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 on 'Reye's syndrome revisited', Leuven, 3 May 1996).

However, as there is a wide spectrum of differential diagnoses in patients meeting the diagnostic criteria, classifying them now in two groups, the 'Reye syndrome' 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' for 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 consequence of infection (influenza and cytomegalovirus respectively) together with extrapyramidal reactions after antiemetics.5

Either one can conclude that the scoring system is not a valid one to differentiate 'non-classical' (low scorers) from 'classical Reye's syndrome' (high scorers). Or one can also assume that high scorers defined by the authors as those with 'onset in mid to late childhood; peak in winter months; influenza-like or extrapyramidal features presenting before change in conscious level' are the ones who most likely have been antiemetics and are indeed the patients with 'classical Reye's syndrome'. This would be a major argument for our hypothesis supported by the data from the Food and Drug Administration—as to the role of the side effects of antiemetics in the report of this syndrome in 1963 (temporal relation with the marketing of the phenothiazines-antiemetics) and for its boom in the seventies.6 7

Later on, once the extrapyramidal reactions and the malignant neuroleptic syndrome got well known, they contributed to the decline of Reye's syndrome as they were no longer mis-diagnosed as 'Reye's syndrome'.8

The agreement on the heterogeneous nature of Reye's syndrome is the crux of the whole discussion. Logically, it implies that the hypothesis of the epidemiological surveys suggesting a link between Reye's syndrome and aspirin is not valid, as the case subjects of these surveys.9

As to the decline, may we draw attention to the erroneous referral to our publications: we never attributed this decline of Reye's syndrome solely to a correct identification of 'Reye-like' inherited metabolic disorders. We mentioned clearly that the apparent decline of 'Reye's syndrome' can be explained by 'an increased recognition of metabolic, viral or toxic diseases'.10

The increase of a more precise diagnosis also proved by the authors' own data, which show a steady rise of revised diagnoses from 18.9% in 1982 to 43.8% in 1990.11

The authors of this letter have no ongoing affiliation or history, or a low Reye score, to any pharmaceutical company nor with any other entity with a financial interest in the subject matter.

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Dr Hall and coauthors comment:

Dr Casteels-Van Daele et al misinterpret our paper and others' publications.

We clearly stated that 'Reye-like' includes not only certain inherited metabolic disorders but also anonspecific one. 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 some enzyme defects undoubtedly remain undiscovered, 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.12 They criticise the non-specificity of our high scoring category and that of the case definition used in the case-control studies even though the 'dilutional' effect of including non-cases strengthens the aspirin association. Our Reye score is new, reflects the limitations of data from national voluntary surveillance systems, but also as 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 antiemetic toxicity should have been made at presentation.

We have no evidence that the highest scorers were those most likely to have received antiemetics. The authors' hypothesis about their role in Reye's syndrome has been criticised13; 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.

Finally, 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 Orlofsky, 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-dysmorphic' patients. The authors concluded that fluosence 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 phenotypic evaluation. Particular attention was paid to minor dysmorphic features associated with DiGeorge/velocardiofacial syndrome, including laterality displacements, narrow upslanting palpebral fissures, prominent nose with hypoplastic nares, small mouth, dysmorphic ears, and slender fingers. Standard karyotyping and fluorescence in situ hybridisation were 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 with one or more syndromic CTHD as isolated were subsequently included in the group of syndromic cases, because of the presence of subtle dysmorphic features 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 dysmorphic evoking features of DiGeorge or velocardiofacial syndromes.4 5 These dysmorphic features are usually recognised, but their presence can be associated with a high prevalence of del22q11.6 A precise phenotypical analysis and clinical work up are essential to...
A negative association between Down's syndrome and neuroblastoma

**EDITORS.—**Only one ganglieneuroma and a poorly documented case of neuroblastoma associated with Down's syndrome have ever been reported in patients with deletion 22q11 microdeletions in tetrylogy of Fallot. **Arch Dis Child** 1994;69:622.


