National Reyes Syndrome Foundation UK

TRUSTEES REPORT
EXTRACTS – 30th September 1994

Significant events

1. Enzymological Studies into the aetiology of Reye's Syndrome

The first phase of the project "Enzymological studies into the aetiology of Reye's syndrome – the role of aspirin" was virtually completed. This project is being undertaken at the Queen's University, Belfast under the direction of Dr John Glasgow. The aim of the study is to investigate the relationship between Reye's syndrome, aspirin ingestion and disturbances to the intra-mitochondrial beta-oxidation.

Shortly after the end of the year, the trustees received a detailed report from the senior research officer, Mr Raymond Moore, regarding the first phase of the project extending over a period of three years, which set out details of earlier problems that the study had encountered relating to staff etc. (the subject of earlier interim reports). The report also confirmed that the methodology regarding the development of assays had run into difficulties but stated that during 1994 the researchers had been fortunate to receive technical assistance from Dr Bruce Middleton of the Queen's Medical Centre, Nottingham who had helped to resolve the problems.

In summary, the report indicated that the project had turned out to be much larger than appreciated initially. As a result of these problems, quite apart from the funding of £50,000 over 3 years made by the Foundation, it had been necessary for the University to inject funds from other sources to keep the project afloat. Dr Glasgow and Mr Raymond Moore are confident that the major difficulties are behind them and that consistent progress can now be made with the study.

2. The incidence of Medium Chain Acyl-CoA Dehydrogenase Deficiency and Feasibility of Population Screening

The pilot-study into the incidence of medium chain Acyl-CoA dehydrogenase (MCAD) Deficiency and Feasibility of Population Screening" was largely completed during the year under review. The results were the subject of a report by Helen Seddon et al, a biochemist at Birmingham Children's Hospital where the project was undertaken. The study had sought to establish and evaluate a methodology suitable for the processing of a large number of specimens and additionally to provide a reliable estimate of the incidence of MCAD deficiency in the Trent and West Midlands Health Regions by screening approximately 10,000 neonatal bloodspot specimens. In the event a total of 10,171 dried blood spot specimens (5,157 from the Trent region and 5,014 from the West Midlands region) were analysed.

From the information acquired, the researchers had calculated the average number of cases of MCAD deficiency they would have expected to have diagnosed over a 5 year period ie 19 cases in Trent and 35 in the West Midlands. In the latter region, there appears to be a significant under diagnosis of MCAD deficiency as they were only aware of 6 cases. The report states that several explanations could account for this shortfall. MCAD deficiency is known to present in different ways with some individuals remaining symptom free and others suffering acute life threatening episodes. The report concluded by suggesting to the trustees two possible lines of action for the future.

3. Reye's Syndrome in Adults – funding.

The trustees had been giving careful consideration to the funding of an additional project "Reye's Syndrome in Adults"

(Note: in the event the Board of Trustees at their meeting on 2nd November 1994 agreed to enter new research commitments concerning projects 1, 2 and 3 above, amounting to £90,200 over the next two years).

4. Reye's Syndrome Surveillance for the 12 years ended 1992/93

Dr Michael Catchpole and Ms Lisa Newton of the PHLS Communicable Disease Surveillance Centre (CDSC) in their statement to the British Paediatric Surveillance Unit (BPSU) provided a table headed 'Reye's syndrome surveillance 1981/82 – 1992/93' ie for a twelve year period (August through to July) which contained inter-alia the following information:-

Total reports from the British Isles	**539**
Revised diagnosis	**131**
Cases of Reye's syndrome	**401**
Number of deaths	**210**

During 1993/94 there have been a further 15 notifications of Reye's syndrome and Reye-like illnesses. At the date of this report further information had been received in respect of 12 of these cases, and 5 patients had their diagnosis revised. The total number of reports to the surveillance scheme continued to fall in the year under review, with the lowest annual reported incidence of Reye's syndrome since surveillance began.

Reye's syndrome has been included on the BPSU report (orange) card since it was established in June 1986; MCAD was included for the first time with effect from March 1994.

National Reyes Syndrome Foundation UK

APPENDIX
BRITISH PAEDIATRIC SURVEILLANCE UNIT
8th ANNUAL REPORT

Reye's syndrome

Background

Surveillance of Reye's syndrome began in August 1981 as a venture shared between the BPA and the Communicable Disease Surveillance Centre (CDSC). Responsibility for case ascertainment transferred to the BPSU in June 1986. In the early years, the results of surveillance showed that the incidence of Reye's syndrome in the British Isles was similar to that in the United States but cases occurred at a younger mean age; there was no clear seasonal (winter) peak, no obvious striking association with influenza and chickenpox, and a higher case fatality rate.

In 1984/85 a study of risk factors mounted on to the surveillance database showed an association between Reye's syndrome and consumption of aspirin. In response to this and similar findings in the United States, the Committee on Safety of Medicines issued public and professional warnings in 1986 about the use of aspirin in children under 12. Subsequently products that contain aspirin are required to carry warning labels.

