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Childhood membranoproliferative glomerulonephritis type I: Limited steroid therapy

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Childhood membranoproliferative glomerulonephritis type I: Limited steroid therapy. Nineteen patients with biopsy proven membranoproliferative glomerulonephritis type I (MPGN I) and a minimum of three years of follow-up (mean 6.5 ± 0.7 years) have been treated with an uncontrolled regimen of limited corticosteroids. Initial therapy ranged from 20 mg per os (po) every other day to 30 mg/kg/day i.v. for three consecutive days, depending on clinical disease severity. Therapy was then decreased based on each patient's improving clinical status. At diagnosis creatinine clearance (C_{Cr}) was < 80 ml/min/1.73 m^2 in 12 patients and < 50 in 2. All patients had hematuria and proteinuria, with 15 in the nephrotic range. Hypertension, present at diagnosis in 13, developed in five others following institution of prednisone, and was controlled medically. Renal biopsy was repeated after two years of therapy prior to cessation of treatment (mean total treatment duration 38 ± 3 months). Follow-up biopsy revealed decreased glomerular inflammatory activity in 88% of patients. All patients have now been off prednisone for 40 ± 9 months. The mean C_{Cr} is 126 ± 5 ml/min/1.73 m^2. Eight patients have normal urinalyses. These data suggest that early therapy with a limited course of corticosteroids, and control of associated hypertension, may forestall progressive renal insufficiency in children with MPGN type I.

Idiopathic membranoproliferative glomerulonephritis (MPGN) is a primary glomerular disease that is a major cause of renal insufficiency in children and young adults [1–4]. MPGN type I, the most common variety, is characterized morphologically by subendothelial deposits and an intact glomerular basement membrane. The natural history of MPGN is variable, however, most patients have a slowly progressive course such that, irrespective of the type, 50% renal survival ranges from six to nine years [1–6].

The treatment of MPGN I remains controversial. Cytotoxic agents [1, 2, 4, 7–10], antimalarials [4], platelet inhibitors [8, 11, 12], anticoagulants [7–9, 12], nonsteroidal antiinflammatory agents [10, 11, 13], and corticosteroids [1, 14–16] have all been prescribed, alone and in combination. However, analysis of many reports, including several controlled clinical trials, has been confounded by the addition of supplementary medications on a random basis within a given patient population [1, 2, 4, 7, 12, 13], or the inclusion of assorted MPGN types within specific treatment regimens [1–3, 12]. Corticosteroids have appeared to produce some of the most encouraging results [1, 14, 15], although some clinical reports have suggested that unacceptable complications may obviate their use [4, 16]. Recently, Donadio and Offord [17] questioned the value of any of the published treatment regimens in affecting the course of MPGN. Using life-table analysis, the authors concluded that none of the available treatment options favorably affect long-term outcome [17]. However, many of these therapeutic regimens were initiated years after the onset of clinically apparent renal disease; one factor which may affect such analytic scrutiny.

Based on the premise that significant inflammatory injury may occur in the nascent stages of disease, and that corticosteroids may ameliorate the inflammatory process, we designed a therapeutic regimen to provide early institution of prednisone. To mitigate undesirable steroid-induced side effects we limited the duration of therapy. The unique features of this regimen include the initiation and gradual reduction of corticosteroid dosage based on clinical parameters reflective of disease severity in conjunction with aggressive control of associated hypertension. The present communication describes our experience since instituting this approach in 1977 [14].

Methods

Patient population

Nineteen children with biopsy-proven MPGN I, and a minimum of three years of follow-up, were treated by the Pediatric Nephrology Service at the University of Colorado School of Medicine and The Children's Hospital, Denver, between July 1977 and October 1991. All patients had idiopathic disease. None had received prior immunosuppressive therapy.

