



**TRUSTEES REPORT
EXTRACTS – 30 SEPTEMBER 1997**

Significant events

1. Studies on the role of Aspirin in the pathogenesis of Reye's Syndrome

The following is a report of Dr. John Glasgow:

The Research Team based at the Department of Child Health, The Queen's University of Belfast, has continued to work fruitfully with Dr Bruce Middleton, Department of Biochemistry, University of Nottingham.

In the past year we have confirmed previous finding of demonstrable inhibition of mitochondrial beta oxidation in intact skin fibroblasts from two groups of children – those who have recovered from Reye's Syndrome (RS) and controls. Two lines of work have been developed. First, using tritiated palmitate, we have accumulated further data to confirm that there is very significant (50%) concentration related inhibition of the pathway by two of the aspirin metabolites salicylic acid (SA) and hydroxy-hippuric acid (HHA). As reported last year the site of action appears to be the long-chain specific hydroxy acyl-CoA dehydrogenase (HAD) enzyme – a component of the so-called trifunctional enzyme (TFE) which is intimately associated with two other enzymes on the mitochondrial membrane. This is significant because HAD controls the rate of beta oxidation in mitochondria. More recently, work has focused on the mechanism of this inhibition. We used specific assays for long- and short-chain HAD (LCHAD & SCHAD); first, with homogenised fibroblasts from the two groups, and second, with the purified enzymes (human TFE as a source of LCHAD and porcine SCHAD). Human TFE was isolated from human liver specially for these studies.

We found that both LCHAD and SCHAD were inhibited by SA and by HHA. The mechanism – i.e. the kinetics – of the inhibition demonstrated that in RS and in control fibroblasts aspirin metabolites are potent inhibitors of the HAD enzyme, which is the rate-limiting step in beta-oxidation, and that this inhibition is complex and depends upon the target enzyme. Thus, the SCHAD enzyme is inhibited in a reversible fashion by a competitive mechanism (where inhibition decreases as the enzyme substrate accumulates) whereas inhibition of LCHAD, though reversible, is of mixed type. This means that inhibition of LCHAD by aspirin metabolites will occur even when its substrates accumulate, ie its inhibition will remain effective under a range of physiological conditions. It was found for example, that LCHAD activity of fibroblasts was inhibited to 30% if its control value – equivalent to the minimal activity present in patients with complete LCHAD deficiency, a rare condition whose clinical presentation is similar to RS. Although there appears to be little difference in basal LCHAD activity between cells from RS and those from controls, we believe that profound inhibition of beta-oxidation could, in susceptible individuals, contribute to the metabolic encephalopathy of Reye's Syndrome.



1. Studies on the role of aspirin in the pathogenesis of Reye's Syndrome (continued)

The response to aspirin metabolites of the beta oxidation of palmitate by intact skin fibroblasts from controls and RS patients was found to differ. The RS patients cells oxidation was significantly inhibited at low concentrations of salicylate whereas the rate of palmitate oxidation was increased by 20% in controls. The difference in response between RS and controls was not present when homogenised, as opposed to intact cells, were used. This suggests that there is an effect related to the presence of an intact mitochondrial membrane and that the difference shown implies that the response of the mitochondrial membrane in RS may be abnormal. Whether, and to what extent, this distinction or abnormality might account for the susceptibility of certain individuals to develop Reye's Syndrome remains a tantalising question.

A huge amount of detailed and meticulous work largely carried out by Dr Alison Gray has gone into these studies since the last report; Dr Gray can take great pride in what has been achieved during this period. During the previous four years she was most ably assisted by Ms Joanne Hill. Finally, Mr Raymond Moore and myself record our sincere indebtedness to these staff, to Dr Bruce Middleton whose knowledge of mitochondrial enzymology has proved invaluable, and to the National Reye's Syndrome Foundation of the United Kingdom for their generous financial support over a number of years. Finally, I would like also to put on record our thanks to Mr Gordon Denney and Mrs Gillian Denney for their abiding interest and constant encouragement throughout.

