LETTERS TO THE EDITOR

Liver toxicity in a nephrotic patient treated with levamisole

EDITOR,—Levamisole along with prednisolone has been used in the treatment of steroid dependent minimal change nephrotic syndrome (MCNS) for many years. The only important side effect cited in the study of levamisole in the treatment of MCNS by the British Association for Paediatric Nephrology (BAPN) is neutropenia.[1]

Laux-End *et al* report a case of vasculitis with circulating autoantibodies in an 11 year old girl with nephrotic syndrome treated with levamisole.[2] Raised levels of aspartate aminotransferase (ALT) have been reported in two out of 11 patients given levamisole for recurrent pyoderma. I wish to report a patient with nephrotic syndrome who developed liver toxicity after four weeks' treatment with levamisole.[3] As far as I am aware there are no reports of liver toxicity in children with nephrotic syndrome treated with levamisole.

A 14 year old boy who has had frequently relapsing steroid sensitive MCNS from the age of 18 months relapsed after a two year treatment free remission. Once again he was steroid sensitive but relapsed three times in seven months and rapidly developed steroid toxicity with cushingoid features with striae and could not be weaned off steroids. His height was 170 cm (on the 97th centile) and weight 78 kg (> 97 th centile). After a steroid induced remission the dose of prednisolone was reduced to 20 mg on alternate days. Blood counts and liver function tests done two weeks previously were normal. Levamisole 50 mg three times a day on alternate days was added to the treatment. Blood counts monitored weekly remained normal.

The remission continued. After four weeks the patient complained of pruritis. There was no skin rash. Liver function tests done at this stage showed an ALT 103 U/l (normal range up to 40), total protein 63 g/l (normal range 60–80), albumin 42 g/l (normal range 35–45), bilirubin 11 µmol/l (normal range 3–20), γ-glutamyltransferase (GGT) 12 U/l (normal range up to 45), alkaline phosphatase 196 U/l (normal range 100–800). The treatment was continued. Two weeks later liver function tests showed ALT 126 U/l, total protein 65 g/l, albumin 43 g/l, bilirubin 12 µmol/l, GGT 27 U/l, and alkaline phosphatase 311 U/l. After a further two weeks on the same treatment ALT had risen to 156 U/l. There were no significant changes in the other liver enzymes or bilirubin. The pruritis had cleared up. At this stage levamisole was stopped and prednisolone reduced to 15 mg on alternate days. Liver function tests done two weeks after stopping levamisole showed ALT 64 U/l, total protein 60 g/l, albumin 40 g/l, bilirubin 12 µmol/l, GGT 14 U/l, and alkaline phosphatase 370 U/l. Prednisolone was gradually tapered off. The patient remains well in remission.

It is fair to assume that the raised levels of ALT on this patient were the result of treatment with levamisole, as liver function tests two weeks before starting treatment were normal and two weeks after cessation the ALT had returned to near normal. The toxicity is likely to relate to the cumulative dose as ALT continued to rise until levamisole was stopped. Because of his size this patient received the adult dose of levamisole. This was, however, less than the 2 mg/kg alternate day dose recommended in the study by the BAPN. The adult dose of 150 mg/day of levamisole is generally well tolerated when given in short courses not exceeding two days for the treatment of worm infections. However when levamisole is used for a long period, even intermittently, as an immunomodulater side effects have been more frequent and diverse.[4]

As treatment of nephrotic syndrome with levamisole would normally last several months, it is important to define a safe upper limit of the dose. Those receiving larger doses of levamisole, as in the patient described, may develop liver toxicity after some time. It is important to monitor liver function tests in such patients.

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Violence in children

EDITOR,—The annotation by Professor Graham on violence in children fails to address the wide body of literature that has looked at the biological basis for violence and crime, and seems to concentrate almost exclusively on the psychosocial basis.[1]

While a psychosocial component of violence cannot be refuted, there is increasing evidence from many authors, including Farrington[2] and Moffit in the Dunedin Study[3] that there is a strong biological component in many situations and especially that the early onset of hyperactivity and conduct disorder makes recurrent offending and ongoing violence extremely likely. There is further confirmation of this from Wall in Australia recently.[4]

The one line mention of a possible biological basis for crime does a great disservice to the many children, adolescents, and adults who have suffered because of the under-recognition of this fact. There is increasing evidence that a significant percentage of current offenders have such a biological basis, aggravated by the environment in which they live.