Treatment regimen

An uncontrolled therapeutic regimen was designed to provide individualized corticosteroid treatment based on pre-established clinical criteria. Methylprednisolone was used for i.v. therapy. Prednisone was administered orally. Following diagnostic renal biopsy, patients were placed in one of four treatment categories based on the severity of their initial clinical presentation (Table 1). Corticosteroid therapy was instituted at 30 mg/kg/day i.v. bolus (maximum 1 g) for three consecutive days in those most severely affected (group IV), at 2 mg/kg/day (maximum 60 mg) as a single oral dose for patients in group III, or as alternate-day therapy for groups I and II. Corticosteroid dosage when then decreased as each patient advanced through the treatment categories based on individual improvement in C_{Cr}, urinary sediment and urinary protein excretion. However,

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Table 1. MPGN I treatment regimen: Disease severity categorized by associated clinical findings

	Group I	Group II	Group III	Group IV
C_{Cr} *ml/min/1.73 m²*	>80	>80	<80	<50
Proteinuria *mg/m²/hr*	<40	>40	>40	±
Corticosteroid therapy	20 mg qod	2 mg/kg/qod[a]	2 mg/kg/day[a]	30 mg/kg/day i.v. × 3 days, then 2 mg/kg/day[a]

[a] Maximum 60 mg per dose

daily corticosteroids generally were not continued for more than eight weeks. In most cases dosage reduction from category II to category I followed a 6 to 12 week tapering schedule, after a patient fulfilled the appropriate clinical criteria. The goal of the regimen was for all patients eventually to receive prednisone at no greater than 20 mg every other day, and to complete at least two years of alternate day corticosteroid therapy. Integral to the regimen, systemic hypertension was aggressively controlled to maintain blood pressure within two standard deviations of the mean for age. Once clinically stable follow-up was every three to six months. The following clinical and laboratory parameters were assessed: blood pressure, height and weight, urinalysis, blood urea nitrogen, serum creatinine, electrolytes, albumin, 24-hour urine for C_{Cr} and protein excretion, C3 and C4, and/or CH50 complement levels. A renal biopsy was repeated in 17 patients after two years of therapy in anticipation of eventual cessation of corticosteroid treatment. The clinical criteria for cessation of prednisone were: (1) a normal C_{Cr}; and (2) an absence of gross hematuria, nephrotic range proteinuria, and active urinary sediment (such as, greater than 20 to 30 RBC/hpf, and the presence of red cell casts). In twelve patients who fulfilled these criteria, prednisone was gradually reduced and discontinued shortly after the follow-up biopsy revealed a complete resolution of glomerular inflammatory activity. Five patients exhibiting biopsy evidence of persistent glomerular inflammation were maintained on alternate-day prednisone until a subsequent biopsy (1 patient), or a significant improvement in the aforementioned clinical parameters (4 patients) suggested a resolution of active glomerular injury. The decision to discontinue prednisone in two patients was based on purely clinical grounds.

Histology

All biopsy specimens were examined using light, immunofluorescent and electron microscopy (EM). A histologic scoring system was designed to assess for active and chronic renal injury. Active disease was determined by scoring for glomerular cellularity, inflammatory activity, and capillary loop patency. Chronic renal injury was evaluated by determining the extent of glomerulosclerosis and interstitial area, largely reflective of interstitial fibrosis. Morphologic scoring was performed in a "blinded" fashion by a single pathologist (P.F.S.) on paraffin embedded 2 to 3 micron thick sections from tissue fixed in Bouin's solution or formalin. Sections were coded and read in random order as follows:

Glomerular cellularity. Glomerular cellularity was estimated from hematoxylin-eosin (H & E) stained sections by scoring each glomerulus on a 0 to 3+ scale. The final cellularity score was expressed as the percentage of the total possible score.

Inflammatory activity. Inflammatory activity also was determined from H & E stained sections by scoring as positive any glomerulus with cellular crescents, overt necrosis, or greater than four neutrophils. The total inflammatory activity was expressed as the percentage of glomeruli with any of these lesions.

Capillary loop patency. Capillary loop patency was estimated from periodic acid Schiff stained sections by scoring each glomerulus on a 0 to 3+ scale: 0 indicated near total compromise of capillary loop patency and 3+ indicated normal loops. The final patency score was expressed as the percentage of the total possible score.

