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Invited review

Idiopathic membranoproliferative glomerulonephritis in childhood

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Abstract. Membranoproliferative glomerulonephritis (MPGN), recognized since 1965, is now known to have three forms, designated types I, II, and III. The types are similar in the frequency of hypocomplementemia and clinical course but are dissimilar in glomerular ultrastructure, pathogenesis, mechanisms of complement activation, predisposition to recur in the renal transplant, and, to some extent, in clinical presentation. Although glomerular proliferation is usually diffuse, it may be focal and segmental particularly in mild cases of MPGN I. Hypocomplementemia, present in about 80% of patients, is the result of hypercatabolism of C3 by three mechanisms as well as of diminished C3 synthesis. The hypocomplementemia is unrelated to clinical course or prognosis. Although MPGN I and III both have a high frequency of an extended haplotype on chromosome 6, which has known associations with autoimmune phenomena, and both have a high frequency of inherited complement defects, they are nevertheless dissimilar in glomerular ultrastructure, complement profile, and immunohistology in ways which suggest a wide difference in pathogenesis. Abnormalities in humoral immunity appear not to be involved in MPGN III. Treatment with anticoagulant, antiplatelet and cytotoxic drugs have, in controlled trials, been either ineffective or marginally effective. Long-term use of alternate-day prednisone in high dosage appears to be the most efficacious regimen in both controlled and uncontrolled studies.

Key words: Membranoproliferative glomerulonephritis – Dense-deposit disease – Hypocomplementemia – Prednisone – Nephritic factor – Complement profile – C3

Introduction

Membranoproliferative glomerulonephritis (MPGN), also known as mesangiocapillary glomerulonephritis, is an old disease [1] whose recognition in 1965 depended on correlating the light microscopic appearance of renal biopsies with low serum levels of C3, the third component of complement [2]. Further study revealed patients with the typical histopathology but normal C3 levels. Eventually study of glomerular ultrastructure led to splitting MPGN into three forms [3, 4] designated types I, II, and III. Type II, or dense-deposit disease, has long been classed as membranoproliferative [3], and the ultrastructural criteria for its diagnosis are clear cut. Acceptance of a type III has come slowly and patients with this type have been classified as type I in the older literature. The three types are similar with respect to clinical presentation and course and in their general response to therapy but differ in basic pathogenesis, including mechanisms of complement activation and role of genetic factors, and in their predisposition to recur in the renal transplant. Conversion from one type to another has not been reported.

In Europe [5] and Canada [6], the frequency of new cases of MPGN dropped by 50% or more in a 6-year period from 1980 to 1985 compared with the previous 5- to 8-year period. As can be seen in Fig. 1, our data, eliminating patients referred from outside the catchment area of this institution, show the frequency of new cases to be fairly constant in the 10-year periods 1965–1974 and 1980–1989, but a definite increase in the 5-year period 1975–1979. Thus we too have seen an approximate 50% decrease in 1980–1984 over the prior 5-year period, but the data suggest that the decrease represents a return to a baseline frequency, defined as that existing from 1965 to 1974.

Presentation

MPGN may present with overt signs of nephritis, with gross hematuria only, or with asymptomatic microhematuria and proteinuria. Presenting signs, other than renal failure, which correlate with a poor prognosis are, in some series, hypertension [7, 8] and, in others, nephrotic syndrome [3, 9]. A persistent nephrotic syndrome is particularly ominous. With all types, the first event may be an episode of gross hematuria, often in association with an

infection, raising the possibility of acute post-streptococcal glomerulonephritis (AGN). With MPGN, the C3 level remains depressed for more then 6 weeks.

Among our patients with MPGN III, the chance discovery of an abnormal urine in the otherwise healthy child led to the diagnosis in 65% (11/17) whereas in only 22% (5/23) of those with MPGN I was the disease detected in this manner ($P < 0.01$) [10]. A presentation with fatigue, pallor, and weight loss, but with normal renal function, was seen in 22% (5/23) of those in our series with MPGN I, but in none with MPGN III [10]. Thus MPGN III tends to have a symptomless, insidious onset with, over an extended period, an abnormal urine as the only manifestation, whereas MPGN I more often presents soon after apparent onset with signs and symptoms typical of glomerulonephritis. Some with MPGN I may, in addition, have symptoms of systemic illness in the months before renal disease is discovered.

