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.

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- 3 Arbeitsgemeinschaft für Pädiatrische Nephrologie. Minimal change nephrotic syndrome (MCNS): long prednisone therapy versus standard prednisone therapy. *Pediatric Nephrology* 1990;4:C60.
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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.
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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.

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

Wheezy bronchitis was originally used to describe preschool children who wheezed only after viral respiratory tract infections and who seemed relatively resistant to sympathomimetic and steroid treatment. It was thought that only a minority of these children went on to develop 'asthma'. With the increasing awareness of the underdiagnosis of asthma in childhood the term was re-examined.² Wheezy bronchitis was attacked as an over used euphemism for childhood wheeze. Far from avoiding the diagnosis 'asthma', implying a chronic illness, the use of 'wheezy bronchitis' led to undertreatment and inappropriate use of antibiotics in many true asthmatics. It was suggested that all who wheezed should be lumped together as asthmatic unless proved otherwise. In keeping with this concept most doctors and many parents now perceive asthma as a common condition with a wide range of severity and symptoms throughout childhood.

Last year Dr Nicola Wilson re-examined the idea of splitting up wheezy disorders in childhood.³ Like Professor Margaret Turner-Warwick, who described different patterns of airflow obstruction in chronic adult asthmatics,⁴ she has argued that difficulties in treating asthmatic preschool children related to a failure in identifying clinical subgroups with different patterns of illness. Lacking a better term, she described a splinter group of 'wheezy bronchitics' as children who wheezed only in response to viral infections with little or no atopy compared with asthmatics of the same age. If the term is to be used at all it should refer to these kind of children. This is clearly not the group of patients studied in Finland. Forty three percent of these were highly atopic and atopic features were common in the rest. We are given no information about a family history of atopy. Although viral infections were identified in 45% of respiratory episodes, wheezing occurred in 73% of respiratory episodes in which no virus was found. These children might have had typical asthma with wheeze secondary to precipitants unrelated to viral infections. Thirty nine percent of children were receiving regular prophylaxis. This might have prevented persistent asthma symptoms that would otherwise have been present.

If childhood asthma is to be split up careful attention must be paid to clearly defining separate subgroups. This is particularly important when considering pathogenesis and treatment of airway narrowing in our young wheezers.

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- 1 Mertsola J, Ziegler T, Ruuskanen O, Vanto T, Koivikko A, Halonen P. Recurrent wheezy bronchitis and viral respiratory infections. *Arch Dis Child* 1991;66:124-9.
- 2 Speight ANP, Lee DA, Hey EN. Underdiagnosis and undertreatment of asthma in childhood. *BMJ* 1983;286:1253-5.
- 3 Wilson NM. Wheezy bronchitis revisited. *Arch Dis Child* 1989;64:1194-9.
- 4 Turner-Warwick M. On observing patterns of airflow obstruction in chronic asthma. *Br J Dis Chest* 1977;71:73-85.

Drs Mertsola, Ruuskanen, Vanto, et al comment: We appreciate the comments of our colleagues and agree that many of our patients can be regarded as asthmatics. However, according

to our present practice, the inclusion criteria used in the study (two or more wheezy bronchitis attacks) do not permit an asthma diagnosis in all these children. At present many authors regard wheezy bronchitis and asthma as the same disorder and children with wheezing attacks are treated with the principles of asthma therapy (as was the case in our study). The use of a term 'wheezy bronchitis' should not lead to undertreatment of patients.

About one third of the children in our study had regular prophylaxis and we agree that this might have prevented wheezing attacks in some children, as discussed in the paper. Recently we re-evaluated the importance of allergen exposure as a cause of wheezing in these children.¹ Although many of the patients were atopic, allergen exposure was not often suspected or proved as a precipitating factor for wheezing. This was probably due to the effective allergen avoidance routinely advised to parents of young children in child health centres in Finland. The early preventive measures are helpful for the patients but make the analysis of these kind of studies even more complex.

- 1 Vanto T, Ziegler T, Mertsola J, Ruuskanen O, Koivikko A. Allergen exposure and respiratory virus infections in young wheezy children (abstract). *J Allergy Clin Immunol* 1991;87:344.