Glomerulosclerosis. Glomerulosclerosis was assessed using Masson trichrome stained sections, and was expressed as the percent of glomeruli with fibrous crescents, segmental fibrosis and adhesion to Bowman's capsule, tuft collapse and massive thickening of Bowman's capsule, or global obsolescence. A mean of 24 ± 3 glomeruli was present on each biopsy specimen for quantitation of glomerular cellularity, inflammatory activity, capillary loop patency, and percent glomerulosclerosis.

Interstitial area. Interstitial area was measured as a percentage of the total tubulointerstitial area by a point count method using Masson trichrome stained sections as follows: An 8-point grid was in the ocular as the 40× field was advanced through the cortex by 1 mm intervals on a mechanical stage. The percent interstitial area was determined by quantitating the percentage of points overlying interstitium. If the grid passed over a glomerulus or artery the field was adjusted for appropriate localization over tubulointerstitial tissue. On each section 52 ± 4 points were counted for calculation of percent interstitial area.

Statistical analysis

Pre- and post-therapy biopsy scores were compared using the Student's paired *t*-test (inflammatory activity, glomerulosclerosis and interstitial area), or the Wilcoxon signed-rank test (glomerular cellularity and capillary loop patency). Biopsy scores of patient cohorts at follow-up were compared using the Student's unpaired *t*-test, or the Mann-Whitney U-test. Clinical differences at follow-up were evaluated by chi-square analysis. Statistical significance was considered at a P value of <0.05. Data are expressed as mean ± standard error (SEM).

Results

Clinical data

Nineteen patients have been followed for 6.5 ± 0.7 years from the time of diagnosis (range 3.2 to 14.3 years). In all cases except one the diagnosis was made and treatment was instituted

Table 2. Clinical and laboratory features of selected patient cohorts

		Initial treatment		Inflammation on F/U biopsy	
	All pts	Alt day	Daily	Absent	Present
"n"	19[a]	7[a]	12[a]	12	5[a]
C_{Cr} at DX *ml/min/1.73 m²*	78 ± 7	108 ± 10	61 ± 5	83 ± 10	62 ± 6
C_{Cr} at F/U *ml/min/1.73 m²*	126 ± 5	125 ± 7	127 ± 7	135 ± 5	107 ± 6
Total Tx months	38 ± 3	43 ± 9	36 ± 2	33 ± 2	51 ± 9
Total months off Tx	40 ± 9	44 ± 22	37 ± 9	54 ± 12	19 ± 5
F/U UA normal	42%	14%	58%	58%	20%
F/U microheme	32%	43%	25%	25%	40%
F/U proteinuria	21%	29%	17%	8%	40%
F/U micro + prot	5%	14%	0	8%	0
F/U low comp	37%	14%	50%	50%	20%

Abbreviations are: F/U microheme, microscopic hematuria with 4 to 10 RBCs/hpf at follow-up; F/U proteinuria, 1 to 2+ proteinuria at follow-up; F/U micro + prot, coexistent microscopic hematuria and proteinuria at follow-up; F/U low comp, persistent low C3, C4, and/or CH50 at follow-up.
[a] Includes patients in whom prednisone therapy was transiently resumed

within one year of clinically apparent disease (mean 5 ± 1 months, range 2 to 18 months). Thus, the total duration of clinically apparent renal disease was 6.9 ± 0.8 years. At diagnosis the mean age was 10.4 ± 0.5 years (range 6.1 to 15.2 years).

The mean C_{Cr} at the time of diagnosis was 78 ± 7 ml/min/1.73 m^2 (Table 2). One patient (5%) began treatment in category I, 6 (32%) in category II, 10 (53%) in category III, and 2 (10%) in category IV. Thus, 12 patients (63%) presented with C_{Cr} of less than 80 ml/min/1.73 m^2, and were initially treated daily. The total daily prednisone dosage in these twelve patients was 1.7 ± 0.1 mg/kg/day. In most cases there was a rapid improvement in C_{Cr} so that 10 patients were changed to alternate-day prednisone (Category II; 0.8 ± 0.05 mg/kg/day) after eight weeks of daily therapy. Patients beginning therapy in groups II to IV had a reduction in prednisone dosage to 20 mg every other day (0.3 ± 0.02 mg/kg/day) over 15 ± 2 months (range 5 to 30 months). At the last follow-up the mean C_{Cr} of all patients was 126 ± 5 ml/min/1.73 m^2.