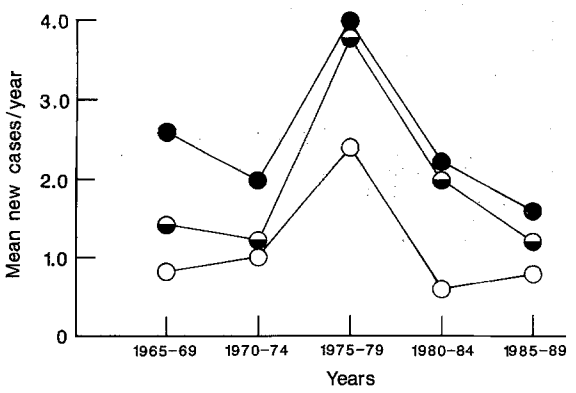

Fig. 1. Mean frequency of new cases of membranoproliferative glomerulonephritis (MPGN) for 5-year periods, 1965–1989 inclusive. Symbols indicate MPGN I ○; MPGN I and III ◒; MPGN I, II and III ●. Patients from outside the catchment area of the medical center are not included

Glomerular morphology

Glomerular ultrastructure

Separation of the types is based on ultrastructural abnormalities of the glomerular basement membrane. As indicated in Table 1, in type I the basement membrane is normal. There is, however, considerable new basement membrane formation at the interface of endothelial cell with interposed mesangial cell and/or subendothelial deposit, giving the well-known "tram-track" appearance by light microscopy. In MPGN II, by both uranyl lead and silver staining, long stretches of lamina densa are thickened and unusually electron dense with normal basement membrane intervening. MPGN III is characterized by segments of severe basement membrane abnormality in association with subepithelial and subendothelial deposits [4]. The abnormality could be interpreted as the result of disruption of basement membrane by the deposits with concurrent formation of new basement membrane where deposits contact endothelial and epithelial cells. This gives the appearance, in silver-impregnated material, of a frayed and laminated basement membrane with deposits apparently intercalated within it. In uranyl lead preparations, a frayed basement membrane is not seen; instead, it appears thickened by intramembranous, circumscribed deposits less electron dense than those in MPGN II. Silver staining makes relatively easy the distinction between the three types.

Light microscopy

In MPGN I, mesangial proliferation is marked. Due to the proliferation, the glomeruli may be markedly enlarged, the capillary lumina greatly compromised and mesangial interposition abundant, resulting in the "tram-track" appearance; neutrophils may be present. By immunofluorescence, deposits are often confined to the periphery of the tuft, suggesting poor centrilobular perfusion, yet the glomerular filtration rate is often normal. In MPGN II, the basement membrane by light microscopy is thickened and in silver preparations is non-argyrophilic. Dense deposits may be distinguished in a segmental distribution in Bowman's capsule and in proximal tubular basement membranes. In

Table 1. General characteristics of glomerular morphology in the three types of membranoproliferative glomerulonephritis (MPGN)

	Basement membrane by EM	Subendothelial deposits[a]	Subepithelial deposits	Mesangial deposits	Mesangial interposition	Glomerular size	Mesangial cellularity[c]
Type I	Normal	+++	+	+++	+++	Usually increased	+++
Type II	Dense "deposits"	+	++	++	+	Normal	++
Type III	Slug-like deposits by uranyl lead[b]	++	++	+	+	Normal	++

EM, Electron microscopy

[a] Grading is + to +++

[b] With silver stains, the glomerular basement membrane appears frayed and disrupted with deposits intercalated within it

[c] Occasional patients with MPGN III have marked mesangial proliferation. Proliferation may be segmental rather then diffuse

MPGN III, mesangial proliferation is usually moderate [10] and often segmental, but cases with severe proliferation have been seen [4]. Open capillary lumina are usually more abundant than in MPGN I [10] and mesangial interposition and tram tracking are less common. There is widespread eosinophilic thickening of the capillary walls [4].