It would be a shame if this information was not made available to your readers as the evidence for there being a biologically based disorder of neurological function, which can be successfully managed, and which predisposes to violence and crime, is beyond dispute and well beyond mere personal bias.

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Professor Graham comments:

The reason why so little attention in my annotation was given to biological factors in the causation of violence and crime is that there is a lack of evidence to suggest they are of more than minor importance. Indeed, in neither of the two important investigations cited by Dr Kewley (the Cambridge and Dunedin studies) were biological factors measured. In the article by Farrington that Dr Kewley quotes, the author explicitly states 'The major risk factors for delinquency include poverty, poor housing, and living in public housing in inner city, socially disorganized communities...' After mentioning as relevant various poor parental child rearing techniques, Farrington adds that other risk factors include impulsivity and low intelligence and attainment ('which may reflect a poor ability to manipulate abstract concepts and deficits in the "executive functions of the brain"'). The emphasis given to biological factors in Farrington's review is closely similar to that in my annotation. I do agree with Dr Kewley that attention deficit and hyperactivity disorder has an important biological component, and that it is a risk factor for later conduct disorder and delinquency. The importance of the hyperkinetic syndrome as a risk factor is clearly stated in my annotation.

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Parental resuscitation techniques after apparent life threatening events in infancy

EDITOR,—The term 'apparent life threatening event' (ALTE) replaces the older term 'near miss cot death' and is used to describe an event perceived by the child's caregiver to be life threatening. The features showed usually involve a combination of a change in colour, tone, and respiratory pattern and may be difficult to differentiate from physiological events during sleep.[1]

Of the 15 babies referred to our hospital for investigation of ALTE in the last six months, only one parent was perceived to have performed resuscitation correctly and appropriately after such an event. One method of stimulation included a mother sticking her tongue into the infant's mouth and another where the family, who were driving at the time of the apparent event, repeatedly braked and accelerated the car in an unsuccessful attempt to rouse the child. Two parents in the group gave mouth to mouth resuscitation but did not know if the baby had actually stopped

breathing first. A further two parents did not have any knowledge of resuscitation; one of these was able to follow guidelines given down the telephone by the emergency services and the other parent was too distressed and had to wait for the arrival of the ambulance crew. Another father, not knowing what to do took his baby outside into the cold and shook him. He was not the only parent in the group unaware that shaking an infant can be dangerous.

Before discharge from our unit, all parents and caregivers are taught full resuscitation and it is during these sessions that a lack of knowledge has become evident. Many neonatal units have introduced programmes for teaching their parents resuscitation skills but very few studies evaluating these are available. Those which do exist have highlighted the fact that training in resuscitation techniques provides parents with an important skill and increases their confidence which in turn leads to reduced anxiety levels.[2] However, none of the infants in our group had been premature and no parent had been taught resuscitation since they had been at school. Health professionals involved in the area of midwifery and paediatrics must continue to promote the Department of Health campaigns against cot death and this should include adequate training in resuscitation.

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Supine positioning of toddlers for throat examination

EDITOR,—Many toddlers are intimidated by the approaches of a doctor who wishes to view the throat. In contrast to the conventional sitting position used for throat examination by paediatricians,[1] dentists use a less threatening approach, with the child lying semirecumbent on the parent's knee.[2] We have compared the acceptability of the two positions in a prospective, randomised case-control study .

With verbal parental consent 36 children (10 in general practice, 26 in hospital) were randomised to the 'supine' or 'sitting' group (17 sitting , 19 supine, giving 17 case-control pairs). The supine position required the mother to lie the toddler supine on her lap with his head resting either on her knee, or on the doctor's knees. With the child supine throat examination took place in a fashion akin to a dental examination or a neonatal intubation.

Only four children—two in either group—had not had their throats examined before. There was no difference in examination time in either position (sitting mean (SD) 17.3 (9.4) sec, supine 16.9 (6.7) sec, unpaired Student's *t* test, p=0.85). Cooperation was equally common in each group (p = 0.28). 12 of 15 (80%) in the 'supine' group who had been examined before thought the supine position was better than the sitting position used previously.