The mean initial duration of prednisone treatment of all patients was 36 ± 2 months (range 25 to 66 months). Corticosteroids have been completely discontinued in 17 patients for 42 ± 10 months (range 5 to 131 months). Low dose alternate-day prednisone was briefly resumed after therapy had been discontinued for more than 12 months in two patients who initially were treated for 29 and 66 months, respectively. Non-nephrotic proteinuria associated with a C_{Cr} of <80 ml/min/1.73 m^2 recurred in the first, while the second developed a recurrence of nephrotic-range proteinuria. Both patients now have normal renal function and persistent mild proteinuria after 5.1 and 10.1 years of clinically apparent renal disease, respectively. The total treatment duration of all patients was 38 ± 3 months (Table 2).

Hypertension, defined as a systolic or diastolic blood pressure greater than 2 standard deviations above normal for age, was noted in 13 patients (68%) prior to therapy. Five additional patients (26%) developed hypertension following institution of prednisone. Only one patient did not receive antihypertensive medication. Eight patients (42%) required three or more antihypertensive medications (maximum of 5), and 17 (89%) received an angiotensin converting enzyme inhibitor (ACEI) at some point during their clinical course. All patients are now normotensive, although eight (42%) remain on ACEI therapy.

Complications of corticosteroid therapy have been minimal. Five patients developed asymptomatic hypertension that was treated successfully. None developed lenticular cataracts. Growth has been maintained with a mean height percentile prior to therapy of 47 ± 6% and at last follow-up 48 ± 6%.

Histologic data

The diagnostic biopsies revealed findings characteristic of MPGN I (Fig. 1A). There was marked endocapillary hypercellularity, with thickening of peripheral capillary loops and mesangial expansion resulting in reduced capillary loop patency. In most cases neutrophil exudation was evident in some glomeruli. Occasionally there were areas of necrosis or cellular crescents, or both. Glomerulosclerosis and interstitial fibrosis were evident in a few cases. Electron-dense subendothelial deposits were documented by EM on the diagnostic biopsy specimens in all patients.

Biopsy scores indicative of active glomerular disease are shown in Figure 2. In most cases the follow-up biopsies revealed a decrease in glomerular cellularity ($P < 0.01$) and inflammatory activity ($P < 0.01$), and a marked increment in capillary loop patency ($P < 0.01$). There appeared to be a decrease in the typical deposits, with a mesangial proliferative morphologic picture present on follow-up biopsy (Fig. 1B). The glomerulosclerosis scores increased from 5 ± 2% at the time of diagnosis to 23 ± 5% following two years of therapy ($P < 0.01$). The percent interstitial area was unchanged from diagnosis (26 ± 4%) to follow-up (22 ± 2%).

At the time of diagnosis patients fulfilling the clinical criteria for daily therapy (groups III and IV; C_{Cr} < 80 ml/min/1.73 m^2) had glomerular morphology scores that were not statistically different from those fulfilling the clinical criteria for alternate-day medication. However, after two years of therapy patients beginning in the severe clinical categories had significantly greater glomerulosclerosis (30 ± 6%) than those starting in groups I and II (5 ± 4%); these data are depicted in Figure 3