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The following is the report of Dr. Susan Hall:

2. Epidemiological surveillance of Reye's Syndrome (RS)

Epidemiological surveillance of RS is an ongoing survey whose principal aims are to monitor trends in the occurrence of the disease, to heighten and maintain diagnostic awareness among clinicians and to provide a resource for further research. Surveillance of RS in children under 16 has been running in collaboration with the Royal College of Paediatrics and Child Health (formerly the British Paediatric Association) since 1981. It played a significant role in identifying aspirin as a casual factor in this disease following which warnings, including product labelling, against its use in children under 12 years of age (except in special circumstances) were instituted in the UK in 1986. Surveillance of any disease for which a major preventive public health intervention has occurred, is essential to evaluate the success of that intervention and to detect any resurgences.

Because of concerns that RS might also be occurring in adults and in teenagers not admitted under the care of a paediatrician, a study was begun in 1995 to determine the most feasible means of monitoring this condition in older patients. Surveillance both of paediatric RS (PRS) and adult (ARS) is funded by the National Reye's Syndrome Foundation. Dr Susan Hall is the medical epidemiologist in charge of both projects and, for the PRS is assisted by Mr Richard Lynn, scientific officer at the British Paediatric Surveillance Unit of the Royal College of Paediatrics and Child Health.



a) Adult Reye's Syndrome Surveillance

The year to September 1997 saw further progress in and consolidation of, the collaborative links previously set up with the Intensive Care National Audit and Research Centre (ICNARC), the Hospital Episode Statistics (HES) Division of the Department of Health and the Office for National Statistics (ONS) and its equivalents in Scotland and Northern Ireland. These are all potential sources of information about cases admitted to hospitals with, or dying of, ARS in the UK.

ICNARC

One of the most important features of this collaboration was the development during the year of two wall posters (one for Intensive Care Units, one for Casualty Departments) which we hope to distribute to hospitals throughout the UK in 1998 in order to raise diagnostic awareness of RS at all ages. One of the problems in ascertaining the 'true' incidence of ARS is that adult physicians are generally unaware that this condition is not confined to children. The aims of the poster (which incidentally also updates the previous poster funded by the NRSF and distributed to paediatric departments nationwide) are:-

- 1) to make clinicians '*Think Reye*' in patients who present with the typical signs and symptoms and, most important, consider the various inherited metabolic disorders (IMD's) which can mimic 'true' RS and which can also manifest for the first time in adulthood;
- 2) to educate them in the most up-to-date methods of investigation and treatment both of RS and of Reye-like IMD's;
- 3) to encourage them to report cases to the surveillance scheme;
- 4) to make them aware of the National Reye's Syndrome Foundation;

The poster has been worded in such a way to make it appropriate for both adult and paediatric departments. Because its content had to be 'state of the art', several drafts were sent for comment to seven national and international experts over the course of the year until a consensus was achieved. This process was lengthy, but a most useful exercise in developing a product of practical value which will benefit patients.

A further step during the year was the development, during meetings with the medical and computing/statistical staff of ICNARC, of a series of diagnostic codes to be used to 'trawl' through ICNARC's Case Mix Programme Database for possible cases of ARS. A follow-up procedure for all cases identified, which would retain ICNARC's commitment to anonymity of their participating ICU's was also agreed. Ascertainment and follow-up cases have since been initiated.



a) Adult Reye's Syndrome Surveillance (continued)

HES

Progress in this collaboration in the year to September 1997 was slow because the HES system itself suffered delays in processing its own data for 1995/96. However, the findings of a preliminary analysis were made available to the RS surveillance scheme at the end of the period. This yielded six cases admitted to hospitals in England and Wales between 1 April 1995 and 31 March 1996 whose discharge diagnosis was coded to the ICD-10 system as RS. Only one was an adult. The data generated many further issues of interest which are currently being pursued with the HES office. The data for 1996/97 was to be available in June 1998.