The supine position for throat examination is at least as acceptable and well tolerated as the sitting position. Explanation of the unfamiliar, supine position takes longer than normal. Once the child is supine the examination usually takes 2 or 3 seconds and does not require the doctor to crouch or peer to view the throat adequately. Positioning of toddlers supine makes throat examination more acceptable to parents and, in our experience, much easier to perform than the traditional sitting position.

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Cerebrospinal fluid nitric oxide metabolites and discrimination of bacterial meningitis from other causes of encephalopathy

EDITOR,—Nitric oxide (NO) is implicated in the pathogenesis of bacterial sepsis.[1] The potential sources of NO include endothelial, smooth muscle, and inflammatory cells. Serum concentrations of nitrogen oxides are increased in patients with bacterial sepsis, compared with non-septic controls.[2 3] NO has also been shown to be a neurotransmitter, and has been implicated in acute and chronic brain pathology.[1] We hypothesised that NO production is increased in bacterial meningitis; that this would be reflected by an increased concentration of nitrogen oxides in the cerebrospinal fluid (CSF); and that the CSF concentrations of nitrogen oxides would discriminate bacterial meningitis from other causes of fever and childhood encephalopathies. Reagent strips have recently been used for the rapid diagnosis of meningitis.[4] We thought that if CSF nitrogen oxides identified children with bacterial meningitis it may be a further step towards improving the current diagnostic accuracy of reagent strips.

Children undergoing lumbar puncture as part of routine investigation were studied prospectively. The study was approved by the institutional ethics committee. A 1 ml aliquot of CSF was centrifuged at 10 000 revolutions per minute for 15 minutes at 2°C, and the supernatant aspirated and stored at −20°C. CSF nitrate was converted to nitrite by incubation of 300 µl of CSF with nitrate reductase and NADPH for 100 minutes at 37°C. The reaction was terminated by addition of zinc sulphate (1.5% w/v, final concentration) to precipitate protein. The sample was centrifuged at 2000 *g* for five minutes at 4°C and the nitrite was determined in the supernatant. Nitrite levels were measured using the reaction of the Griess reagent with NO_2^- forming a chromophore. An aliquot of 100 µl of sample was added to 100 µl of freshly prepared Griess reagent in a microtitre plate. After a five minute period to allow colour development, the absorbance was determined in a Behring plate reader at 570 nm. The concentration of NO_2^- was quantified by comparison

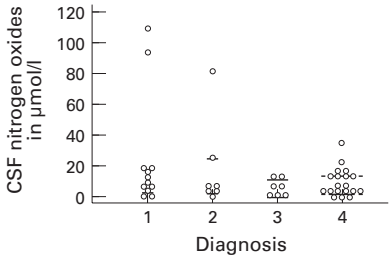

Figure 1 CSF nitrogen oxide concentrations by diagnostic group. Diagnosis: 1 = bacterial meningitis; 2 = viral meningitis; 3 = encephalopathy of unknown aetiology; 4 = fever with no central nervous system infection. Interquartile range shown as horizontal bars.

with a standard curve constructed using known concentrations of NO_2^- (0.1-100 µmolar).

Other data recorded were: CSF total and differential white cell count; CSF protein and glucose concentration; viral and bacterial culture results; and the final diagnosis, based on CSF results, other investigations, and clinical findings. The CSF nitrogen oxide assay was performed by one investigator (AS) blinded to the clinical and laboratory details.

Forty six children were studied. The number of subjects (in parentheses) and the median values of nitrogen oxides according to diagnostic group were: bacterial meningitis (12), 10.5 µmol/l; viral meningitis (7), 5.8 µmol/l; encephalopathy of unknown aetiology (7), 6.9 µmol/l; fever with no central nervous system infection (19), 6.6 µmol/l (fig 1). There were no differences in CSF concentrations of nitrogen oxides between the four groups (Kruskal-Wallis test, p = 0.50). One child with encephalitis due to mycoplasma, who did not fit clearly into any of the diagnostic groups, had a CSF nitrogen oxide concentration of 482 µmol/l; the assay was repeated with the same result. Overall there were no relationships between CSF nitrogen oxide concentrations and CSF white cell count (p=0.60). Such a relationship would not be surprising if the major source of nitrogen oxides in acute central nervous system disease were inflammatory cells. We conclude that measuring CSF nitrogen oxides will not reliably distinguish bacterial meningitis from other causes of fever requiring lumbar puncture. Use of the nitrite patch on reagent strips is unlikely to add to the diagnostic yield that can be achieved by testing for protein, glucose, and leucocytes.[4]