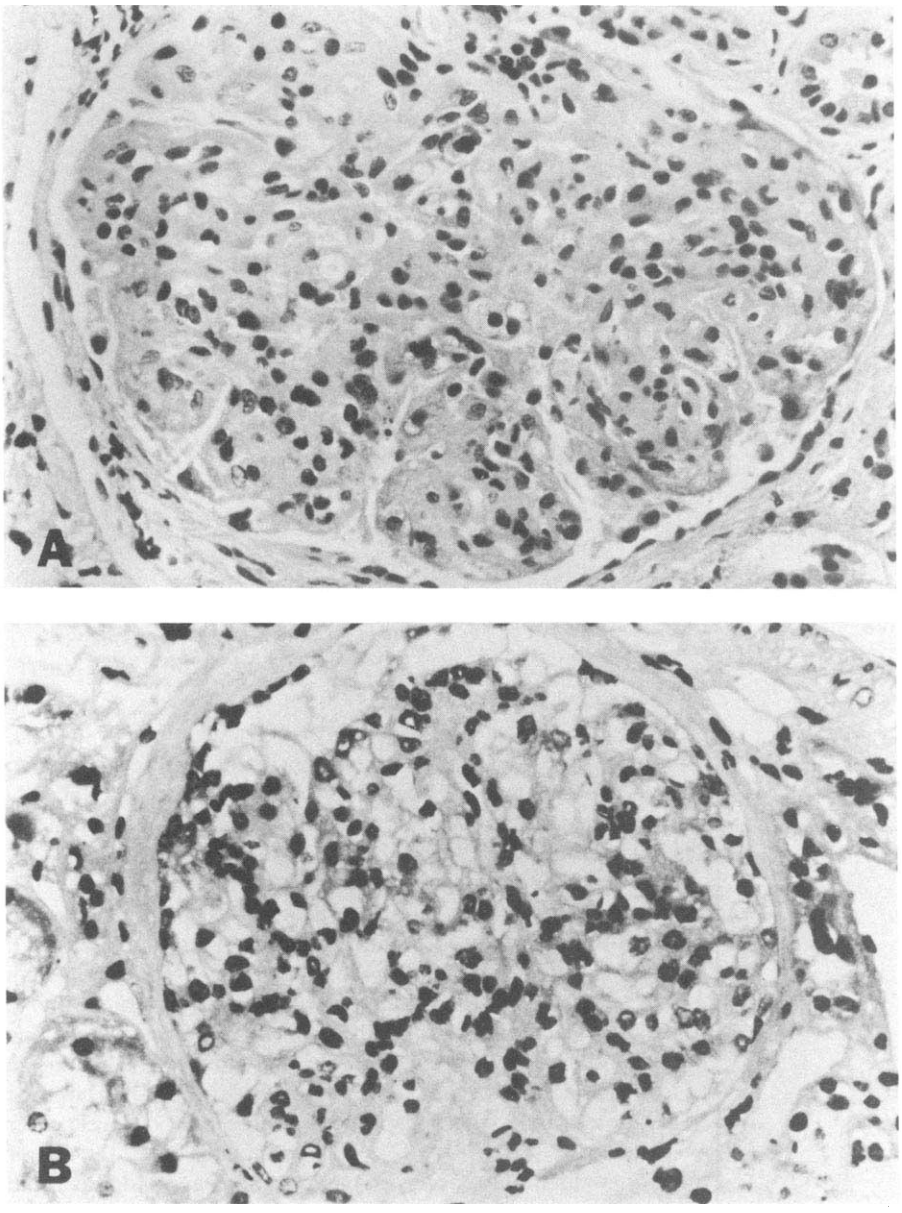

Fig. 1. *Representative photomicrographs of renal biopsy findings at the time of diagnosis* (**A**), *and following two years of prednisone therapy* (**B**).

($P < 0.05$). In spite of these histologic differences, 58% of those fulfilling the initial clinical criteria for daily therapy demonstrated normal urinalyses at follow-up, in contrast to 14% of those begun on alternate-day medication (Table 2). The C_{Cr} of these patient cohorts at follow-up was comparable, as was the percentage of patients from both cohorts that developed hypertension and were treated with ACEIs.

Glomerular inflammatory activity was improved in 15 patients, and completely resolved in 12 (Fig. 2) who were treated with prednisone for 33 ± 2 months. Five patients, including two in whom prednisone therapy was transiently resumed, were treated for a more extended period (51 ± 9 months) for biopsy evidence of persistent inflammatory activity (20 ± 4%). These five patients were noted to have a lower mean C_{Cr} at follow-up than those in whom active inflammation was resolved ($P < 0.02$), but have still maintained normal renal function (Table 2). Those with persistent glomerular inflammation also tended to have more glomerulosclerosis at follow-up (36 ± 11%) than those with a resolution of inflammatory activity (18 ± 5%, $P > 0.05$). Alternate-day therapy was discontinued in these patients after a subsequent biopsy (1 patient) or a significant improvement in clinical parameters (4 patients) suggested a resolution of active glomerular injury.

