Eight and 12 week courses of cyclophosphamide in nephrotic syndrome

SIR,—We read with great interest the report on cyclophosphamide treatment of steroid dependent nephrotic syndrome recently published in this journal by Ueda *et al.*¹ Surprisingly the authors could not find any difference in the number of patients who remained in sustained remission after treatment with cyclophosphamide for either eight or 12 weeks, contrary to our previous finding.² We would like to comment on the conclusions of this study, as we find considerable differences in the treatment procedures used in their study and ours, in addition to the age differences in patients described by the authors.

Most notable is the difference in the initial treatment of nephrosis. All of our patients were treated initially according to the standard treatment protocol of the Arbeitsgemeinschaft für Pädiatrische Nephrologie (APN), that is, 60 mg/m²/day continuously for four weeks, followed by treatment on alternate days with 40 mg/m²/48 hours prednisone. In contrast, the duration of the initial treatment of patients in the study by Ueda *et al* was significantly longer, that is, four weeks of continuous steroid administration, followed by three to four months' treatment with tapered down prednisone dose (reduction of 5 to 10 mg/m² every two weeks). Thus the total amount of prednisone in the initial treatment was 2240 mg/m² in the APN study, but about 4620 mg/m² in the study of Ueda *et al*. It has been shown recently that the intensity of the initial treatment is a critical factor in the outcome and prognosis of steroid sensitive nephrotic syndrome—that is, the longer and more intensive the initial treatment is, the lower the number of patients who relapse, and the number of relapses and frequent relapsers.³ We therefore would assume that the patients of Ueda and his colleagues represent a highly selective group, who suffer from a more severe nephrotic syndrome than the patients treated by the APN protocol, and where steroid dependency could not be prevented by any intense initial treatment. Otherwise it could not be explained why the cumulative percentage of sustained remission rates after eight or 12 weeks' cyclophosphamide were only 24% or 25%, respectively, which is lower than all other published results of cytotoxic drug treatment for steroid dependent nephrotic syndrome.⁴⁻⁹ We therefore strongly suggest that the differences in the results of the two studies are due to the selection of patients who were treated with cyclophosphamide. The longer duration of the trial (five years Ueda *et al* v 2 years in the APN study) and the higher number of patients in the study by Ueda *et al* seem to play only a minor part in these results (see table) as all but one of the patients of

Ueda *et al* relapsed within two years after treatment with cyclophosphamide. Therefore our study was sufficient to judge the effectiveness of cyclophosphamide treatment, which was later confirmed in a five year evaluation of APN study groups.¹⁰

In summary, we cannot agree with the general conclusion of Ueda *et al* that the effect of an eight week course of cyclophosphamide appears to be the same as that of a 12 week course in children with steroid dependent minimal change nephrotic syndrome. This is probably only true for such groups of patients who were as intensively treated initially as in the study of Ueda *et al*. For those who were treated less intensively, by the International Study of Kidney Diseases in Children (ISKDC) and APN, our conclusion can be maintained that cyclophosphamide should be used for eight weeks in patients who relapse frequently and are not steroid dependent and for 12 weeks in patients who relapse frequently but are steroid dependent.

B OEMAR
J BRODEHL
Arbeitsgemeinschaft für Pädiatrische Nephrologie,
Department of Pediatric Nephrology
and Metabolic Disease,
Medical School Hannover,
D-3000 Hannover 61,
Federal Republic of Germany

1 Ueda N, Kuno K, Ito S. Eight and 12 week courses of cyclophosphamide in nephrotic syndrome. *Arch Dis Child* 1990;65:1147-50.
2 Arbeitsgemeinschaft für Pädiatrische Nephrologie. Cyclophosphamide treatment of steroid dependent nephrotic syndrome: comparison of eight week with 12 week course. *Arch Dis Child* 1987;62:1102-6.
3 Arbeitsgemeinschaft für Pädiatrische Nephrologie. Minimal change nephrotic syndrome (MCNS): long prednisone therapy versus standard prednisone therapy. *Pediatric Nephrology* 1990;4:C60.
4 Brodehl J, Krohn HP, Ehrlich JHH. The treatment of minimal change nephrotic syndrome (lipoidnephrosis): cooperative studies of the Arbeitsgemeinschaft für Pädiatrische Nephrologie (APN). *Klin Padiatr* 1982;194:162-5.
5 Barratt TM, Bercowsky A, Osofsky SG, Soothill JF, Kay R. Cyclophosphamide treatment in steroid sensitive nephrotic syndrome of childhood. *Lancet* 1975;ii:55-8.
6 Cameron JS, Chantler CS, Ogg, White RHR. Long-term stability of remission in nephrotic syndrome after treatment with cyclophosphamide. *BMJ* 1974;iv:7-11.
7 Chiu J, Drummond KN. Long term follow-up of cyclophosphamide therapy in frequent relapsing minimal lesion nephrotic syndrome. *J Pediatr* 1974;84:825-30.
8 Garin EH, Pryor ND, Fennell RS, Richard GA. Pattern of response to prednisone in idiopathic, minimal lesion nephrotic syndrome as a criterion in selecting patients for cyclophosphamide therapy. *J Pediatr* 1978;92:304-8.
9 McDonald J, Murphy AV, Arneil GC. Long-term assessment of cyclophosphamide therapy for nephrosis in children. *Lancet* 1974;ii:980-2.
10 Krohn HP, Brodehl J. Cytotoxic drug study I of the APN: 5-year follow-up. *Helv Paediatr Acta* 1986;41:107.

