LETTERS TO THE EDITOR

The changing clinical pattern of Reye's syndrome 1982-90

EDITOR,—We read with interest the paper by Dr Hardie and colleagues.1 We all agree now on the non-specificity of the case definition and on the heterogeneous nature of Reye's syndrome.2

1 Updated Reye's syndrome is not a specific clinicopathological entity, but a descriptive term used to designate the condition of a child presenting with an unexplained non-inflammatory encephalopathy and signs of liver dysfunction (international workshop 'Reye's syndrome revisited', Leuven, 3 May 1996).

However, as there is a wide spectrum of differential diagnoses in patients meeting the diagnostic criteria,2 classifying them now in two groups, the 'Reye group' and the 'Reye-like inherited metabolic disease group' is inaccurate: the Reye group again is heterogeneous, composed of patients with infections (and fever), and of patients with toxic and other diseases. This classification again enhances the risk of epidemiological biases.3

Whether the scoring system devised by the authors is a valid predictor of 'Reye' (high score) versus 'Reye-like' (low score) has to be challenged as well. This scoring system does include exclusion criteria for Reye's syndrome (for example a patient with positive cerebrospinal fluid can still be diagnosed as having Reye's syndrome), and in several sections a not recorded feature does increase the score in such a way that an insufficiently documented patient already gets a score of 8 simply by not measured or not recorded features.

Moreover, when applying this 'Reye score' to the patients reported earlier on they would both be high scorers, namely 17 and 19 respectively.4 Yet—by including careful analysis of the preadmission medication—we proved that their 'Reye's syndrome' was a toxic effect after antiemetic administration (influence of antiemetics in the article of this paper and others' publications).

We clearly stated that 'Reye-like' includes not only certain inherited metabolic disorders but also other conditions. We emphasised the former because they can mimic 'classic' Reye's syndrome in every detail and their prompt recognition can prevent death and disability. For the latter enzyme defects undoubtedly remain undiagnosed, so an unexplained Reye-like illness may still be due to such a disorder, especially in children under 3 years, those with recurrences, a family history, or a low Reye score.

The 'epidemiological biases' described in the authors' previous publications have been refuted.5 They criticise the non-specificity of our high scoring category and that of the case definition used in the controlled studies even though the 'dilutional' effect of including non-cases strengthens the association. Our Reye score is new, reflects the limitations of data from national voluntary epidemiological studies and, as we stated, requires further validation. We are pleased that Casteels-Van Daele et al tried it on their two cases; however, in practice, scoring would have been unnecessary because a diagnosis of antiepileptic toxicity should have been made at presentation.

We have no evidence that the highest scorers were those most likely to have received antiepileptics. The authors' hypothesis about their role in Reye's syndrome has been criticised; their interpretation of the Food and Drug Administration's conclusion is inaccurate.

The authors confuse numbers and proportions when referring to our data showing a 'rise in revised diagnoses 1982-90'. The numbers were equal in the two study periods, the proportion rising as the total annual numbers fell.

Finaly, our data clearly demonstrated a high scoring subgroup of Reye's syndrome associated with aspirin exposure. Experience at referral centres is that there has been a dramatic decline in patients with these clinical features (JFT Glasgow, unpublished data; J. Orlowski, discussion at international workshop 'Reye's syndrome revisited', Leuven, 3 May 1996). This should not have occurred if the decline in reported Reye's syndrome is due to improved diagnostic classification.


Chromosome 22q11 microdeletion and isolated conotruncal heart defects

EDITOR,—We read in a recent issue of the journal the paper by Trainer et al on 22q11 microdeletion (del22q11) in patients with tetralogy of Fallot.1 Del22q11 was detected in patients with classic and mild DiGeorge/velocardiofacial syndrome, but also in ‘non-dystrophic’ patients. The authors state that fluorescence in situ hybridisation (FISH) for del22q11 should routinely be performed in all patients with tetralogy of Fallot. Our experience on a large sample of patients with isolated conotruncal heart defects (CTHDs) demonstrated, on the contrary, that clinical examination can select the patients at risk for del22q11.2 From 1993 to 1996 we evaluated 315 children with CTHD (table 1). All patients underwent phenotypical evaluation. Particular attention was paid to minor dysmorphic features associated with DiGeorge/velocardiofacial syndrome,1 including laterally displaced nasal bones, narrow upslanting palpebral fissures, prominent nose with hypoplastica nares, small mouth, dystrophic ears, and slender fingers. Standard karyotyping and fluorescent in situ hybridisation was performed, and FISH was used for detecting del22q11 in all cases.3 Patients presenting with CTHD that was associated with one or more extracardiac anomalies were considered as syndromic. The distribution of syndromic and isolated cases in the different types of CTHD and the presence of del22q11 is shown in table 1. Only one of the children with isolated CTHD presented del22q11. Five patients presenting with syndromic CTHD as isolated were subsequently included in the group of syndromic cases, because of the presence of subtle facial dysmorphisms which was previously overlooked.

