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Results of a controlled drug trial in membranoproliferative glomerulonephritis

DANIEL C. CATTRAN, CARL J. CARDELLA, JANET M. ROSCOE, RICHARD C. CHARRON, PHILLIP C. RANCE, SUSAN M. RITCHIE, and PAUL N. COREY

Departments of Medicine and Preventive Medicine and Biostatistics, University of Toronto, and The Toronto Glomerulonephritis Study Group, Toronto, Ontario, Canada

Results of a controlled drug trial in membranoproliferative glomerulonephritis. A prospective randomized drug trial was carried out on 59 patients with confirmed membranoproliferative glomerulonephritis (MPGN). The treatment group (27 patients) received cyclophosphamide, coumadin, and dipyridamole for 18 months, and the control group (32 patients) received no specific therapy. Complications of the renal disease such as hypertension and fluid retention were treated similarly in both groups. Entrance criteria included confirmed renal pathology demonstrating either types I or II MPGN, a corrected creatinine clearance (C_{Cr}) of less than 80 ml/min/1.73 m^2, and/or proteinuria greater than 2 g/day. Actuarial survival was not different between the treatment and the control groups in either MPGN type and was 85% in type I and 90% in type II at 2 years. The change in renal function, as measured by both the slope of C_{Cr} and the plasma creatinine reciprocal (1/Cr) at 6, 12, and 18 months was not significantly different between treatment and control groups in either types I or II when tested by both parametric and nonparametric analysis. The age, sex, and initial level of C_{Cr} did not influence the rate of decline. Control and treatment group proteinuria was not different at any time point in either types I or II MPGN. The small numbers of type II MPGN cases do not give sufficient power to allow conclusions regarding this therapy in type II. We can conclude that this treatment is ineffective in altering the natural history of type I MPGN.

Résultats d'un essai médicamenteux contrôlé dans la glomérulonéphrite membrano-proliférative. Un essai médicamenteux prospectif randomisé a été entrepris chez 59 malades atteints de glomérulonéphrite membrano-proliférative confirmée (MPGN). Le groupe traité (27 malades) a recu de la cyclophosphamide, de la coumadine et du dipyridamole pendant 18 mois, et le groupe contrôle (32 malades) n'a pas recu de traitement spécifique. Les complications de la néphropathie telles que l'hypertension et al rétention liquidinne ont été traitées de facon identique dans les deux groupes. Les critères d'inclusion comprenaient une histologiérénale confirmée démontrant une MPGN de type I ou de type II, une clearance de la créatinine corrigée (C_{Cr}) de moins de 80 ml/min/1,73 m^2 et/ou une protéinurie de plus de 2 g/jour. La survie actuarielle ne différait pas entre les groupes traité et contrôle dans aucun des types de MPGN, et était de 85% dans le type I et de 90% dans le type II à 2 ans. La modification de la fonction rénale, mesurée à la fois par la pente de C_{Cr} et par l'inverse de la créatininémie (1/Cr) à 6, 12, et 18 mois n'était pas significativement différente entre les groupes traité et contrôle, dans les types I ou II, paranalyse paramétrique et non paramétrique. L'âge, le sexe, et le niveau initial de la C_{Cr} n'influencaient pas la vitesse du déclin. La protéinurie des groupes contrôleet traîté ne différait pas à aucun moment dans les MPGN de types I ou II. Le petit nombre de cas de MPGN de type II ne donnait pas une puissance suffisante pour permettre des conclusions en ce qui concerne ce traitement dans le type II. Nous pouvons conclure que ce traitement est incapable d'altérer l'histoire naturelle de la MPGN de type I.