Ultraviolet microscopy of sections stained with thioflavin T can distinguish MPGN II [11]. The dense deposits give a linear green fluorescence. Green fluorescence is also seen with systemic lupus erythematosus (SLE), other types of MPGN, amyloidosis, and certain gammopathies, but it is diffuse and non-linear. The dense deposits also bind wheat germ agglutinin, suggesting *N*-acetylglucosamine as a prominent component [12].

MPGN variants

In one variant of MPGN I, occasionally seen with MPGN III, the lesions are focal and segmental [7, 13]. Whereas this form may present with signs typical of chronic glomerulonephritis, the prognosis is usually excellent [7, 13, 14].

Chronic lobular glomerulonephritis is a form of MPGN I characterized by enlarged glomeruli with centrilobular hyaline nodules which displace the capillaries to the periphery of the lobules [15]. The hyalinosis is the apparent consequence of severe mesangial proliferation. Severe proliferation persists at the periphery of the nodules but with little mesangial interposition. Relatively normal capillaries festoon the hyaline cores. Cases of typical MPGN I have been seen to evolve into the lobular form [15].

Frequency of types

Three factors confuse data concerning the frequency of the three types. As Swainson et al. [16] have pointed out, reliance on light microscopy to determine type, as used in many series, can result in errors which, in their experience, underestimate the frequency of type II. Secondly, accurate distinction between types I and III requires electron microscopy of silver-impregnated specimens [4], a technique not widely used. Thirdly, series confined to adults often have a relatively low percentage of MPGN II since this type presents more commonly in childhood [9]. A series in which electron microscopy of silver-impregnated specimens was used to distinguish types is that of Anders [17]. In 50 German children, the frequencies of types I, II, and III were, 54%, 32%, and 14%, respectively. In our series of 75 children, using the same methods and diagnostic criteria, the frequency is 44%, 20%, and 36%. The reason for the differences is not clear. The frequency of MPGN II in Japan may be less; in a report by Ohi et al. [18], in which the method of distinguishing types is not given but 70% of the patients presented under the age of 20 years, the frequency of MPGN II was 6% ($n = 632$).

Hypocomplementemia of MPGN

Frequency and significance

Hypocomplementemia, defined in this review as subnormal levels of C3, is found in all types of MPGN but not in all patients. Under the age of 20 years, the frequency is 77% (59/77) in our experience [19] and 64% (28/44) in the series of Cameron et al. [9]. In our series, it was present in 68% of those with MPGN I, 82% with MPGN II, and 84% with MPGN III.

Hypocomplementemia at presentation is not a prognostic indicator. In most patients, the hypocomplementemia disappears rapidly with initiation of an alternate-day prednisone regimen but it may, for unknown reasons, persist in a few patients despite adequate dosage and compliance [20]. Persistence of hypocomplementemia does not necessarily indicate that the disease is active or that glomerular morphology is deteriorating [20].

Causes

The hypocomplementemia of MPGN is mainly the result of hypercatabolism of C3 although diminished C3 synthesis often serves to intensify it. Three causes of hypercatabolism have been identified. First, the classical pathway can be activated in MPGN I [19, 21], presumably the result (as in SLE [22]) of the reaction of complement with circulating immune complexes. The composition of the complexes in MPGN I is, however, not known.

Second, an autoantibody reactive with activated factor B, a component of C3b,Bb (the alternative pathway C3 convertase), is found in MPGN II and in partial lipodystrophy (PLD). C3b,Bb is constantly being formed in the circulation and its half-life, normally very short, is increased tenfold by reaction with this antibody [23, 24]. This stabilized convertase increases the turnover of the C3b amplification loop, markedly lowering C3 levels and slightly lowering factor B levels but with little effect on the levels of terminal components [19]. C5 catabolism is normal [25]. The complement profile is distinctive; C3 is markedly depressed and C5 and factor B levels are normal or slightly depressed. This nephritic factor has been designated NF_{II} [26], or NF_a [19] for nephritic factor of the amplification loop.