The occurrence of del22q11 in our series of true isolated CTHDs is extremely low. In order to define the exact prevalence of del22q11 in non-syndromic CTHDs it is essential to exclude patients with subtle dysmorphisms evoking features of DiGeorge or velocardiofacial syndromes.4 These dysmorphisms may be barely recognisable, but their presence can be associated with a high prevalence of del22q11. A precise phenotypical and clinical low up are essential to
Table 1  Clinical and molecular findings in our series of patients with CTHDs

<table>
<thead>
<tr>
<th>Cardiac defect</th>
<th>Total No of patients</th>
<th>DG/VCF</th>
<th>Other</th>
<th>Isolated patients</th>
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<tbody>
<tr>
<td></td>
<td>With del22</td>
<td>Without del22</td>
<td>With del22</td>
<td>Without del22</td>
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<tr>
<td>TF</td>
<td>161</td>
<td>16</td>
<td>7</td>
<td>0</td>
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<tr>
<td>TGA</td>
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<td>0</td>
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<tr>
<td>TF with PA</td>
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<td>3</td>
<td>0</td>
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<td>Heterotaxia</td>
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<td>0</td>
<td>0</td>
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<tr>
<td>DORV</td>
<td>14</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>TA</td>
<td>12</td>
<td>2</td>
<td>1</td>
<td>0</td>
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<tr>
<td>IAA</td>
<td>4</td>
<td>3</td>
<td>0</td>
<td>0</td>
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Abbreviations: del22, microdeletion 22q11; DG, DiGeorge syndrome; DORV, double outlet right ventricle; IAA, interrupted aortic arch; TA, truncus arteriosus; TF, tetralogy of Fallot; TGA, transposition of the great arteries; VCF, velocardiofacial syndrome.

distinguish syndrome from isolated CTHD. We believe that accurate clinical evaluation is generally sufficient for a first screening to identify patients at risk for del22q11, and only syndrome cases should be screened for this chromosomal anomaly. Routine FISH analysis in both syndromic and isolated cases is valuable as a research tool to evaluate the exact prevalence of del22q11 in isolated CTHD. The finding in patients with different types of cardiac malformation, but we feel that in clinical practice this technique could be reserved for patients previously selected by clinical evaluation.

LETTERS TO EDITOR

M C DIGLIO
A GIANNOTTI
B DALLAPICCOLA
Medical Genetics and Paediatric Cardiology, Bambino Gesù Hospital, 00165 Rome, Italy


A negative association between Down's syndrome and neuroblastoma

EDITOR,—Only one ganglioneuroma and a poorly documented case of neuroblastoma associated with Down's syndrome have ever been published. In order to obtain population based data an epidemiological study was conducted in seven European countries, five with specialised registries (Denmark, Belgium, Italy, Switzerland), one with four regional registries (Netherlands), and one with centralised registration of treatment of children with neuroblastoma (France), covering the whole population to make a comparison between those who had been counselled as described and those who had not.

Only three of 18 families who

A study of bereavement care after a sudden and unexpected death

EDITOR,—Dent et al state that no studies have concentrated on parents' perception of standards of bereavement care in sudden death.1 In 1986 Ward et al reported the findings in 100 families who had experienced a sudden infant death who were visited at home by a social worker.2 Serious deficiencies were highlighted.

Our Lady's Hospital for Sick Children, serving the south side of Dublin city, produced new procedures based on discussion between nurses, chaplains, social services, and paediatric staff with involvement of police and funeral directors. Specific responsibilities were given to each professional. A parents' booklet explained their roles.

A senior paediatrician led the group and the parents saw the paediatrician immediately. He gave them the necropsy results in two to three days. He saw them again in six to eight weeks and ongoing liaison was maintained through the casualty ward sister who maintained an open line of communication. The family doctor and public health nurse were informed.

An independent review was conducted by The Irish Sudden Infant Death Association in 1989. This confirmed that the guidelines were effective. Families found the system helped, was sympathetic, honest, and informative. Good procedures can avoid longstanding dissatisfaction among families. Of greater importance however are the long term benefits. A review by Powell made it possible to make a comparison between those who had been counselled as described and those who had not.