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Glomerulonephritis remains the commonest recognized cause of endstage renal disease in both adults [1, 2] and children [3]; membranoproliferative glomerulonephritis (MPGN) is the type most frequently documented that results in terminal renal failure [4]. The natural history and clinical pathological correlations in MPGN have been known for several years and have been recently reviewed [5–7]. Because pathological classification has changed, we now classify MPGN into types I and II [8–12]. Habib et al [13, 14] showed a 50% statistical mortality between 9 and 10 years in types I and II when all patients with crescents were excluded. Kincaid-Smith [15] and other investigators [13, 14, 16] subsequently demonstrated a much worse prognosis with only a 30% 3-year survival once the patients had significant proteinuria or a reduced creatinine clearance. Other features which may indicate a worse prognosis include the early age of onset of the disease, acute nephritic presentation, hypertension, and the presence of crescents on renal biopsy. Microscopic and/or macroscopic hematuria do not seem relevant to prognosis [11–16]. The complement component, C3, may be depressed in both types of MPGN, but the literature varies whether or not its level has any prognostic value [13, 14, 17–21].

The effects of various forms of therapy, including indomethacin [22], prednisone [23–25], and indomethacin combined with cyclophosphamide [26], on the outcome of this type of glomerulonephritis have been variable and difficult to interpret because of the absence of suitable control subjects and the small number of patients in the published papers. Recently, Donadio and Holley [6] and Donadio et al [27] suggested that a combination of aspirin and dipyridamole may be effective. The most dramatic published results were by Kincaid-Smith [28] who demonstrated a very significant improvement in kidney survival in a small uncontrolled trial in severely affected patients treated with a combination of cyclophosphamide, coumadin, and dipyridamole. Since 1975, the Metropolitan Toronto Glomerulonephritis Registry [29] has been conducting a randomized prospective drug trial to compare the effects of this drug

combination versus no specific therapy in a similarly affected group of patients with types I or II MPGN.

Methods

Trial entrance criteria included a renal biopsy specimen with a minimum of eight different glomeruli demonstrable, taken within 12 months of trial entry and of sufficient size to allow examination by light, immunofluorescent, and electron microscopy. Although a single nephropathologist's diagnosis of MPGN was sufficient to include the patient, quarterly meetings of all involved pathologists reviewed the material to confirm the initial impression. Previously established criteria were used to classify this tissue into types I or II [7, 9, 12, 13]. All patients with crescents were excluded. All patients entered also had to demonstrate proteinuria greater than 2 g/day and/or a corrected endogenous creatinine clearance (C_{Cr}) of less than 80 ml/min. Secondary causes of MPGN were ruled out and only idiopathic cases were entered.

Other exclusion criteria included active infection, previous tuberculosis, a history of radiological evidence of peptic ulcer disease, and uncontrolled hypertension (diastolic greater than 110 mm Hg despite therapy). The study was approved by the University of Toronto Human Ethics Committee, and all patients were entered only after an informed consent was signed. No specific immunosuppressive drug, steroids, antiplatelet agents, or anticoagulants were allowed within 6 months of trial entry.

The physicians called the Glomerulonephritis Registry [29] after the patient consented to the trial. The registrars then stratified the patients into types I or II MPGN and assigned the patients to either the treatment (T) or control (C) groups. The clinical and laboratory followup was a minimum of once per month for 6 months and every 2 months for the subsequent 12 months.

Cyclophosphamide dosage was 1.5 to 2.0 mg/kg. If the absolute white cell count fell below 3,000 cu/ml, the dose was reduced.

Dipyridamole was started at 25 mg q.i.d. and increased by 100 mg/24 hr weekly, until the full dose of 100 mg q.i.d. was reached.

Coumadin was given as a single daily dose and adjusted to maintain the one step prothrombin 2 to 2.5 times the control value.

Blood pressure and edema were controlled by diuretics and/or antihypertensive agent(s) of the physician's choice, but the diastolic pressure was to be maintained at less than 100 mm Hg in the sitting position.

A standard history and physical examination were recorded at each visit [29]. Routine laboratory tests included endogenous creatinine clearance (corrected for surface area), 24-hr proteinuria, plasma creatinine, electrolytes and uric acid, blood urea nitrogen, hemoglobin, hematocrit, white cell count and differential, platelet count, and complete urinalysis.