Third, a recently described [26] nephritic factor differs from NF_a in that it converts C3 more slowly, activates terminal components forming C5b-9 (the membrane attack complex) [27], and is ineffective in the absence of properdin [26, 28]. These properties indicate that it stabilizes the alternative pathway C3/C5 convertase which can be designated, $P,C3b_2,Bb$. Conversion with this nephritic factor in vitro is slow because spontaneous formation of this more complicated convertase in serum is less frequent than that of C3b,Bb. It has been designated NF_t [19], or nephritic factor of the terminal pathway. Simple and precise in vitro methods for distinguishing NF_t from NF_a, particularly when they are present in low concentration, have not been devised but from the frequency of depressed levels of C6, C7, and C9 in MPGN III, it has been concluded that NF_t is

the only complement-reactive material circulating in that type [19]. By this criterion, it is also present in at least 20% (7/35) of the patients with MPGN I (29% of hypocomplementemic MPGN I patients) [19]. It therefore has also been designed $NF_{I,III}$ [26].

Of unknown significance in altering the complement profile is a third nephritic factor which stabilizes the classical pathway C3 convertase, C4b,2a, in the same manner the other factors stabilize the C3b-dependent convertases [29]. Since C4b,2a is not formed spontaneously, addition of this nephritic factor to serum does not cause C3 conversion [29]. Thus, for the factor to contribute to hypocomplementemia in vivo, there must be ongoing C4b,2a production via the classical pathway. This factor has been variously designated NF_c (nephritic factor of the classical pathway), F4,2, and C4NeF. It was first found in a patient with acute post-infectious glomerulonephritis [29] and subsequently in SLE [30], and in MPGN I [31].

Distinguishing MPGN type by complement profile

When hypocomplementemia is severe, measurement of three proteins (C4, C3, and C5) can be helpful in determining the type of MPGN [19]. Of the classical pathway components, C4 is the most responsive to classical pathway activation and a low level, together with a low C3 and C5, is indicative of MPGN I, if SLE, chronic bacteremia, and the early stage of AGN are excluded. A normal level of C4, a depressed C3 and a normal or minimally depressed level of C5 indicates MPGN II or PLD. The combination of markedly depressed C3 and C5 levels with normal C4 rules out MPGN II and SLE and could be seen with either MPGN I or III.

Diminished C3 synthesis

Metabolic studies in hypocomplementemic patients have shown that the fractional catabolic rate of C3, although high when hypocomplementemia is severe, cannot account for a severely depressed C3 level and that, as C3 catabolism increases, diminished synthesis of C3 plays an increasing role in producing the hypocomplementemia [32]. The data would suggest that the circulating C3 breakdown product, C3dg, depresses C3 synthesis by negative feedback. Synthetic rates are lowest when C3dg is circulating. With hypocomplementemia unaccompanied by circulating C3dg, synthetic rates are normal [32].

Pathogenesis

General factors involved in the pathogenesis of MPGN I and III

Evidence for a genetic basis for at least some cases of MPGN I and III is the observation that, on the short arm of chromosome 6, the extended haplotype HLA-B8, DR3, SC01, GL02 constituted 13% of the disease-associated haplotypes and 1% of control haplotypes [33]. This haplotype is also found with high frequency in insulin-dependent diabetes mellitus [34], gluten-sensitive enteropathy [35], and SLE [36]. The observations suggest an origin for these types of MPGN in autoimmune phenomena. With this haplotype in MPGN, the prognosis tended to be poor [33]. There is no evidence for a genetic basis for MPGN II.

Probably also bearing on pathogenesis is the observation that a significantly high percentage of those with MPGN I and III have inherited defects of the complement system [37]. The frequency reported from this laboratory in 1983 was 22.7% (10/44) compared with defects in 6.7% (11/163) of normal subjects ($P < 0.002$). Since that time, new patients have been encountered and the frequency of defects remains essentially the same at 21.8% (12/55). To the present, the inherited deficiencies have involved C1q, C2, C3-factor B, C6-C7, C7, C8, and the C1 inhibitor. In no case was there a complete deficiency, and why partial deficiencies are so frequently present is not clear.