CHARLES A STILLER
Childhood Cancer Research Group, University of Oxford, Department of Paediatrics, Oxford OX2 6HJ

HERVE RUBIE
Medicniele Infanteel BCHU Purpan, 31059 Toulouse Cedex, France

CHARLES A STILLER
Childhood Cancer Research Group, University of Oxford, Department of Paediatrics, Oxford OX2 6HJ

had had medical counselling had long term unresolved grief problems (18%), as against 17 of 23 (74%) who had not had medical counselling.

Good procedures can be of long term benefit and every district should review its working practices in the light of the study of Dent et al.¹

O C WARD
Department of Pediatrics,
University College,
Dublin, Ireland


Jenner, romanticism, and research

EDITOR,—I read the annotation ‘Jenner, romanticism, and research’ and I note that Chiswick gives all the credit of this immunization discovery to Jenner.¹ Yet Reeves and Todd in their book Lecture Notes on Immunology describe how a kind of smallpox immunization was used in the Ottoman Empire around 1700, much earlier than Jenner’s use of cowpox inoculation in 1796. Apparently, Mary Pierrepont Montagu wrote of her observations from Istanbul (then Constantinople) in 1717 and subsequently introduced the method into England. I am writing this historical note to indicate that Jenner’s important discovery was related to Mary Pierrepont-Montagu’s letters.

S ÖZSOYLU
Turkish Health and Therapy Foundation,
Çiftlik Cad No 57,
06510 Emek, Ankara, Turkey

Professor Chiswick comments: Quite right. Mary Pierrepont-Montagu introduced into England from the Ottoman Empire the practice of inoculating individuals with material obtained from smallpox crusts (variolation).


The new antiepileptic drugs

EDITOR,—In the recently published current topic on new antiepileptic drugs,² reference 45 (CD Ferrie et al) was unfortunately misquoted. The reported synergism in controlling typical absence seizures was between lamotrigine and sodium valproate and not, as quoted, between lamotrigine and ethosuximide.

There is, however, evidence (as yet unreported and again anecdotal, including the author’s own experience), that the combination of lamotrigine and ethosuximide may also be effective in treating previously ‘drug resistant’ typical absence seizures.

RICHARD E APPLINGTON
The Roald Dahl EEG Unit,
Royal Liverpool Children’s Hospital (Alder Hey),
Eaton Road,
Liverpool L12 2AP


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<thead>
<tr>
<th>Event</th>
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<tr>
<td><strong>MEETINGS</strong></td>
<td><strong>IN 1997</strong></td>
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<td><strong>Neonatal Society</strong></td>
<td>6 March, London</td>
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<td><strong>Paediatric Palliative Care Conference</strong></td>
<td>14 March, Edinburgh</td>
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<td>14–15 March, Norwich</td>
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<td><strong>Spectrum of Developmental Disabilities M/X: Mental Retardation and Associated Deficit</strong></td>
<td>17–19 March, Baltimore, USA</td>
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<td>27–30 April, Assisi, Italy</td>
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<td><strong>XVI Congress of the European Society for Paediatric Haematology and Immunology</strong></td>
<td>14–17 May, Thessaloniki, Greece</td>
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<td><strong>30th Annual Advances and Controversies in Clinical Paediatrics</strong></td>
<td>15–17 May, San Francisco, USA</td>
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<td><strong>12th Annual Meeting of the German Society for Paediatric Gastroenterology and Nutrition</strong></td>
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<td><strong>26th Annual Congress of the European Society of Paediatric Allergy and Clinical Immunology (ESPACI) and the II Iberian Meeting of Pediatric Allergy and Clinical Immunology</strong></td>
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<td><strong>British Association of Perinatal Medicine</strong></td>
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<td><strong>6th Congress of the European Society for Gynaecological Endoscopy</strong></td>
<td>7–10 December, Birmingham</td>
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The three main conclusions of an Oxford study of deliberate self harm in under 16 year olds (British Journal of Psychiatry 1996;169:202-8) were that paracetamol poisoning has increased (from 20% of episodes in 1976-81 to 55% in 1988-93), nearly 10% repeat the self harm within a year, and psychiatric referral should be made in all cases. Of 854 episodes in 755 patients, 801 were poisonings alone and a further 23 were poisonings plus self injury. Girls outnumbered boys by nearly 6:1 and only 12 patients were less than 12 years old. Clashes with parents were the most common problem volunteered.