The trial was for 18 months unless one of the following stop points was reached:

(1) Cerebral hemorrhage; *(2)* significant gastrointestinal hemorrhage, that is, any overt melena or hematemesis or covert bleeding as demonstrated by unexplained hemoglobin decrease greater than 2 g/dl; *(3)* recurrent bleeding into the urinary tract, skin, or muscle with a fall in hemoglobin greater than 2 g/dl (When a single acute episode of bleeding occurred, the anticoagulants and antiplatelet agents were to be discontinued but the trial could be re-instituted if no active bleeding point was determined and the source was either gastrointestinal or genitourinary.); *(4)* sustained diastolic pressure greater than 110 mm Hg despite vigorous antihypertensive therapy; *(5)* a leukocyte count less than 3,000/ml^3 repeated, platelet count less than 60,000/ml^3, bilirubin greater than 1.5 mg/dl, or persistent nausea.

Cyclophosphamide was temporarily discontinued if any of these parameters were reached and then restarted at 50% of the previous dose and adjusted according to the symptoms and/or laboratory values. If any or all of the symptoms reoccurred at this lower dose, the trial was discontinued.

(6) Progression of the renal disease: If the plasma creatinine increased by more than 5 mg/dl from the initial value or reached a value more than 10 mg/dl (corrected C_{Cr} less than 10 ml/min), the trial was to be discontinued. *(7)* During any acute systemic illness, the physician could decrease or discontinue any or all medications. The therapy was to be reinstituted once the acute infection cleared.

Statistical analysis

Data were collected on a standardized form [29]. The data management and statistical analysis were carried out using the statistical analysis system (SAS) [30]. Each patient had a slope calculated using the information derived from the endogenous C_{Cr} and the time interval between each visit at 6, 12, and 18 months after trial entry. Another set of slopes was derived applying the same method but using the reciprocal of the plasma creatinine against time. The 24-hr protein excretions were assessed on each patient at 6, 12, and 18 months. Analyses were made on the total treatment and control group and again after separation into types I and II treatment and control.

Analysis of variance was used to compare the response variables, C_{Cr} and 1/Cr, between the treatment and control groups, adjusting for disease type and sex. Analysis of covariance allowed adjustments for age, severity of initial proteinuria, and initial C_{Cr} level. Treatment and control groups were compared both with the Student's t test and the more robust Mann-Whitney test. For all analyses, two-tailed P values are reported.

Results

Seventy-five patients were clinically assessed, although only 64 were deemed pathologically and clinically acceptable, and were willing to participate in the study. Three patients were excluded from subsequent analysis because of drug intolerance within 3 weeks of trial entry. Two other patients were excluded because they reached a C_{Cr} of less than 10 ml/min within 1 month of trial entry (one patient in the control group and one patient in the treatment group). All reported analyses were done on the remaining 59 patients, 27 T and 32 C. In the type I group, there were 23 males (15 C, 8 T), 24 females (10 C, 14 T), and in the type II group there were 7 males (4 C, 3 T) and 5 females (3 C, 2 T). The incidence of hypertension at presentation was similar in both groups, 41% T and 48% C. Patient clinical and laboratory profiles at trial entry in the T and C groups are outlined in Table 1. The mean slopes of the corrected creatinine clearance in the C and T group in types I and II at 6, 12, and 18

