebo-treated group, more likely would provide a better estimation of the natural history of idiopathic MN.[22-25] However, these studies also can be biased with respect to the true natural history of the disorder because they often exclude certain categories of patients from the trial and the control of other factors contributing to progression (such as hypertension and hyperlipidemia) generally is better than that achieved in usual practice. The observation effect in such trials cannot be discounted. Furthermore, additional factors influencing outcomes, such as gender, race, ethnicity, and progression-associated genes (such as human leukocyte antigen genes), are not taken into account in many studies. Therefore, analysis of the natural history of idiopathic MN from the published literature must be interpreted with some caution because it may not be truly representative of MN as it exists in the population as a whole.

With these caveats in mind, several parameters readily identifiable at the time of presentation have been associated with a more unfavorable course of idiopathic MN, primarily the tendency to pursue a progressive course to ESRD. These are older age at onset, male sex, ethnicity (African American, Caucasian), persistent heavy proteinuria ($>$3.5 g/d), decreased serum albumin levels, poor protein selectivity, or persistent excretion of large amounts of β2 microglobulin or other low molecular weight proteins usually absorbed by the tubules, abnormal renal function (elevated serum creatinine level) at discovery, persistent or untreated hypertension, persistent hyperlipidemia, chronic tubulointerstitial fibrosis and tubular atrophy, advanced stages of glomerular disease (including focal and segmental glomerular sclerosis), crescentic glomerulonephritis, persistent excretion of complement degradation products (C5b-C9, C3d) in the urine, and the presence of certain human leukocyte antigen specificities.[1,2,11]

Among these progression factors, quantification and characterization of the quality of proteins excreted in the urine may be the most important. Patients with persistent nonnephrotic proteinuria ($<$3.5 g/d; typically $>$0.2 and $<$2.0 g/d) have a low risk ($<$5%) for developing ESRD, whereas the risk for ESRD increases step-wise with increments in proteinuria above 3.5 g/d. Indeed, the risk for progressive disease can be reasonably predicted reliably based on the quantity of protein excreted daily over a 6-month period of observation after factoring the initial serum creatinine value.[26] Sequential measurements are essential for accurate prediction because the initial values alone show only a weak association with outcome. It is the average amount of protein excreted daily over a specified time interval that yield the best estimate of likely long-term outcome. For example, excretion of greater than 8 g/d for over 6 consecutive months is associated strongly with a high risk for future progressive disease. Even at equivalent quantities of protein excretion, the quality of protein excreted has an important bearing on prognosis. Poor selectivity of proteinuria, especially when combined with the excessive excretion of low molecular weight plasma proteins (such as α2 microglobulin or β2 microglobulin) associates with a poorer prognosis than with nephrotic range proteinuria alone.[27] The serial assessment of proteinuria (as a 24-hour excretion rate or as a protein: creatinine ratio on first morning urine), sequential measurement of renal function (serum creatinine), evaluation of the stage and activity (electron-dense versus electron-lucent deposits; extent and intensity of C3 deposition) of the glomerular disease, and estimation of the severity of the chronic tubulointerstitial lesions in the kidney biopsy examination are the cornerstones of evaluation of the prognosis in patients with idiopathic MN.

With these caveats and prognostic markers in mind, one can address the overall prognosis of