A study of bereavement care after a sudden and unexpected death

**EDITORS.—**Dent et al state that no studies have concentrated on parents' perception of standards of bereavement care in sudden death. In 1986 **J Med Genet** reported the findings in 10 families who had experienced a sudden infant death who were visited at home by a social worker. 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 service, 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 immedi- ately. 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 helpful, was sympathetic, honest, and informative. Good procedures can avoid short term 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. Only three of 18 families who
distinguish syndromic 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 syndromic 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 patients. In order to obtain rates 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**

### Table 1 Clinical and molecular findings in our series of patients with CTHDs

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**Abbreviations:** del22, microdeletion 22q11; DG, DiGeorge syndrome; DORV, double outlet right ventricle; IAA, interrupted aortic arch; PA, pulmonary atresia; TA, truncus arteriosus; TF, tetrylogy of Fallot; TGA, transposition of the great arteries; VCF, velocardiofacial syndrome.
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
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Jenner, romanticism, and research

EDITOR,—I read the annotation ‘Jenner, romanticism, and research’ and I note that Chiswick gives all the credit of this immunisation discovery to Jenner. Yet Reeves and Todd in their book Lecture Notes on Immunology describe how a kind of smallpox immunisation 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.

Department of Paediatrics,
University College Dublin Ireland

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, 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.

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### MEETINGS IN 1997

**Neonatal Society**
6 March, London
20–21 June, Edinburgh
30 October, London
*Further details:* Dr Neena Modi, Department of Paediatrics and Neonatal Medicine, Royal Postgraduate Medical School, Hammersmith Hospital, Du Cane Road, London W12 0NN (for London meetings) or Professor Neil McIntosh, Department of Child Life and Health, 20 Sylvan Place, Edinburgh EH9 1UW (for Edinburgh meeting)

**Paediatric Palliative Care Conference**
14 March, Edinburgh
*Further details:* Index Communications Meetings Services, Crown House, 28 Winchester Road, Romsey, Hampshire SO51 8AA

**Paediatric Research Society**
14–15 March, Norwich
12–13 September, London
*Further details:* Dr Alistair Thomson, Leighton Hospital, Middletich Road, Crewe, Cheshire CW1 4QT

**International Paediatric Respiratory Congress**
16–19 March, Sydney, Australia
*Further details:* Congress Manager, GPO Box 2609, Sydney, NSW 2001, Australia

**Spectrum of Developmental Disabilities M IX: Mental Retardation and Associated Deficit**
17–19 March, Baltimore, USA
*Further details:* Office of Continuing Medical Education, Johns Hopkins Medical Institutions, Turner Building 20, 720 Rutland Avenue, Baltimore, MD 21205-2195, USA

**9th Asian Congress of Paediatrics: Paediatric Priorities in the 21st Century**
23–27 March, Hong Kong
*Further details:* Congress Secretariat, Meeting Planners (HK) Ltd, 12A Dai Fat Street, Tai Po Industrial Estate, Tai Po, NT, Hong Kong

**Clinical Genetics Society**
25 March, London
*Further details:* Dr Peter Farndon, Clinical Genetics Unit, Birmingham Women’s Hospital, Edgbaston, Birmingham B15 2TG

**XVIIth Course of Paediatric Dermatology**
1–4 April, Arcachon, France
*Further details:* Professor A Taieb, Unite de Dermatologies Pediatrique, Hopital Pellegrin-Enfants, 33076 Bordeaux, France

**Consensus Conference on Anti-D Prophylaxis**
8–9 April, Edinburgh
*Further details:* Education, Audit and Research Department, Royal College of Physicians, 9 Queen Street, Edinburgh EH2 1JQ

**25th Annual Pediatric Trends**
14–19 April, Baltimore, USA
*Further details:* Office of Continuing Medical Education, Johns Hopkins Medical Institutions, Turner Building 20, 720 Rutland Avenue, Baltimore, MD 21205-2195, USA

**Royal College of Paediatrics and Child Health Annual Meeting**
15–18 April, York
*Further details:* Miss Rosalind Topping, Royal College of Paediatrics and Child Health, 5 St Andrews Place, Regent’s Park, London NWI 4LJ

