National Reyes Syndrome Foundation UK

TRUSTEES REPORT
EXTRACTS FROM – YEAR ENDED 30th SEPTEMBER 1995

Significant events

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

The following is based on a report of Dr John Glasgow

The second phase of the project "Enzymological studies into the aetiology of Reye's syndrome - the role of aspirin" began in January 1995. The 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 intra-mitochondrial beta oxidation.

Dr Glasgow has informed us that the primary phase of the project was completed by December 1994. This included setting up in the laboratory, and then validating, methods for the measurement of the activity of key enzymes in the pathway of mitochondrial beta oxidation. This pathway has to do with the provision of energy inside body cells. There is much evidence which indicates that in Reye's syndrome beta oxidation fails with devastating effects both in the liver and the brain.

These methods are being applied, developed using semi-purified enzyme solutions, to actual preparations from human fibroblasts. These were taken as tiny biopsies from the skin of surviving children who have had the syndrome, and controls. Such cells contain the enzymes in which there is particular interest. The work of growing sufficient cells for the assays and the assays themselves is both intricate and time consuming.

A variety of hypotheses have been proposed as to the way ASA (aspirin) might interfere with the series of enzymatic steps in beta oxidation. These are now being tested within the laboratory.

So far results of experiments indicate that there may be a biochemical explanation for the statistical correlation between ASA ingestion and Reye's syndrome. However, much work remains to be carried out using both semi-purified enzyme preparations and human fibroblasts.

The ongoing experiments are being carried out in collaboration with Dr. Bruce Middleton, Department of Biochemistry, The Medical School, Nottingham, who was formally invited to join this project at the commencement of this new phase.

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2. Regional Variations in Medium-Chain Acyl-CoA Dehydrogenase Deficiency (MCAD)

The results of the study into Regional variations in medium-chain Acyl-CoA dehydrogenase deficiency (MCAD), funded by the Foundation, was undertaken by:-

Department of Clinical Chemistry, West Midlands Regional Laboratory for Inherited Metabolic Disease, Children's Hospital Birmingham

Institute of Child Health, London and

Neonatal Screening Laboratory, Children's Hospital, Sheffield

were published in The Lancet on 14 January 1995.

It is the intention to publish the technical details of assessment of the Delphia method for the detection of the G 985 mutation in neonatal blood spots.

3. Surveillance of Adult Reye's Syndrome

A surveillance scheme for adult Reye's syndrome in the UK commenced during the year. The two areas of concern which prompted the study were firstly that adult Reye's syndrome (including those Reye-like inherited metabolic diseases which mimic it) is under-recognised in the UK and secondly that, if adult Reye's syndrome is occurring, an opportunity for primary prevention may be being missed if, like paediatric cases, it is associated with aspirin. The survey is based at Sheffield Children's Hospital. The first year's work largely consists of setting up collaborations with appropriate adult specialities and their professional organisations, in order to develop a rapid and sensitive reporting scheme and to raise diagnostic awareness. Collaborations organised so far are with neurologists, intensivists and pathologists.

4. Communicable Disease Surveillance Centre – Restructuring

The trustees received a letter from Dr Michael Catchpole of the Public Health Laboratory Service, stating that the Communicable Disease Surveillance Centre (CDSC) is withdrawing from the surveillance of paediatric Reye's syndrome before 31st March 1996. The letter continues "this difficult decision has been made as part of the process of restructuring within CDSC consequent upon a reduction in core funding from the Department of Health. The CDSC and the PHLS as a whole, has to make savings in excess of 10%. For CDSC this has meant a reduction of surveillance activity for several diseases, and the withdrawal of all activity for a smaller number of diseases, including Reye's syndrome."

5. Surveillance of Reye's Syndrome

The trustees received a letter from Dr Susan Hall of Sheffield Children's Hospital giving reasons why it is unwise to discontinue surveillance of a condition of significant public health importance on the grounds of a sustained low incidence following a preventive intervention. The trustees were advised initially that the cost of surveillance could be found from the adult Reye's syndrome scheme. Thereafter the annual cost would amount to some £3,000 per annum. The trustees have taken due note of Dr Susan Hall's remarks and will shortly give consideration as to whether they are prepared to take on a long term commitment regarding surveillance of Reye's syndrome.