Table 1. Patient profile at trial entry

	Group			
	Control (N = 25)		Treatment (N = 22)	
	Mean	Range	Mean	Range
MPGN type I				
Earliest known renal abnormality, *years*	33	(4.5 to 70)	37.5	(11 to 77)
Age at trial entry, *years*	34	(6 to 70)	38	(12 to 77)
Initial creatinine clearance, *ml/min/1.73 m²*	64	(18 to 135)	65	(16 to 113)
Initial plasma creatinine, *mg/dl*	1.8	(0.7 to 7.0)	1.7	(0.7 to 5.9)
Proteinuria, *gm/day*	5.2	(0.85 to 16.4)	3.6	(0.4 to 8.3)
MPGN type II	(N = 7)		(N = 5)	
Earliest known renal abnormality, *years*	16.5	(4 to 57)	17.5	(6 to 26)
Age at trial entry, *years*	19	(7 to 58)	19.7	(6 to 28)
Initial creatinine clearance, *ml/min/1.73 m²*	87	(51 to 131)	63	(37 to 115)
Initial plasma creatinine, *mg/dl*	0.9	(0.3 to 1.2)	1.2	(0.7 to 2.1)
Proteinuria, *g/day*	4.3	(0.1 to 11.7)	6.8	(1.7 to 12.8)

Table 2. Change in corrected creatinine clearance, ml/min/year[a]

		Months		
MPGN type	Group	6	12	18
I	Control	9.5	−4	−8
	Treatment	−5	−6	0
		P = 0.5	= 0.9	= 0.4
II	Control	−31	17	−1
	Treatment	−31	−18	−14
		P = 0.9	= 0.3	= 0.5

[a] The values at 6, 12, and 18 months represent the mean change in C_{Cr} in each group and type studied. The P values reported are the standard two-tailed t tests based on means, but tests were also performed using the Mann-Whitney test (Wilcoxan two-sample test) with again no statistical difference seen between the control and treatment groups in either types I or II MPGN.

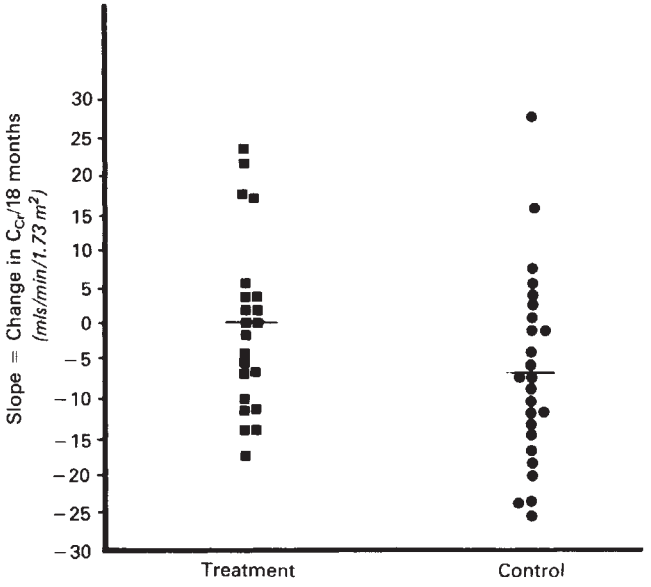

Fig. 1. *The slope* (points) *or change from "0" in creatinine clearance (C_{Cr}) during the 18-month study in the type I MPGN patients.* The start of the slope was the initial C_{Cr} in each patient. In the treatment group, the mean change in C_{Cr} at 18 months was 0 ml/min/1.73 m² while in the control group the mean change in C_{Cr} was −9 ml/min/1.73 m². This was of no statistical significance ($P > 0.4$).

months are illustrated in Table 2. There was no statistical difference by either Student's t test or Mann-Whitney between the C and T group in either types I or II MPGN. The slope or change from the initial C_{Cr} as defined by "zero" to the final C_{Cr} at 18 months is depicted for each individual patient in the T and C groups for types I and II in Figures 1 and 2. Analysis of the slopes created from the reciprocal of the plasma creatinine versus time also showed no statistical difference between groups in either type of MPGN. Mean daily proteinuria at 6, 12, and 18 months is outlined in Table 3. Statistical analysis showed no difference between the groups in either types I or II by Student's t test or by Mann-Whitney. Analysis of covariance was then used to compare the mean difference in these two variables, that is, C_{Cr}, and the reciprocal of plasma creatinine in the types I and II treatment and control groups. This analysis adjusted for differences between the two groups in terms of age at trial entry, sex, initial creatinine clearance, and initial proteinuria. None of these factors proved to be of independent significance in either types I or II nor were they responsible for the lack of difference found between the treatment and control groups. Variations in the slopes of creatinine clearance over the 18-month period in each patient related to both age and to initial creatinine clearance in both types of MPGN is graphically illustrated in Figures 3 and 4.