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WESTMINSTER BRIEFING

The following items are from *Children & Parliament*, Autumn 1996. *Children & Parliament* is an abstracting service based on *Hansard* and published fortnightly by the National Children's Bureau while parliament is sitting. It covers all parliamentary business affecting children and is produced in either printed or CD-ROM form. Both are available on subscription from the Library and Information Service, National Children's Bureau, 8 Wakley Street, London EC1V 7QE (tel: +44(0)171 843 6035). (The *Hansard* reference is given first followed by the issue number and date of *Children & Parliament*.)

Measures announced in the Queen's Speech of October 1996 include the Education Bill allowing more pupil selection in grant maintained schools, nurseries in such schools, and Ofsted inspection of local education authorities, and bills aimed at maintaining closer supervision of sex offenders.

Between 1990 and 1995 the number of twins born annually in the UK rose from 8932 to 9889 and of triplets from 222 to 318, although the number of completed pregnancies fell from 792 924 to 725 338. There was no appreciable trend in higher order births. The contribution of infertility treatments to these figures is not clear.
(14 Oct 96, Cols 700, 748-9, 695; 243, 5.11.96)

A 1969 Act made it illegal to tattoo anybody under the age of 18 but other forms of body piercing are permitted. The Law Commission is reviewing the subject.
(5 Nov 96, Col 435-436; 244, 19.11.96)

The number of 15 or 16 year olds remanded to adult prisons in England and Wales was 134 in 1991 and 216 in 1995. Nobody knows how long they spent there.
(7 Nov 96, Col 639-640; 244, 19.11.96)

Adopted children who are born British nationals keep that nationality whatever the nationalities of their adoptive parents and can only renounce it themselves as adults.
(12 Nov 96, Col 127; 245, 3.12.96)

In 1982 there were 692 127 live births in Great Britain; the number rose steadily to 772 113 in 1990 and has since then gradually fallen to 708 189 by 1995.
(12 Nov 96, Col 177-178; 245, 3.12.96)

Of 12 European Union countries for which data are available, five give better overall unemployment figures than the UK and four give better youth employment figures.
(12 Nov 96, Col 139; 245, 3.12.96)

There were 454 SIDS deaths in 1994 and 398 in 1995.
(25 Nov 96, Col 124; 246, 17.12.96)

In 1967 in England and Wales there were 792 offences involving the use of a firearm; by 1977 the figure was 5302. In 1987 it was 9002 and by 1992 it had reached 13 305. It has stayed more or less steady since then.
(25 Nov 96, Col 4-5; 246, 17.12.96)

In the 14 health regions of England in 1994 the proportion of babies weighing less than 1500 g at birth who survived to four weeks varied from 76 to 87%.
(4 Dec 96, Col 689-90; 246, 17.12.96)

The unemployment rate for 16–24 year olds in Great Britain was 10.0% in 1990, 15.3% in 1995, and 14.8% in 1996. The figures are currently greater for London than for the rest of England and Wales.
(27 Nov 96, Col 302-303; 246, 17.12.96)

The proportion of children staying on at school to the age of 18 has risen from 15% in 1979 to 40% in 1995.
(10 Dec 96, Col 110; 247, 07.01.97)

In England 20 new paediatric intensive care beds and eight high dependency beds were in use by November 1996 and a further eight intensive care and two high dependency beds were planned to open by April 1997.
(16 Dec 96, Col 457; 247, 07.01.97)

The number of deaths from ecstasy poisoning in England and Wales each year from 1991 to 1995 was six, five, 12, 10, and 15.
(16 Dec 96, Col 434-436; 247, 07.01.97)

The number of pupils taking free school meals in England has risen gradually from 1 001 968 in 1992 to 1 260 426 in 1996.
(9 Dec 96, Col 13-14; 247, 07.01.97)

In 1990 13.6% of the males and 15.2% of the females found guilty of or cautioned for indictable offences in London were aged 16 or under. In 1995 it was 12% and 18%. The number of girl offenders aged 12–16 was 1906 in 1990 and 2323 in 1995.
(10 Dec 96, Col 147-148; 247, 07.01.97)