Because of the relatively small number of patients there was no statistical relationship between persistent hypocomplementemia at follow-up and the presence of hematuria, proteinuria, or continued inflammatory activity on repeat renal biopsy. Nor was there any statistical correlation between the findings on urinalysis at follow-up and the presence of ongoing inflammatory activity. However, in seven of eight patients with normal urinalyses at follow-up, glomerular inflammation was completely resolved.

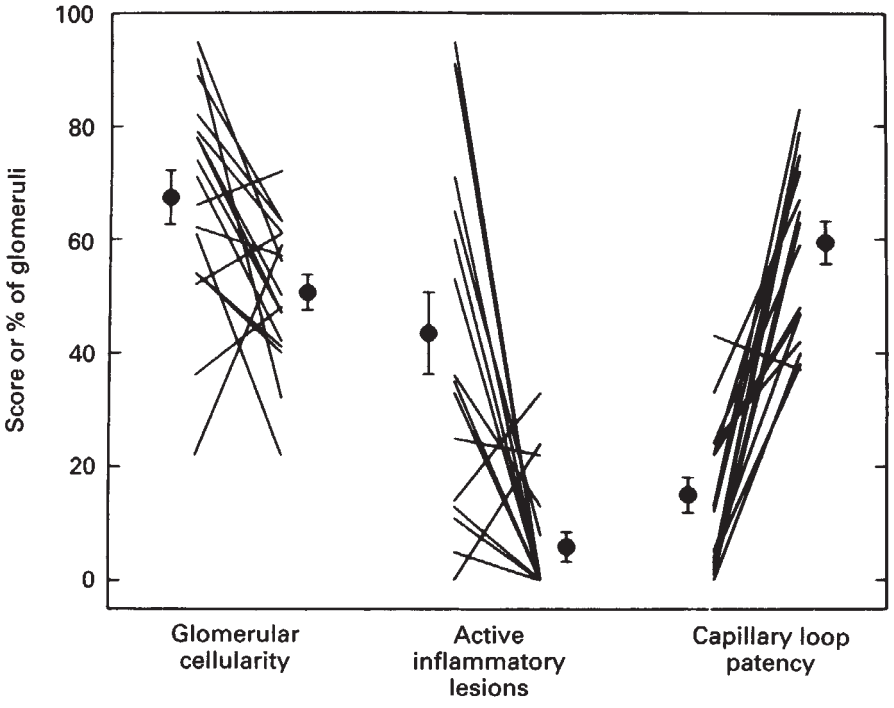

Fig. 2. *Glomerular cellularity, inflammatory activity and capillary loop patency scores of seventeen patients at the time of diagnosis and following two years of prednisone therapy.*