All patients, once included in the treatment group, were assumed to remain on the medications until the final analysis (Table 2). Six patients did not complete the full 18 months of triple therapy, mostly because of drug complications. A list of major and minor drug-related problems is given in Table 4.

The statistical analysis was repeated on those patients who completed the full 18 months of treatment (type I, 17 patients; type II, 4 patients). The mean slope of the C_{Cr} at 18 months in this treatment group, type I, was −3 ml/min/year versus control −8 ml/min/year (Mann-Whitney $P > 0.7$) and treatment group, type II −16 ml/min/year versus control −1 ml/min/year (Mann-Whitney $P > 0.3$).

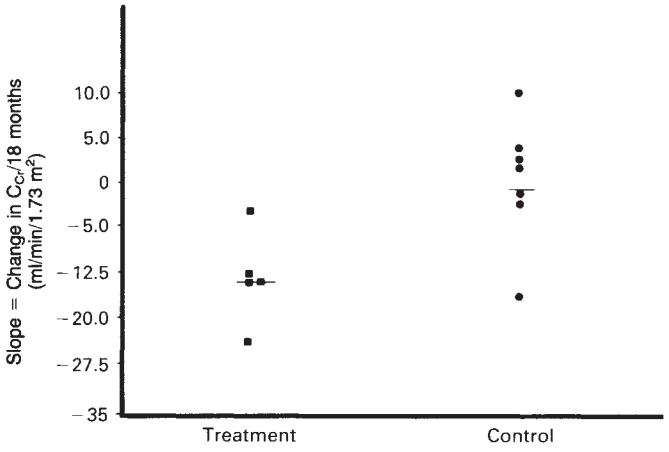

Fig. 2. *The slope* (points) *or change from "0" in creatinine clearance (C_{Cr}) during the 18-month study in the type II MPGN patients.* The start of the slope was the initial C_{Cr} in each patient. The mean change in C_{Cr} was −14 ml/min/1.73 m² in the treatment group versus a change of +1 ml/min/1.73 m² in the control group. This was of no statistical significance (P 0.5).

Table 3. Proteinuria, g/24 hr[a]

MPGN type	Group	Number of months		
		6	12	18
I	Control	4.9	4.8	4.2
	Treatment	4.4	4.2	3.5
		P = 0.6	= 0.2	= 0.6
II	Control	3.9	2.7	2.6
	Treatment	7.69	6.8	6.9
		P = 0.5	= 0.4	= 0.5

[a] The numbers refer to the mean 24-hr proteinuria in grams at the end of the time intervals. The P values reported are the t tests but repeat on medians (Mann-Whitney) showed no significant difference at any time between treatment and control group in either type.

Discussion

MPGN remains the most common type of glomerulonephritis documented to progress to endstage renal disease in adults [4]. Donadio and Holley [6], in a controlled trial, compared a placebo to ASA combined with dipyridamole in idiopathic MPGN patients and did show a treatment benefit. This benefit was statistically marginal in preservation of glomerular filtration rate (GFR, $P \sim 0.04$) and showed no effect on proteinuria. Zimmerman et al [31] recently reported a beneficial effect of combined Warfarin and dipyridamole in patients with type I MPGN. In their study, although a statistical benefit was seen in the unpaired data relative to the reciprocal of the serum creatinine ($P < 0.025$), the original trial design was a crossover study; in the paired data analysis differences between the T and C groups were not significant. Proteinuria was not altered by treatment in their study by either paired or unpaired analysis. The complication rate in that study was high with significant hemorrhagic problems occurring in 37% of the treated patients including one death due to intracerebral hemorrhage during therapy. McEnery, McAdams, and West [24] and McEnery,