Additional evidence for genetic factors is the low frequency of the disease in blacks and examples of MPGN occurring in families. In our series, the frequency in blacks is 1.3% ($n = 75$) and in a series of patients with MPGN II from the Southwest Study Group [38], 6% ($n = 16$). In a series from Michael Reese Hospital in Chicago, none were black ($n = 22$) [15]. The disease has been reported in sibships, in one instance one sibling had MPGN I and the other MPGN III [39]. There is also a report of MPGN I in related males which clearly reveals an X-linked inheritance [40]. Immunofluorescence of a renal biopsy revealed glomerular C1q and C4 as well as C3, but there was no hypocomplementemia. No marker for the female carrier state could be found. In another family, PLD, nephritic factor, and MPGN were found in two generations [41]. In this family, the glomerulonephritis was reported as MPGN I but the photomicrographs conform more to the appearance of MPGN III. Although MPGN II is usually seen with PLD, other types can occur [42, 43].

Changes in the frequency of the disease in the same direction in several Caucasian populations worldwide (vide supra) would suggest that an environmental factor(s) is also important in etiology.

Pathogenesis of MPGN I

Several lines of evidence indicate that MPGN I is the glomerular response to the subendothelial deposition of circulating immune complexes. First, the glomerular morphology of MPGN I can develop when immune complexes are known to be circulating, as with an infected atrio-ventricular shunt or with chronic active hepatitis [44, 45]. Secondly, 54% (12/22) of hypocomplementemic patients (34% of all patients) with MPGN I have a complement profile compatible with classical pathway activation [19]. Thirdly, as would be expected with deposition of circulating immune complexes, C4 is present in the glomeruli in 73% (11/15) and IgG in 96% (24/25) of first biopsies of normo- and hypocomplementemic patients with MPGN I [19]. Possibly related to immune complexes in the circulation are the symptoms of systemic illness present in some of these patients prior to diagnosis [10].

Pathogenesis of MPGN II

The pathogenesis of dense-deposit disease is not known. It is a systemic disease as evidenced by: (1) the high incidence of recurrence in renal allografts [46]; (2) the presence of dense deposits in ocular basement membranes which have a drusen-like appearance by fundoscopy [47, 48]; (3) the presence of deposits similar to those in the glomerular basement membrane in the spleen [49, 50] as well as in Bowman's capsule and in renal tubular basement membranes [11]. The cause of the increased electron density of these structures is not known. Transplant biopsies and biopsies of patients with PLD have indicated that the basement membrane change precedes the development of nephritis.

Why NF_a is apparently the only nephritic factor found in MPGN II and PLD (vide supra) is not known. Hope that the recent discovery that the serine protease, adipsin (made by adipocytes) is factor D of the complement system [51] would provide insight into the NF_a-PLD association has not been realized. The only known function of factor D is to convert factor B of the preconvertase, C3b,B, to its activated form, C3b,Bb. Addition of factor D to serum fosters C3 conversion [52]. Adipsin (factor D) levels are depressed in genetically obese mice and those made obese by glucose infusion [51]. Levels are elevated in catabolic states such as starvation and experimental diabetes [53]. There are no data on adipsin levels in PLD but, as a lipolytic state, it is attractive to postulate elevated levels fostering convertase formation and predisposing to production of anticonvertase antibody. However, more information is needed before such a scenario can be considered.

The nephritis which can develop in patients with PLD and NF_a could be the result of faulty disposal of immune complexes because of the hypocomplementemia. However, the frequent absence of IgG, C1q, and C4 from glomerular deposits [54, 55], the usually normal serum levels of C4 [19, 54], and the frequency with which MPGN II patients present with normocomplementemia [19, 54] provide little support for this pathogenesis.