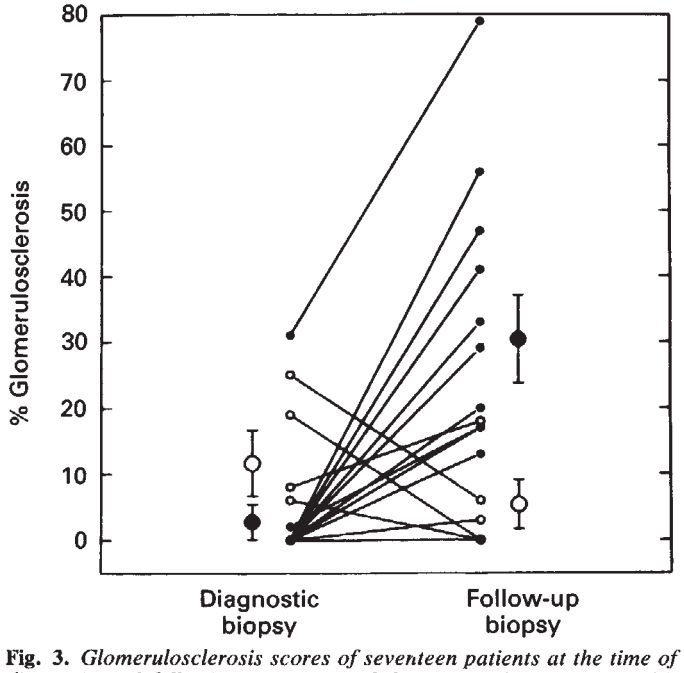

Fig. 3. *Glomerulosclerosis scores of seventeen patients at the time of diagnosis and following two years of therapy.* Patients treated with alternate-day therapy are depicted in the open circles; those initially treated daily are shown in the closed circles.

Discussion

Although membranoproliferative glomerulonephritis was described over 20 years ago by Gotoff et al [18] and West et al [19], independently, optimal therapy remains controversial. Indeed, Donadio and Offord [17], using life-table analysis in a review of published treatment regimens, concluded that none of the presently available treatment options favorably affect outcome. It is noteworthy, however, that the duration of clinically apparent renal disease prior to the initiation of therapy in the clinical trails reviewed [17], was either not stated [16, 20], unavailable [21], or greater than one [7] to three years [11–13]. Ten year survival by life-table analysis ranged from 60% to 85%. In the study of McEnery, McAdams and West [1], patients were separated into those beginning prednisone within one year of presentation and those beginning therapy after a mean of 42 months. Those beginning prednisone within one year fared much better. Of nine patients with MPGN I in the less-than-one year group, none progressed to ESRD, in contrast to three of nine who began therapy more than one year after presentation [1]. West [22] has speculated that the major inflammatory injury occurs in the nascent stages of disease, and that subsequent damage may be due to alterations in glomerular hemodynamics. Our experience employing a limited course of corticosteroids combined with vigorous blood pressure control is consistent with this view.

Other studies also have suggested that corticosteroids may benefit children with MPGN I. Life-table analysis of the initial International Study of Kidney Disease in Children (ISKDC) experience [16], using a 50% decrement in glomerular filtration rate as the sole end-point, found a five-year success rate of 57% in the control group, compared to 95% in those treated with alternate-day steroids. Although severe hypertension was thought to nullify any salutary effect of therapy [16], a report from the ISKDC in 1987 [23] again suggested a beneficial effect of prednisone. Furthermore, while concerns have been expressed regarding an increase in hypertension with the usage of corticosteroids in MPGN [4, 16], all patients in the present report were successfully managed with antihypertensive medication. It is reasonable to conjecture that the control of hypertension may have contributed to the observed outcome, as

others have suggested that hypertension portends a worse prognosis [1, 6]. Whether treatment with ACEIs is of special significance, due to their glomerular hemodynamic effects, is also speculative [24]. An additional small controlled clinical trial from Mexico has suggested that children with MPGN I respond favorably to corticosteroids [15]. Four of 10 patients treated with placebo developed ESRD over a mean of 6.5 years, in contrast to none of eight treated with prednisone. Finally, although there may be differences between the pediatric and adult disease [2], it is interesting to note that a cohort of adult patients in a report by Narita and Koyama [21] fared best when treated with a combination of prednisone and cyclophosphamide.

The treatment of patients in the present report was not controlled by prospective random design. However, all patients except one began corticosteroid treatment within one year of clinical presentation (mean 5 months) with the level of therapy adjusted according to the patients' severity of illness. Twelve of 19 had an initial C_{Cr} of less than 80 ml/min/1.73 m^2 and two, less than 50. Fifteen patients were nephrotic and all but one were hypertensive. At present the mean C_{Cr} of all 19 patients is 126 $\pm$ 5 ml/min/1.73 m^2 following a limited course of prednisone, averaging 38 $\pm$ 3 months in length. Forty-two percent of patients have normal urinalyses, and none are nephrotic after 6.9 $\pm$ 0.8 years of clinically apparent renal disease.