In the early 1980s a group of young male orphan elephants was transferred from South Africa’s Kruger National Park to a smaller game reserve after their herd had been culled. They were reared without maternal input and lacking the discipline which older bulls are known to administer to young aggressive bulls in the mating season, and that, say, elephant experts, may explain why there has been an increase in attacks on other animals and on people by these elephants in recent years (New Scientist 1996;July 20:5). In future the integrity of families will be preserved when elephants are transferred between reserves.

A study of 19 adult volunteers in Augusta, Georgia (Ophthalmology 1996;103:1139-43) may have implications for the correction of minor degrees of anisometropia in children. When unilateral myopia, hyperopia, or astigmatism was induced by wearing appropriate lenses the volunteers showed significant deterioration in binocular function and a suppression zone (scotoma) appeared in the ametropic eye. Significant loss of stereoscopic vision occurred with small (1 dioptre) degrees of anisometropia. It may be necessary to correct even small differences of visual acuity between the two eyes in children in order to preserve full binocular vision.

Experiments on the sciatic nerve of a toad may result in improved hearing for cochlear transplant recipients (Nature Medicine 1996;2:928-32 and 860-2). Adding background noise to the system improved the nerve response to vowel sounds as delivered to the nerve through a cochlear implant device. Improving the information content of systems by adding random ‘noise’ is called stochastic resonance (Greek, stochastikos, a guess or conjecture, applied to randomness) and the mathematical theory involved was first applied to climatology.

About one in 20 children presenting to a skin clinic in Italy with nappy rash had characteristic dry, glazed, papyraceous, brown skin largely confined to the inguinal and gluteal skin folds (Dermatology 1996;193:36-40). Personal or family atopy was common. The usually upper class parents had changed the nappies frequently and washed the skin with acidic liquid detergent. Less frequent nappy changes, stopping detergent washes and zinc oxide preparations, and substituting oil based detergents and emollient creams produced resolution within two weeks.

Twenty two American children aged 3-14 years had marrow transplants from sibling donors for severe sickle cell disease (New England Journal of Medicine 1996;335:369-76). One to four years later 15 of them were cured. Two died, one from intracranial bleeding and one from graft-versus-host disease, and four others had graft rejection or late graft failure. One had no symptoms 18 months after transplantation but had mixed chimerism with 30% haemoglobin S.

Studies in AIDS patients may provide answers to the treatment of atypical mycobacterial infections. An American study of adults with AIDS and Mycobacterium avium bacteremia (New England Journal of Medicine 1996;335:377-83) showed a combination of rifabutin, ethambutol, and clarithromycin to be better than four drug treatment with rifampicin, ethambutol, clofazimine, and ciprofloxacin.

A study of 141 young people aged 12–16 years who had had neonatal intensive care in Ontario, Canada after being born weighing less than 1000 g (Journal of the American Medical Association 1996;276:453-9) has shown that most of them rated their health related quality of life (HRQL) highly despite a 27% rate of neurological impairment. Some 71% of the extremely low birthweight survivors and 73% of controls rated their quality of life at 95% of maximum or higher. Mean HRQL scores were 87% for extremely low birthweight subjects and 93% for controls.

A financially driven move in the USA towards outpatient tonsil and adenoid surgery makes it important to define those children for whom it is safe. At the Cincinnati Children’s Hospital (Archives of Otolaryngology - Head and Neck Surgery 1996;122:811–4) the following criteria are taken to indicate overnight stay or postponement of operation: upper respiratory infection within four weeks, age under 3 years, significant associated medical conditions (such as neuromuscular problems or chromosomal anomalies), and a history of airway obstruction (breathing difficulty in sleep, restlessness in sleep, or loud snoring with apnoea). Children who do not snore seem to be at low risk of postoperative airway problems.

Prolonged lactation necessitates maternal calcium mobilisation and over six months there is about 5% loss in bone mineral density but the mechanisms controlling the mother’s calcium turnover during this time are unclear. Raised prolactin concentrations may lead to relative hypostrogenism with consequent bone mineral loss but data from the USA (Journal of the American Medical Association 1996;276:549-54) suggest an important role for parathyroid hormone related peptide (PTHrP). This substance, first identified in patients with hypercalcaemia of malignancy, may be produced in response to hypothalamic oxytocin and prolactin. Its exact role in controlling bone loss during lactation, and subsequent recovery, remains to be clarified.

The 11 year old children of mothers who in the early 1980s ate Lake Michigan fish contaminated with polychlorinated biphenyls had decreased full scale IQs and problems with memory, reading, and attention (New England Journal of Medicine 1996;335:783-9). These compounds have been banned as insulating materials in transformers and capacitors for 20 years but they are still around and may contaminate dairy foods and fatty meats as well as fish.