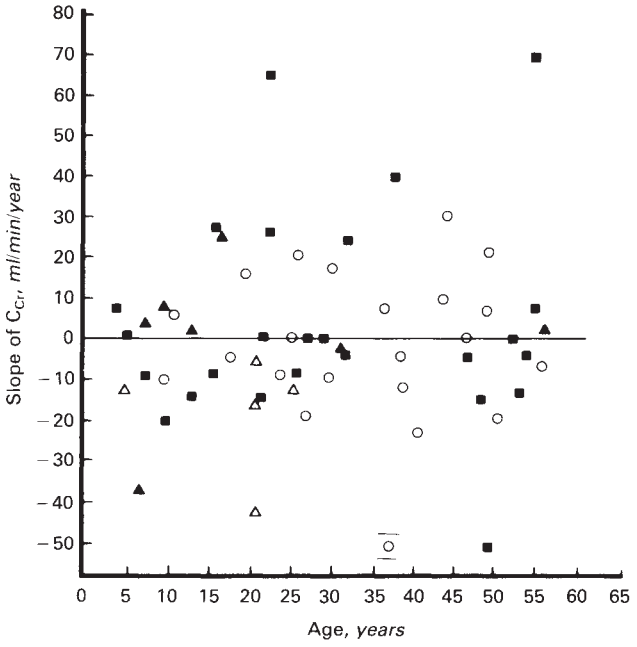

Fig. 3. *The lack of effect of age on the rate of change in renal function as defined by the slope of the creatinine clearance C_{Cr} in all study patients.* Symbols are: type I MPGN: ■ control, ○ drug; type II MPGN: ▲ control, △ drug.

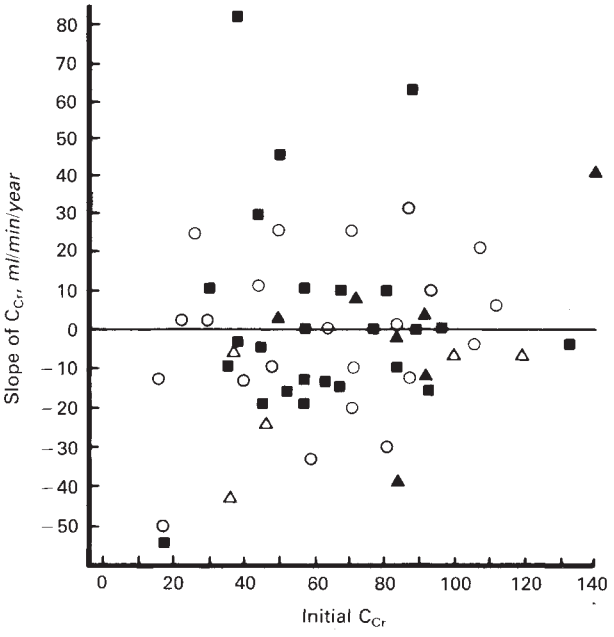

Fig. 4. *The initial level of creatinine clearance (C_{Cr}) does not effect the rate of change of renal function as defined by the slope of the C_{Cr}.* Symbols are: type I MPGN: ■ control, ○ drug; type II MPGN: ▲ control, △ drug.

West, and McAdams [32] demonstrated an improvement in survival using longterm alternate day steroids, but the trial had no control group, many patients were excluded from the analysis, some patients received more therapy than prednisone alone, and the study was restricted to children. A recent report disputes their results and suggests that when substantial side

Table 4. Drug complications

Major[a]			Minor[c]	
Type	Number	Time[b] *months*	Type	Number
Leukopenia	2	12, 13	Infection	2
Alopecia	1	9	Hypotension	3
Leukopenia, hematuria	1	16	Nausea	5
Recurrent hemoptysis	1	15	Macroscopic hematuria	1
Voluntary withdrawal	1	12		