6. Reye's Syndrome Surveillance for the 13 years ended 1993/94

Dr Michael Catchpole and Ms Lisa Newton of the PHLS Communicable Disease Surveillance Centre (CDSC) in their statement to the British Paediatric Association Surveillance Unit (BPASU) provided a table headed "Reye's syndrome surveillance 1981/82 – 1993/94" for a thirteen year period (August through to July) which contained inter-alia the following information:-

Total reports from the British Isles	**554**	
Revised diagnosis	**136**	
Cases of Reye's syndrome	**404**	
Number of deaths	**210**	**(for table see Appendix)**

During 1994/95 there have been a further 17 notifications of Reye's syndrome and Reye-like illnesses (subject to confirmation). The trustees note that the total number of reports from the British Isles to the surveillance scheme reached a peak of 93 in 1983/84 but since then the number of reports has consistently fallen each year until 1993/94 when the number of reported cases totalled 14. It is therefore a matter of regret that the number of notifications for 1994/95 show a slight increase compared with the previous year. The BPASU in conjunction with Dr Susan Hall is now undertaking the scientific administration of the study.

7. European Aspirin Foundation's International Symposium – 30th June 1995

A number of members of the Foundation's Medical and Scientific Advisory Board took part in the proceedings of the European Aspirin Foundation's International Symposium on the "Paediatric Use of Aspirin" held in London on 30th June 1995. The conference chaired by Professor Neil McIntosh (Professor of Child Health, Edinburgh) focused particularly on the subject of Reye's syndrome and the use of aspirin. The Hon Administrator and his wife attended as observers. A report, summarising the presentations and subsequent discussion, has been prepared for the trustees by Dr Susan Hall.

8. Professor Alex Mowat

Since the preparation of this report the trustees have learned with sadness of the sudden death of Professor Alex Mowat on 11th November 1995 whilst on a lecture tour in Santiago, Chile. It is typical of Alex that he was working right to the end. His co-trustees wish to place on record that as Chairman of the Medical and Scientific Advisory Board, Professor Mowat could always be relied upon to give helpful advice and encouragement, not only at the time of the establishment of the Charity but throughout the twelve years of the Foundation's existence. Notwithstanding his commitments he has made a very significant contribution to the work of the Charity and he will be sadly missed. To his wife Ann the trustees offer their sincere sympathy.

National Reyes Syndrome Foundation UK

APPENDIX
BRITISH PAEDIATRIC ASSOCIATION SURVEILLANCE UNIT
9th ANNUAL REPORT

Reye's Syndrome

Background

Surveillance of Reye's syndrome began in August 1981 as a venture shared between the BPA and CDSC. Responsibility for case ascertainment was transferred to the surveillance unit 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 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 years. Since then, products that contain aspirin have been required to carry warning labels.

In 1991 the surveillance questionnaire was modified to collect further information about inherited metabolic disorders, because of concern that these disorders may be under recognised. Data on the past medical history of the child, family history, and specific investigations for inherited metabolic disorders were collected over a two year period. A new simplified questionnaire was introduced at the beginning of August 1993.

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:

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

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

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

* **characteristic fatty infiltration of liver (biopsy or autopsy).**

Study duration

This study began in June 1986 and is due to end in July 1996.

Analysis

Between August 1981 and July 1994 a total of 554 suspected cases of Reye's syndrome were reported to the surveillance scheme but diagnosis was subsequently revised in 136 cases (25%). Over half (64%) of the revisions were to one of the inherited metabolic disorders. In the year to July 1994, 15 reports were received and follow up was complete on 12 at the time of writing. Five of the 12 diagnoses had been subsequently revised, two cases did not meet the case definition, clarification of necropsy results were awaited on another, in one case the diagnosis was indeterminate, and in one report the onset of illness was before August 1993 and the case was allocated to the surveillance year 1992/93. Two cases were confirmed.