**Second European Forum on Quality Improvement in Health Care**
24–26 April, Paris, France
*Further details:* BMA Conference Unit, PO Box 295, London WC1H 9TE

**Complex Hydrocephalus and Hydrocephalus Complications**
27–30 April, Assisi, Italy
*Further details:* PTS Congress, Via Pietro Tacchini, 19, 00197 Rome, Italy

**Pediatric Allergy and Immunology for the Practitioner**
8–9 May, Baltimore, USA
*Further details:* Office of Continuing Medical Education, Johns Hopkins Medical Institutions, Turner Building 20, 720 Rutland Avenue, Baltimore, MD 21205-2195, USA

**XVI Congress of the European Society for Paediatric Haematology and Immunology**
14–17 May, Thessaloniki, Greece
*Further details:* Congress Secretariat, 4 Filidionn Street, 105 57 Athens, Greece

**30th Annual Advances and Controversies in Clinical Paediatrics**
15–17 May, San Francisco, USA
*Further details:* University of California, Office of Continuing Medical Education, 1855 Folsom Street, MCB-630, Box 0742, San Francisco, CA 94143-0742, USA

**12th Annual Meeting of the German Society for Paediatric Gastroenterology and Nutrition**
15–17 May, Kloster Irsee bei Kaufbeuren/Allgäu, Germany
*Further details:* Congress Organisation C Schäfer, Karl-Theodor-Str 64, 80803 München, Germany (please note that the congress language is German)

**VIII Annual Congress of the European Society of Pediatric Allergy and Clinical Immunology (ESPCAI) and the II Iberian Meeting of Pediatric Allergy and Clinical Immunology**
17–20 May, Lisbon, Portugal
*Further details:* Congress Secretariat, AV Barbosa do Boscage, 87-2º-1050 Lisbon, Portugal

**Advanced Pediatric Life Support**
9–11 June, Baltimore, USA
*Further details:* Office of Continuing Medical Education, Johns Hopkins Medical Institution, Turner Building 20, 720 Rutland Avenue, Baltimore, MD 21205-2195, USA

**Society for Research into Hydrocephalus and Spina Bifida**
2–5 July, Manchester
*Further details:* Miss CA Sobkowiak, Child Development Centre, Darlington Memorial Hospital, Hollyhurst Road, Darlington, Co Durham DL3 6HX

**Pediatrics in the Community—2000+**
6–10 July, Jerusalem, Israel
*Further details:* ISAS International Seminars, PO Box 34001, Jerusalem 91340, Israel

**8th International Congress on Cleft Palate and Related Craniofacial Anomalies**
7–12 September, Singapore
*Further details:* Congress Secretariat, Academy of Medicine, Singapore, College of Medicine Building, 16 College Road 1-01, Singapore 0316

**British Human Genetics Conference**
15–17 September, York
*Further details:* Dr Peter Farndon, Clinical Genetics Unit, Birmingham Women’s Hospital, Edgbaston, Birmingham B15 2TG

**British Association of Perinatal Medicine**
18–19 September, London
*Further details:* Dr PA Hamilton, Department of Child Health, Lanesborough Wing, St George’s Hospital, Tooting, London SW17 0RE

**Pediatries for the Practitioner Update ’97**
18–19 September, Baltimore, USA
*Further details:* Office of Continuing Medical Education, Johns Hopkins Medical Institutions, Turner Building 20, 720 Rutland Avenue, Baltimore, MD 21205-2195, USA

**European Respiratory Society Annual Congress**
20–24 September, Berlin, Germany
*Further details:* ERS, 1 Boulevard de Grancy, CH-1006 Lausanne, Switzerland

**6th Congress of the European Society for Gynaecological Endoscopy**
7–10 December, Birmingham
*Further details:* ESGE 97 Secretariat, Congress House, 65 West Drive, Cheam, Sutton, Surrey SM2 7NB
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, papery, 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 rifampin, 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, restless 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 hypoestrogenism 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.