Dr Ueda comments:
I read with interest the comments by Dr Oemar and Professor Brodehl, and I wish to thank them for their thoughtful remarks. There are indeed some differences between their study and ours. However, I cannot agree with the suggestion that we had a highly selective group of patients as a result of different initial steroid treatment, because the remission rate in their patients treated for eight weeks is similar to those reported by us. I might add that the longer steroid treatment seems not to affect the subsequent course when it is used once nephrotic patients are steroid dependent, although this has an impact on the outcome when it is used as initial treatment.¹

Perhaps the important differences may relate to the criteria for steroid dependence and the age of the patients studied. The criteria for steroid dependence they adopted is somewhat different from ours as they included the patients other than those relapsed while receiving steroids or within 14 days after stopping steroids ('fast' relapser). Such patients could be more responsive to cyclophosphamide than those with 'fast' relapse. In addition, the most striking difference is the age at which cyclophosphamide was instituted. The age at entry into the study of their patients treated for 12 weeks, who had higher relapse free rate, is higher than that of those treated for eight weeks and of our patients with relapse, but is similar to that of our patients without relapse. Cyclophosphamide appears more effective in older patients than in the younger,² thus the distribution of the age at entry should be strictly the same in a comparative trial of such a drug. Finally, I am sure that Oemar and Brodehl would agree with me that their data must be interpreted with caution because of the retrospective nature of their study and the small number of patients in their study group. Thus in their study if the only two patients treated for 12 weeks relapsed, the differences in the efficacy of the two regimens would be insignificant.

In summary, if the data including the total time off steroids, the number of the patients without 'fast relapse' before cyclophosphamide, the age at entry into the study of patients with and without relapse, and the recent outcome after the completion of their study are available, the discrepancy between their and our results could be more clarified. We believe that the two regimens have an equivalent efficacy when a patient selection is carefully performed as described above.

1 Ueda N, Chihara M, Kawaguchi S, *et al*. Inter-mittent versus long-term tapering prednisolone for initial therapy in children with idiopathic nephrotic syndrome. *J Pediatr* 1988;112:122-6.
2 Barratt TM, Bercowsky A, Osofsky SG, Soothill JF, Kay R. Cyclophosphamide treatment in steroid-sensitive nephrotic syndrome of childhood. *Lancet* 1975;ii:55-8.

Characteristics of steroid dependent patients in study groups

	Ueda <i>et al</i> ¹		APN ²	
	12 Weeks	8 Weeks	12 Weeks	8 Weeks
Male:female	28:13	26:6	7:11	9:9
Mean age at onset of nephrosis (years)	6.40	6.00	5.80	4.90
Mean steroid dose for initial treatment (mg/m ²)	4620	4620	2240	2240
Mean age at entry to cyclophosphamide study (years)	7.80	7.70	8.60	6.90
Mean duration of nephrosis before cyclophosphamide (months)	19.20	18.80	34.80	22.80
No of relapses (12) or (6) months before entry	5.1 (12)	4.5 (12)	4.4 (6)	4.8 (6)
Total cumulative dose of prednisone before cyclophosphamide (mg/kg/patient/month)	18.50	19.30	27.40	26.40
No of patients with relapse after cyclophosphamide/total patients	31/41	24/32	6/18	14/18
Cumulative % of sustained remission	24	25	67	22

Acute wheezy bronchitis—lumping and splitting

SIR,—Mertsola and colleagues have carried out a very comprehensive and worthwhile study on the association between viral infection and wheezing in childhood.¹ However, their terminology 'wheezy bronchitis' as an appropriate diagnostic term for their study population should be reconsidered. It is an emotive term, and its definition far from clear.