Confirmed cases year to July 1994

Both cases were male and aged 3.$^{1/2}$ months and 5.$^{1/2}$ months respectively. One child lived in England, the other in Wales. One became ill in June, the other in November. One infant survived the sequelae, although no specific details were given. The outcome of the other case was unclear when the questionnaire was completed. One case had received paracetamol and amoxycillin for prodromal flu-like symptoms and gastroenteritis before admission. Both infants were investigated for inherited metabolic disorders. Details of specific investigations were not given. No abnormal results were reported.

Revised diagnosis cases

Three of the five cases were reported to have an inherited metabolic disorder: one had a possible defect of fatty acid oxidation, one possible fructose intolerance, and the third had a probable, but unspecified, inherited metabolic disorder. The ages of these three patients ranged from 3 weeks to 8.4 years (mean 34.8 months; standard deviation 57.1 months). No definitive diagnoses were made in the remaining two cases, but liver biopsy or necropsy results were considered to be inconsistent with Reye's syndrome.

Comment

The annual totals of reports to the surveillance system and confirmed cases of Reye's syndrome have fallen steadily since the peak of 93 reports (81 cases) in 1983/84. Between 1988/89 and 1991/92 the annual incidence remained moderately stable (*table below*). In the past two years, however, total reports to the scheme have declined and the annual total cases of Reye's syndrome has fallen dramatically. Several factors may have contributed to these trends. Paediatricians have become more aware of inherited metabolic disorders in young children and infants. Also they are more aware of the difficulty of diagnosing Reye's syndrome in children under 5 years, because of the many disorders that mimic the syndrome in this age group. Infants reported to the scheme are likely to be more thoroughly investigated and perhaps have their diagnoses subsequently revised than was the case in earlier years. In addition, the public and professionals have been warned about the use of aspirin in children under12 years. These factors do not appear however, to account for the fall in confirmed cases of Reye's syndrome in the two most recent surveillance years.

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In an analysis of 10 years of reports to the surveillance scheme, medium chain acyl-CoA dehydrogenase deficiency (MCAD) was the inherited metabolic disorder most commonly identified in children who presented with an illness like Reye's syndrome. (Reference 1 below). It may be that some cases that had previously been reported as suspected Reye's syndrome have more recently been reported to the BPASU as suspected MCAD. It is proposed that cases reported as suspected MCAD whose diagnoses are subsequently revised should be reviewed for evidence of Reye's syndrome.

Reference

1. **Newton L, Hall SM. Reye's syndrome in the British Isles: report for 1990/91 and the first decade of surveillance.** ***Communicable Disease Report 1993;*** **3:R11-6.**

Dr M Catchpole
Ms L Newton
PHLS Communicable Disease Surveillance Centre

Table ***Reye's syndrome surveillance 1981/82-1993/94***

Reporting period (August-July)	Total reports	Revised diagnoses (inherited metabolic disorder)		Number of cases	Number of deaths (case fatality rate)	
1981/82	47	7	(3)	40	26	(65)
1982'83	69	10	(6)	59	33	(56)
1983/84	93	12	(3)	81	36	(44)
1984/85	64	8	(2)	56	32	(57)
1985/86	53	13	(4)	40	22	(55)
1986/87	47	21	(11)	26	13	(50)
1987/88	44	12	(3)	32	19	(59)
1988/89	31*	12	(6)	18	9	(50)
1989/90	24*	8	(5)	15	7	(47)
1990/91	25	12	(7)	13	5	(38)
1991/92	24+	6	(5)	16	6	(38)
1992/93	19**	10	(6)	6	2	(33)
1993/94	14++	5	(3)	2	0	(-)
	554	136	(64)	404	210	(52)

* Detailed information not available for 1 case + Follow up not yet received for 2 cases. **F Follow up not received for 2 cases and 1 case did not meet the case definition. ++ Follow up not received for 3 cases; a further2 did not meet the case definition ; 1 case was allocated to 1992/93; detailed information unavailable for 2 cases.