Spontaneous resolution of congenital nephrotic syndrome in a neonate

SIR.—We were interested to read the article by Banton *et al* referring to a baby with congenital nephrotic syndrome whose condition resolved.¹ We too have observed a child with congenital nephrotic syndrome who made a spontaneous recovery, and whose case raises important ethical considerations.

The mother had a raised serum α foeto-protein concentration on routine screening in pregnancy and amniocentesis, performed at 21 weeks' gestation, showed an α foetoprotein concentration of 325 mg/l (normal <20) with normal cholinesterase. An ultrasound scan showed no gross fetal abnormalities. A diagnosis of congenital nephrotic syndrome was made and the mother was offered termination of her pregnancy but declined on religious grounds. A boy was born at term weighing 3750 g, the placenta weighing 1000 g. He had gross proteinuria (Albustix 4+) at birth but no haematuria. He also became hypocalcaemic, with a serum albumin of 18 g/l at 2 weeks. He had mild pitting oedema in the first week but none subsequently and at no time did he become hypertensive. The selectivity index (IgG urine : serum as a percentage of transferrin urine : serum ratio) was initially <7% (highly selective proteinuria) but rose to 17% at 7 weeks. The level then fell back to 9% at 10 weeks of age and the proteinuria had resolved by 10 months. A renal biopsy specimen at 2 months of age showed normal glomeruli by light microscopy with the exception of one obsolescent glomerulus. The tubules, interstitium, and blood vessels appeared normal. Immunofluorescent stains for complement components and immunoglobulins were all negative, and these findings were compatible with 'minimal change' nephrotic syndrome. He was treated with a high protein diet (6 g/kg/day), replacement immunoglobulin, and penicillin prophylaxis up to 5 months of age; neither steroids nor diuretics were used. The child is now 6 years old, has not relapsed, and is entirely well.

The congenital nephrotic syndrome is heterogeneous and various types can be recognised histologically. The Finnish type, and the forms exhibiting diffuse mesangial sclerosis, or focal segmental glomerulosclerosis all have a poor prognosis. A policy of prenatal diagnosis is therefore justified in families with a previously affected child whose clinical course or histological type is known to be adverse. However from time to time screening for neural tube defects by maternal α foetoprotein in serum and amniotic fluid will lead unexpectedly to the diagnosis of congenital nephrotic syndrome^{2,3} and the type of congenital nephrotic syndrome and the actual prognosis will not be known. In view of the benign course of our patient, and the one described by Banton *et al*, the counselling of such families can be extremely difficult.

A review of patients with congenital nephrotic syndrome at this hospital over a period of 24 years (S Yoshiara, RHR White, F Raafat, unpublished data) showed that, of 26 cases proved at biopsy, eight were of the Finnish type, three had the form exhibiting diffuse mesangial sclerosis, 12 had focal segmental glomerulosclerosis, and three the histological appearances compatible with minimal change nephrotic syndrome. Of the latter, two siblings were steroid resistant and continue to have mild proteinuria at 19 years of age, with normal renal function, although one is hypertensive. The other child responded to prednisolone 60 mg/m²/day and remained in complete remission until 5 years of age, when proteinuria recurred; a further biopsy specimen taken at this time showed type 1 mesangiocapillary glomerulonephritis. One of the 12 infants with focal segmental glomerulosclerosis was partially steroid responsive and is currently in remission after treatment with cyclophosphamide.

The distinction between the histological subtypes can sometimes present difficulties. Although the glomeruli in Finnish nephrotic syndrome show mild mesangial hypercellularity, this can also be a feature of minimal change nephrotic syndrome. Moreover the cystic tubular dilatation which characterises Finnish nephrotic syndrome is of variable severity and also occurs in focal segmental glomerulosclerosis, while segmental sclerosis in the latter condition may initially be so minimal as to escape detection in a renal biopsy specimen obtained during the first three months of life. Experience in differential diagnosis can only be gained if patients are referred to regional paediatric nephrology centres for evaluation.

If the differential diagnosis remains in doubt, it is reasonable to offer a trial of corticosteroid treatment, with antibiotic prophylaxis because of the increased risk of infection, rather than to dismiss the condition as untreatable. The counselling of a woman who had not previously had a child with congenital nephrotic syndrome requires an awareness that there is, perhaps, as much as a 10% prospect of steroid responsiveness if she produces an affected, liveborn infant.

The authors are grateful to Dr James Partridge for permission to report this patient.

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