[a] The trial was discontinued.
[b] The time after trial entry is represented.
[c] Temporary reduction in drug therapy was made.

effects are considered steroids do not alter the overall prognosis [25]. Kincaid-Smith's [28] study showed that coumadin, dipyridamole, and cyclophosphamide dramatically influenced renal survival in patients with MPGN. Her study had several problems in interpretation including no concurrent controls and variations relative to hypertension and/or fluid retention management. However, because of her dramatic results, we were encouraged to examine the same medication in a prospective, controlled trial. Kincaid-Smith [28] and McEnery, McAdams, and West [24] both noted patients on their drug regimens who responded dramatically within the first year of treatment. Our results indicate this type of improvement can happen spontaneously (Figs. 1 and 2). Two type I and one type II C patients had dramatic improvement with a positive slope of greater than 12 ml/min/year. We also observed the reverse with acute nephritis apparently superimposed on biopsy-proven chronic MPGN (8 C, 4 T). This resulted in a rapid decline of previously stable renal function. We observed an equal number of remissions from this acute deterioration in the C group (4) as "responses" in the T group (3) and conclude that even an acute change in a previously stable MPGN patient does not necessarily indicate irreversible renal failure.

Spontaneous resolution of proteinuria can occur [13]. Fifteen patients in our study achieved a level of proteinuria less than 300 mg/24 hr on at least one occasion (8 C, 7 T). In only eight was the remission prolonged (5 C, 3 T). This type of spontaneous change can strongly influence the interpretation of studies where there are no or only historically control patients. Many factors have been suggested as guides to prognosis. Cameron et al [7] recently emphasized that patients with nephrotic range proteinuria at the beginning or at some time within their illness indicates a bad prognosis. Although we did not look at this specifically, we did include degree of initial proteinuria along with age, sex, and initial C_{Cr} in our analysis to adjust for the potential bias that differences in these factors between the treatment and control group might have on the results. The lack of significant difference in the mean slopes between the T and C groups was not altered by these factors nor did they have any independent prognostic significance.

In 1975, when the study was started, precise numbers required to avoid a beta error were not assessed. The 12 type II patients entered were followed the entire 18 months. Their complications were no greater than type I. The case accumulation rate was much slower than type I, and this low number does not allow us sufficient power to conclude anything regarding the lack of effect of therapy on this type of MPGN. However, using a standard formula for sample size [33], the present study would allow an 80% chance at the conventional 5% level of detecting a 25% difference in the mean slope of C_{Cr} between the treatment and control groups in type I MPGN. We felt that this difference was in the appropriate range considering the potential risks of the drugs. Our results would indicate that there is no significant benefit to this therapy on GFR or proteinuria in type I. The prognosis in both types, however, does not appear to be as bad as suggested by other authors [7, 13–15, 23, 28]. Our actuarial survival curves, using as an endpoint a C_{Cr} less than 10 ml/min, showed a type I survival of 85% at 2 years and 68% at 5 years and a type II survival of 90% at 2 years and 70% at 5 years.

Side effects of the medication were considerable, resulting in 22% of our treatment group unable to complete the study. Many other patients had complications of a minor nature manageable by a reduction in dosage (Table 4). Although these complications resulted in no mortality and no significant longterm morbidity, others [31] using a similar combination have recorded a higher incidence of serious hemorrhagic problems.

This drug trial suggests that any MPGN study must consider our observed variations in the natural history before conclusions regarding prognostic indicators and/or effects of medications can be reached. Certainly, we can conclude that this therapeutic regimen is not applicable to the average patient with type I MPGN since, in this controlled study, no significant benefit could be observed over a period of 18 months.

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Reprint requests to Dr. D. C. Cattran, Tri-Hospital Nephrology Service, Mount Sinai, Toronto General and Women's College Hospital, 101 College Street, CW 3-217, Toronto, Ontario, M5G 9Z9 Canada

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