Objectives:

To describe the epidemiological and clinical features of Reye's syndrome in the British Isles, to monitor long term trends, and to provide a database for detailed clinical, laboratory, and aetiological studies.

Case definition:

A child under 16 years old with:

a) unexplained non-inflammatory encephalopathy, *and one or more of:*

b) serum hepatic transaminases elevated to at least three times the upper limit of normal;

c) blood ammonia elevated to at least three times the upper limit of normal;

d) characteristic fatty infiltration of liver (biopsy or autopsy)

Study duration:-

This study began in June 1986; an end date has yet to be determined.

Analysis:

Between August 1981 and July 1993 a total of 539 cases of Reye's syndrome were reported to the surveillance scheme, but the diagnosis was subsequently revised in 131 cases (24%). Trends in annual totals are shown in the *table below.* Eighteen reports were received in the year to July 1993, 16 of which had been followed up at the time of writing. Of these, the diagnosis in 10 had been subsequently revised and one other case did not meet the case definition.

Confirmed cases:-

Confirmed cases; year to July 1993: Two of the five cases were males and three were female. Their ages ranged from 5.2 months to 12.6 years (mean, 43 months; standard deviation 61.2; median 24.7 months). All cases lived in England and no seasonal distribution could be discerned because of the small number of cases. Two cases survived with no sequelae reported and two died, giving a case fatality rate of 40%, identical to that seen in 1991/92. One child survived with sequelae, but no details were given.

Three children were reported to have received medication before admission to hospital: one had received paracetamol; one cough mixture of unknown brand; and a 12 year old patient had been treated with "Disprin" for flu-like symptoms over a period of three days. Two children had past medical histories, but in neither case were the events compatible with an underlying metabolic disorder. One patient had a significant family history; a cousin who had died of an illness similar to Reye's syndrome in infancy/childhood.

Specific investigations for inherited metabolic disorders were undertaken in four of the five cases. Plasma amino acids, urine amino acids, and urine organic acids were assayed in three patients, urine orotic acids were measured in two; in one case a series of investigations were reported to be negative two months after admission, but no details of the investigation were given.

Revised diagnosis cases:

***Six* of the ten cases whose diagnosis was subsequently revised were reported to have inherited metabolic disorders. Three cases had a possible fatty acid oxidation disorder, including twins diagnosed with a possible medium chain acyl CoA dehydrogenase deficiency (MCAD); one with an ornithine transcarbamylase deficiency (OTC); one with a disorder of the fructose pathway; and one with an unspecified inherited metabolic disorder. Mean and median ages of these patients were older than those reported in the previous year; mean 57.5 months; standard deviation 36.1; median 41.5 months (compared with mean 24.9 months; standard deviation 35.0 median 13.6 months in 1991/92). The four remaining cases were diagnosed, respectively as Alpers disease, encephalopathy of unknown cause, overwhelming viral infection (organism not known), and sudden infant death syndrome.**

Comment:

The total number of reports to the surveillance scheme fell in the year to July 1993, with the lowest annual reported incidence of Reye's syndrome since surveillance began and a marked increase in the proportion of cases whose diagnosis was revised subsequently (*Table below*). It is difficult to draw conclusions from such small numbers of cases, but the decline probably represents increasing awareness among paediatricians of inherited metabolic disorders in infants who present with an illness like Reye's syndrome. The gradual increase in the median age of cases from nine months in 1989/90 and 16.5 months in 1991 to 24.7 months in 1992/93 supports this explanation. Young patients are now more likely to be investigated for inherited metabolic disorders and an alternative diagnosis made. The increase in the median age of cases whose diagnosis was subsequently revised to a metabolic disorder may suggest that paediatricians are also investigating older children for inherited metabolic disease.

It was encouraging that no cases under 12 years had been exposed to aspirin before admission to hospital, although one 12 year old who subsequently died was treated with aspirin before admission.

It seems likely that small numbers of cases will continue to be reported. Six of the eight reports received by May 1994 have been followed up, of which one patient's diagnosis has been revised.

Dr M Catchpole, Ms L Newton
PHLS Communicable Disease Surveillance Centre

Table ***Reye's syndrome surveillance 1981/82 – 1992/93***

Reporting years (August – July)	Total reports from the British Isles	Revised diagnosis	Cases of Reye's syndrome	Number of Deaths (case fatality rate)
1981/82	47	7	40	26 (65)
1982/83	69	10	59	33 (56)
1983/84	93	12	81	36 (44)
1984/85	64	8	56	32 (57)
1985/86	53	13	40	22 (55)
1986/87	47	21	26	13 (50)
1987/88	44	12	32	19 (59)
1988/89	31+	12	18	9 (50)
1989/90	24+	8	15	7 (47)
1990/91	25	12	13	5 (38)
1991/92	24*	6	16	6 (40)
1992/93	18**	10	5	2 (40)
TOTAL	539	131	401	210 (52)

\+ Detailed information not available for one case

* Follow up not received for two cases

** Follow up not received for two cases and one case did not meet the case definition