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 findings.2 We would like to make 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 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—5 We therefore would assume that the patients of Ueda and his colleagues represent a highly selected 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.6—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 not true, as only true steroid resistant patients, who were as intensively treated initially as in the study of Ueda et al. For those who were treated less intensively, the International Study of Kidney Diseases in Children (ISKD) 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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6 Brodehl J, Krohn HP, Ehrich JHH. Cyclophosphamide treatment of steroid dependent nephrotic syndrome. 6-40

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Acute wheezy bronchitis—lumping and splitting

Sir,—Merril 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.

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Characteristics of steroid dependent patients in study groups

<table>
<thead>
<tr>
<th>Ueda et al</th>
<th>APN²</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 Weeks</td>
<td>8 Weeks</td>
</tr>
<tr>
<td>Male/female</td>
<td>28:13</td>
</tr>
<tr>
<td>Mean age at onset of nephrosis (years)</td>
<td>6±40</td>
</tr>
<tr>
<td>Mean steroid dose for initial treatment (mg/m²)</td>
<td>46±20</td>
</tr>
<tr>
<td>Mean duration of cyclophosphamide treatment (months)</td>
<td>7±80</td>
</tr>
<tr>
<td>Mean duration of nephrosis before cyclophosphamide (months)</td>
<td>19±20</td>
</tr>
<tr>
<td>No of relapses (12) or (6) months before entry</td>
<td>5±1 (12)</td>
</tr>
<tr>
<td>Total cumulative dose of prednisone before relapse (mg/patient/month)</td>
<td>18±50</td>
</tr>
<tr>
<td>No of patients with relapse after cyclophosphamide/totalexposed</td>
<td>3±1</td>
</tr>
<tr>
<td>Cumulative % of sustained remission</td>
<td>6±18</td>
</tr>
</tbody>
</table>
Wheezy bronchitis was originally used to describe preschool children who wheezed only after viral respiratory tract infections and who seemed to respond relatively well to symptomatic 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 children, the use of the term 'wheezy bronchitis' has been diminishing, and it is now considered to be a heterogeneous group of conditions.

Last year Dr Nicola Wilson re-examined the idea of splitting up wheezy disorders in childhood. Like Professor Margaret Turner-Warwick, who described different patterns of airway disease in children with allergic asthma, 1 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, these can be described as the split renal 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. It is too early to give any 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. They were 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.

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

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The con genital 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 histology makes it known to be severe. However from time to time screening for neural tube defects by maternal α-fetoprotein in serum and amniotic fluid will lead unexpectedly to the diagnosis of congenital nephrotic syndrome of the usual type, and the 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 Banty 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 (5 Yoshira, 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 in 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 resistant 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 cavitary tubular dilatation which characterises Finnish nephrotic syndrome can cause renal vein thrombosis, which can lead to venous hypertension, and also occurs in focal segmental glomerulosclerosis, while segmental sclerosis in the latter condition may initially be so minimal that it is considered to be a normal 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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