untreated MN, recognizing the uncertain influence of variable nonspecific treatment of such factors as hypertension, hyperlipidemia, dietary protein intake, and the age, sex, and ethnicity of the patient. The 5-year renal survival (alive, free of ESRD) of idiopathic MN has been estimated at about 80% to 85%, the 10-year renal survival at 50% to 60%, and the 15-year renal survival at about 40% to 50%.[1,5,11-25] Overall, about 6% to 23% (average about 16%) of patients with MN (regardless of the level of proteinuria) require dialysis after about 10 years of follow-up. Women, Asian (Japanese) patients, younger adults, those with early stage disease, and those with persistent nonnephrotic proteinuria would be expected to have a better outcome. Because the average age of onset of MN is in the 5th to 6th decade overall, patient survival, including those on renal replacement regimens of treatment, may not be greatly different in untreated patients with MN than a comparable age-matched population of patients without renal disease.[16] Of course, untreated patients who present with the nephrotic syndrome will have a higher risk for developing a complication of the nephrotic syndrome (eg, thrombosis, accelerated atherogenesis) than patients who are treated successfully and enter into remission.[5] Progressive impairment of renal function (as evidenced by doubling of the initial serum creatinine level) occurs predominantly in patients with sustained nephrotic range proteinuria. After 2 to 3 years of follow-up, doubling of the serum creatinine level was found in about 12% of untreated patients by Noel et al[12] and by Donadio et al.[16] In the control arm of the treatment trial of Ponticelli et al,[24] the serum creatinine level had doubled in 23% by 2 years of follow-up and in 33% by 5 years of follow-up. In the control arm of the Collaborative Study of the Nephrotic Syndrome,[22] doubling of the serum creatinine level compared with baseline values had occurred in 44% by 2 years. In the control arm of the treatment trial of the Medical Research Council[23] the average serum creatinine level increased from 130 μmol/L (1.5 mg/dL) at baseline to 300 μmol/L (3.4 mg/dL) after 3 years of follow-up. According to a retrospective analysis of patients with MN having been followed-up for at least 10 years, it is uncommon for progressive renal insufficiency to be manifest sooner than 3 years after initial presentation, but progression can be noted to occur as late as 13 years after presentation.[13] Remissions of proteinuria can occur at any time but are most likely to develop in the first 3 years after presentation. The reasons underlying this variability in early progression of disease are not clear, but could be owing to variations in the prognostic factors mentioned earlier at entry into the trials.

Untreated patients can and do enter into spontaneous complete or partial remissions of proteinuria. Several studies have suggested a complete or partial remission rate among patients with the nephrotic syndrome on presentation in about 30% to 35% within 5 years of follow-up and about 40% to 50% in patients followed-up for 10 years or more.[11-25] In the study of Schieppati et al[19] of 100 untreated Italian patients with MN (37% of whom had nonnephrotic proteinuria), 65% of the patients (including those with initial nonnephrotic proteinuria) had entered into or maintained a complete or partial remission by 5 years. In the control, untreated arm of a treatment trial of nephrotic patients with MN, also in Italy, Ponticelli et al[24] reported that 47% of patients developed at least one complete or partial remission by 10 years of follow-up. Because of relapses, 33% were in a complete (5%) or partial (28%) remission rate at the last follow-up 10 years after entry into the trial. Patients who entered into a complete remission had no further relapses about 50% of the time, one or more relapses of nephrotic syndrome about 30% of the time, and one or more relapses of nonnephrotic proteinuria 20% of the time. Patients who experienced at least one complete remission did very well over the long term, even if relapses occurred.[28] Progression to ESRD was uncommon ($<$1%) in those who had experienced at least one complete remission and permanent remission was observed eventually in about 75% of patients.[28] Donadio et al[16] reported a complete and partial remission rate of 67% at the end of the follow-up period (about 5 y) in 140 untreated adults with MN having varying levels of initial proteinuria. Progressive renal disease was seen predominantly in patients excreting over 10 g/d. In the untreated arm of the treatment trial of the Collaborative Study of the Nephrotic Syndrome,[22] 18% of the patients were in complete or partial remission at the end of follow-up (approximately 2 y).

Thus, from the overall perspective (recognizing variability among individual populations of patients) it can be estimated that about 20% of adult patients with idiopathic MN will present with non-