Pathogenesis of MPGN III

Signs of classical pathway activation in MPGN III are minimal. In 16 hypocomplementemic patients, the mean serum C1q and C4 levels did not differ significantly from those in normal subjects, but there was a slight depression of C2 of borderline significance [19]. The hypocomplementemia in this type appears to be largely due to NF_t (vide supra). Glomerular deposits in MPGN III contain little or no C4 or IgG. In our series, C4 was absent in 94% (15/16) and IgG in 50% (10/20) of patients. In 90% of those with IgG, the intensity of fluorescence was 1+ or trace and the pattern did not conform to that of C3. In contrast, in MPGN I the deposits in 73% (11/15) contained C4 and in 96% (24/25) IgG [19]. The observations suggest that complement-reactive immune complexes are not circulating as they are in MPGN I and SLE, and that the glomerular deposits are of unique composition. The deposits appear to have a marked effect on the capillary wall. Concurrently, they appear to lyze basement membrane and to stimulate new basement membrane formation. They seem to have little effect on the mesangium; mesangial proliferation is significantly less than in MPGN I [10]. By immunofluorescence, the deposits, in our experience, always contain C3, C5, and properdin, the constituents of the alternative pathway C3/C5 convertase. It can be inferred that the membrane attack complex is also present since in these diseases its distribution is the same as that of C5 [56]. It could be hypothesized that the primary event in MPGN III is a change in a membrane of the glomerular capillary wall so that it becomes an alternative pathway activator. Whether this would be the endothelial cell or the basement membrane itself is not clear. With continuous access to circulating plasma, deposits composed of convertase and membrane attack complex could accumulate with adverse effects on the basement membrane. There are several examples of cell membranes becoming alternative pathway activators as result of viral infection of the cell [57].

Other observations, however, give little support for this pathogenesis. First, there is no ancillary evidence of glomerular viral infection. Second, there is no precedent for deposits composed exclusively of complement components without immunoglobulin. Third, all of the diseases mentioned above which are strongly associated with the extended haplotype HLA-B8, SC01, DR3, GL02 [34–36] appear to have a pathogenesis based on an abnormality in humoral and cellular immunity and it is incongruous to include in this group one based on a change in the reactivity of glomerular membranes. Further, the similar frequency of inherited complement defects in MPGN I and III [37] and the presence of MPGN I and III in siblings [39] are difficult to reconcile with two widely differing pathogeneses. The need for additional study of pathogenic mechanisms in MPGN is obvious.

Treatment

Approaches to treatment have included immunosuppression, minimizing glomerular fibrin deposition with anticoagulants, inhibiting platelet-induced injury with dipyramidole, and use of steroidal or non-steroidal anti-inflammatory agents. There have been five randomized clinical trials. Four of the five employed dipyramidole, combined in two with cyclophosphamide and warfarin, combined in one with warfarin alone and in one with Aspirin; the fifth was of alternate-day prednisone. Patients in the two trials employing cyclophosphamide, warfarin, and dipyramidole [58, 59] had a number of toxic complications and a beneficial effect was not seen. In a crossover trial of warfarin and dipyramidole [60], improvement was noted if the treatment period was first but for all paired data, changes in serum creatinine concentrations during control and treatment years were not significantly different. An advantage for the treatment years was seen only in unpaired comparison of control and treatment years. There were a number of hemorrhagic complications. In a 1-year trial employing dipyramidole and Aspirin [61], renal function was more stable in the treatment group, but on prolonged follow-up neither patient survival nor survival free of renal failure

was improved by this combination [62]. Since many of the patients in these trials had glomerular filtration rates less than 50% when treatment was started, the results might depend more on the ability of the regimen to slow non-immunological hyperfiltration glomerular injury [63, 64] as opposed to abrogating the immunological injury which presumably initiates the disease.

For the past 16 years, the Cincinnati group has advocated the prolonged use of a high-dose alternate-day prednisone regimen. By 1985, 45 patients with diffuse, as opposed to focal, disease had received the regimen in an uncontrolled trial [20]. Survival was significantly improved over that of untreated patients recorded in other series. Serum albumin levels remained normal or increased in 80%, hematuria disappeared in 80%, proteinuria in 27%, and crescents in 6 of 7 patients. In 2-year follow-up biopsies, open capillary lumina significantly increased, mesangial matrix prominence significantly decreased, but there were significant increases in glomerular sclerosis and tubular atrophy. In biopsies obtained 6–11 years after the start of the regimen in 4 patients with MPGN II, the capillary loops became either totally free of dense deposit or the segments of basement membrane bearing dense deposits diminished in length [65]. These changes were concurrent with other signs of improved glomerular morphology. In a later report from this group [66] in which the number of children receiving the regimen had increased to 71, survival was still significantly better than in other series, whether survival was taken as time from diagnosis or time from the start of the alternate-day regimen [62].