At the time of diagnosis patients with the greatest reduction in renal function (groups III and IV) had histologic scores that were not statistically different from those with clinically milder disease (groups I and II). Conversely, after two years of therapy those with greater clinical severity had more glomerulosclerosis than those presenting with less severe disease (Fig. 3). The initial degree of clinical disease severity may, therefore, more accurately reflect the extent of primary renal injury than any subtle differences in histology. The observation that proteinuria was decreased at follow-up in those initially treated daily (Table 2), compared to those treated with alternate-day medication, suggests a role for more vigorous corticosteroid therapy in the severe clinical groups, despite the increment in glomerulosclerosis of this patient cohort at follow-up. It could be argued that treatment with daily steroids may have increased the severity of glomerulosclerosis (Fig. 3); however, this seems unlikely in view of the generally favorable clinical outcome. Whether daily prednisone therapy would have resulted in less proteinuria at follow-up if employed at outset in the milder treatment categories is unknown.

The histologic indicators of active glomerular disease (glomerular cellularity, inflammatory activity and capillary loop patency) were improved in the majority of patients. In contrast, the percent glomerulosclerosis was increased, and the interstitial area was unchanged. However, since none of our patients has demonstrated a progressive loss of renal function, no histologic parameter can be assessed as an indicator of clinical prognosis. In light of these histologic findings, ongoing inflammatory injury does not appear to be a significant factor in most patients after several years of disease. Indeed, the initial disease activity may have been attenuated by the early use of corticosteroids.

Neither persistent hypocomplementemia nor abnormal urinalysis at follow-up correlated statistically with renal functional or histologic outcome. However, seven of eight patients with normal urinalyses at follow-up had a complete resolution of glomerular inflammatory activity on follow-up biopsy. Thus, a repeat renal biopsy may be unnecessary in the presence of a normal or mild urinary sediment at two to three years of follow-up when associated with normal renal function and normal blood pressure.

Donadio and Offord have stressed the need for well designed, appropriately controlled, randomized clinical trials to evaluate the efficacy of therapies in MPGN and other chronic diseases [17]. However, many published clinical trials have had significant limitations. For example, the controlled clinical trials of Cattran et al [7], Zimmerman et al [12] and Tiller et al [20] all allowed other forms of therapy up to six months preceding the study protocols despite a duration of clinically apparent renal disease of one [7] to three years [12]. Because MPGN I is a chronic disease with progression over many years it does not seem appropriate to include patients who may have been treated with any of a variety of medications [1–16] prior to entering a controlled clinical trial. Furthermore, the alternate-day prednisone therapy described by McEnery et al [1], West [22] and others included patients who were treated with various immunosuppressives, while Lagrue's description of nonsteroidal antiinflammatory therapy in 53 patients with MPGN states that 14 (26%) were pre-treated with immunosuppressive medications [13]. In the present report all patients were treated with corticosteroids and antihypertensive medication, with the level of steroid therapy adjusted according to the patients' initial degree of renal functional impairment. In view of the chronicity of MPGN, future controlled clinical trials should exclude patients who have been treated with any medication that may confound data analysis.

In summary, 19 children with biopsy proven MPGN I and 6.9 $\pm$ 0.8 years of clinically apparent renal disease have maintained normal renal function following a limited course of prednisone. Hypertension was readily managed, and did not preclude ongoing therapy. The data suggest that prednisone, administered early in the disease process, may attenuate progressive inflammatory injury in children with MPGN type I. It is important to note, however, that the control of associated hypertension, particularly with ACEIs, may contribute to the preservation of renal function by improving glomerular hemodynamics [1, 6, 22, 24]. These and other [1, 14–16, 22, 23] preliminary data emphasize the need for a well designed prospective randomized placebo controlled clinical trial to confirm whether early steroid therapy is, indeed, useful in MPGN type I. A multicenter collaborative endeavor will likely be necessary to answer this question definitively.

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Appendix. Abbreviations

MPGN - Membranoproliferative glomerulonephritis

ACEI - Angiotensin converting enzyme inhibitor
ESRD - End-stage renal disease
H & E - Hematoxylin-eosin
EM - Electron microscopy
C_{Cr} - Creatinine clearance
po - Per os
i.v. - Intravenous
ISKDC - International Study of Kidney Disease in Children

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