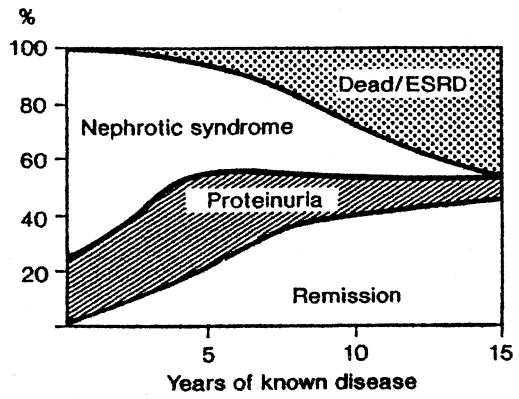

Fig 1. The course of primary (idiopathic) MN as estimated from literature reports. Note that slightly over 20% of patients with MN initially present with nonnephrotic proteinuria and slightly less than 80% present with the nephrotic syndrome. Evolution to ESRD or death usually is slow, and predominantly occurs among patients who do not experience a remission of nephrotic range proteinuria. It is estimated that about 50% of patients will have a sustained remission or have persistent nonnephrotic proteinuria 15 years after discovery of MN. (Reprinted with permission from Parikh C, Teitelbaum I, Cameron JS: The long term outcome of glomerular diseases, in Schrier RW, ed: Diseases of the Kidney (ed 7). Philadelphia, Lippincott, Williams Wilkins, 2001, pp 2003-2007.[5])

nephrotic proteinuria and subsequently will experience a favorable long-term course in the absence of specific treatment so long as the nephrotic syndrome does not subsequently develop. About 80% of adult patients with idiopathic MN will present with nephrotic range proteinuria. Of these patients, without any specific treatment, about 40% to 50% will enter into a complete or partial remission within 10 years of follow-up, which may relapse, but with continued stable renal function; about 20% to 30% will continue to have nephrotic range proteinuria, with or without progressive impairment of renal function (this will depend on the quantity and quality of protein excreted in the urine and other prognostic factors); and about 40% to 50% will progress to ESRD or die of renal or nonrenal causes, usually between 6 and 13 years of follow-up (see Fig 1). Of course, untreated patients with persistent nephrotic range proteinuria will be exposed to the undesirable biochemical features of the nephrotic state, such as hyperlipidemia and a thrombotic tendency, and would be expected to have a higher risk for complications such as coronary artery or thromboembolic disease compared with patients who experience a spontaneous or treatment-induced remission. Nevertheless, the overall life expectancy of an untreated patient with idiopathic MN is not greatly different than a comparable age population of individuals without renal disease.[16]

Based on the information concerning the natural history of idiopathic MN, one can appreciate the need for carefully conducted, randomized, controlled trials with prolonged follow-up (5 y or longer) to establish the efficacy and safety of proposed treatment regimens. In addition, the application of algorithms or formulae that take into account prognostic factors present at initial discovery or that develop after a relatively brief period of follow-up (6 mo to 1 y) permits the application of therapeutic regimens having significant risks for complications and side effects to patients at the greatest risk for progressive disease.[26] Of course, selection of such patients for treatment trials based on an adverse profile of prognostic factors also may result in a selection of patients for treatment who are intrinsically less likely to respond to treatment. For example, delaying the application of an effective treatment regimen until after renal function has shown a tendency to decline and after a period of observation for a spontaneous remission may result in the treatment of a patient less likely to respond or more likely to develop a complication of therapy. This is but one of the conundrums raised by studies of the natural history of MN. More precise questions to be asked in future natural history studies include: What factors are responsible for spontaneous remissions (and relapses) of disease? When in the course of persistent disease are irreversible or self-perpetuating components introduced? How can we reliably identify the patients who are destined to progress (or destined to remit) at the time of discovery of disease? Based on current evidence from natural history studies, candidates for treatment who have idiopathic MN appear to be middle-aged or older adults, with persistent nephrotic range proteinuria ($>$6 mo), and reasonably well-preserved renal function (serum creatinine level $<$3.0 mg/dL). Other factors that need to be taken into account in therapeutic trials include assessment of the activity of disease (as assessed by the appearance of the glomerular deposits and perhaps the excretion rates of complement components, such as C5b-9), genetic factors predisposing to progression, the excretion rates of low molecular weight tubular pro-

teins, glomerular protein selectivity, and the degree of chronic, irreversible changes in glomeruli (glomerulosclerosis), and the tubulointerstitial area (atrophy and fibrosis). In controlled randomized studies it is important that factors potentially involved in progression are well balanced between the untreated and treated arms of the study. Studies involving small numbers of patients with MN followed-up for short period of time may be influenced greatly by the variable natural history of MN, leading to erroneous conclusions regarding the efficacy (or lack thereof) of a proposed new therapeutic regimen.

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