It was initially concluded from a double-blind controlled study of the alternate-day regimen conducted by the International Study of Kidney Disease in Children (ISKDC) [67] that the regimen was of no value largely because of the high frequency of toxic complications. In this trial, the dose of prednisone was approximately two-thirds that used by the Cincinnati group. Subsequently, additional data from the ISKDC study reversed this conclusion [68]. Other groups [69, 70] including the Cincinnati group [20], have not experienced complications of the alternate-day regimen requiring its discontinuance, as reported in the ISKDC study [67, 68]. Subsequently, others, in uncontrolled [69–72] and controlled [73] trials, have reported improvement in patients treated with the alternate-day regimen.

The dose of prednisone used has been variable. In some series, pulse therapy with methylprednisolone has preceded the alternate-day regimen [71], particularly in those with severe disease [69]. In the Cincinnati series [20], the regimen started with a prednisone dose of 2.0–2.5 mg/kg, with a maximum of 80 mg, every other day, dropping, on the average, to 1.75, 1.5, 1.0, and 0.6 mg/kg in the 2nd, 3rd, 4th, and 5th years, respectively. A number of patients receiving the regimen for 5 or more years have not relapsed when it was stopped. Others have reported success with lower doses [69, 71, 73]. In the ISKDC trial [67, 68] and that reported by Mota-Hernandez et al. [73], the alternate-day dose was approximately 1.5 mg/kg (40 mg/m^2) with a maximum of 60 mg and was continued for 5 years. In six patients with MPGN I, Warady et al. [69] used doses of 20 mg every other day, 2 mg/kg every other day, and 2 mg/kg every day depending on the severity of the disease. The higher doses were reduced relatively rapidly to reach 20 mg every other day before the end of a course lasting 2 years. All patients did well and have not relapsed.

The goal of the alternate-day regimen is to suppress either the immunological process(es) producing the glomerular inflammation, or the inflammation itself to render the disease "inactive". Criteria of inactivity which would insure against relapse are, however, not well defined. Histopathological criteria of activity are helpful but frequent biopsies are not practical or desirable. Observations based on 45 patients in the Cincinnati series [20] suggest that the disease is inactive when hematuria, as measured by dipstick, becomes trace or absent. Hematuria usually disappears after proteinuria ceases or abates. With the alternate-day regimen, disappearance of hematuria, as well as marked improvement in glomerular morphology, has been achieved most rapidly in those with MPGN I with a stormy onset with characteristics of an acute nephritic syndrome. On the other hand, patients presenting with only gross hematuria or with asymptomatic nephrotic syndrome have initially improved but relapsed after rapid dose reduction in the 3rd year of the regimen (patients 44 and 45 from [20]). Relapses are manifested by an episode of gross hematuria (patient 45) or, indicating greater glomerular injury, an increase in proteinuria with return of the nephrotic syndrome (patient 44). Whereas a relapse can be reversed by increasing the dose of prednisone, its cost can be additional renal damage and further growth retardation.

Relapses have occurred with all three types. Experience with MPGN II, although limited, suggests that relapses with this type are more damaging (patient 2 from [74]) and can occur even after prolonged use of the regimen has seemingly produced a lasting remission. For example, a patient with this type who had had several successful pregnancies and had minimal proteinuria was receiving a dose of 20 mg on alternate days 17 years after onset. The regimen was finally discontinued after 19 years and 3 years later she had a relapse manifested by severe nephrotic syndrome.

The previous study [20] suggested that delay in starting the regimen could reduce its effectiveness. If the regimen was started more then 1 year after diagnosis, the intervals required for disappearance of hypoalbuminemia and proteinuria were longer than in those starting the regimen promptly. These differences were, however, not significant and over the period of observation, a significant difference in survival was not apparent [20, 66]. However, the average yearly loss of 3%–4% of glomeruli in the untreated patient [74], combined with continuing loss at the same rate for several years after the regimen is started, as a consequence of undetectable but irreversible injury sustained pretreatment [20, 74], argues for early initiation of the regimen.

Although, in our hands, many patients receiving the alternate-day regimen have done well, a few in whom success was predicted have progressed to end-stage renal disease. A treatment more universally effective and unaccompanied by growth retardation would be welcome.

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