ONS

There were no deaths ascribed to ARS in the year ending September 1997.

b) Paediatric Reye's Syndrome Surveillance

In their annual report to the British Paediatric Surveillance Unit Dr Hall and Mr Lynn provided a table headed "Reye's syndrome surveillance 1981/82 – 1995/96" for a fifteen year period (August through to July) which contained inter-alia the following information:

Total reports from the British Isles	598	
Revised diagnosis	148	(70 inherited metabolic disorder)
Cases of Reye's syndrome	432	
Number of deaths (of cases)	226	

The narrative states inter-alia that in the year to July 1996, 18 reports of new cases were received and follow up was complete on 17 of these at the time of writing. Two of the 17 diagnoses had subsequently been revised leaving 15 cases whose clinical and pathological features were compatible with Reye's syndrome. All cases except one were reported via the BPSU. One patient was ascertained via a death entry alone. This was an 11 year old male who died suddenly at home. One further case was ascertained via death entry in 1995/96. This was a 14 year old male who had an illness-diagnosed as Reye's syndrome in 1982 at age 5 months; he was not reported to the surveillance scheme at the time. He was left with severe neurological damage and died from bronchopneumonia in 1996.

An important finding of the surveillance scheme was that four cases in 1995/96 had taken aspirin, the highest proportion since the 1986 warning. Moreover, six aspirin-associated cases since 1986 were aged over 12 years. These observations were also conveyed to the Medicines Control Agency in 1997, in the expectations that there might be consideration of the need for further publicity about the dangers of aspirin and reconsideration of the age limit on the current warning. Full details of the PRS surveillance findings are contained in the *BPSU 11th Annual Report* published by the Royal College of Paediatrics and Child Health. (See Appendix below)



3. Medium chain acyl-CoA Dehydrogenase (MCAD) deficiency

A study has been undertaken into MCAD deficiency which commenced in March 1994 and ended in March 1996. *The BPSU 11th Annual Report* provides details and states that the findings of this survey are being prepared for publication. We consider it is sufficient for our report this year to quote from the background information provided about the disease.

MCAD is an inborn error of fatty acid oxidation with a variable presentation. Some patients develop hypoketotic hypoglycaemia or an acute encephalopathy (similar to Reye's syndrome), whereas others may present with hypotonia, hepatic dysfunction, or they remain asymptomatic. The sudden and unexpected death of some cases may be attributed to sudden infant death syndrome.

Studies of the frequency of the common mutation in heterozygotes suggest that MCAD deficiency is relatively common, with birth prevalence of about one in 10,000. It seems, however, that the proportion diagnosed varies greatly, both internationally and from one region of the UK to another. (The Trustees report for 1994/1995 recorded the Foundation had part-funded a study *inter alia* to provide a reliable estimate of the incidence of MCAD deficiency in the Trent and West Midlands Health Regions). In many places less than 50% of the predicted cases are diagnosed clinically. Neonatal screening for MCAD deficiency by tandem mass-spectrometry is a feasible proposition and has been performed on over 80,000 babies in the USA.

4. Information for Aspirin products – EC directive

Following correspondence in the Times newspaper in the latter part of 1996 the Foundation was informed in a letter dated 30 April 1997 from the Medicines Control Agency that:

"The provision of full and accurate information for aspirin products is being met under the requirements of the EC Directive on labelling and package leaflets, in a separate initiative which is currently in progress. The Directive requires comprehensive information for the user in an accompanying package leaflet, or where space permits, on the label. We currently propose that in addition to a label statement on aspirin containing products warning against use in children under 12 except on a doctor's advice, the package leaflets where available will refer to the association of aspirin with Reye's Syndrome. All formulations containing aspirin, including cold and flu remedies as well as analgesics, will be included. At present this exercise for aspirin products is scheduled to be carried out in late 1997".



APPENDIX

BRITISH PAEDIATRIC SURVEILLANCE UNIT EXTRACT FROM 11th ANNUAL REPORT

Reye's syndrome

Background

Surveillance of Reye's syndrome began in August 1981 as a venture shared between the (then) British Paediatric Association and the Public Health Laboratory Service Communicable Disease Surveillance Centre (CDSC). Responsibility for case ascertainment was transferred to the surveillance unit in June 1986 and from CDSC to the Department of Paediatrics at Sheffield in 1995. 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 striking association with influenza and chickenpox (although such cases did occur) 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.

There is increasing recognition that a number of inherited metabolic disorders –most notably those affecting fat oxidation and ureagenesis, may present as a 'Reye-like' illness, clinically and pathologically indistinguishable from Reye's syndrome. The surveillance questionnaire, although currently in its simplest and shortest format since 1981, therefore seeks information on whether patients have been investigated for these disorders.

In addition to BPSU reporting, cases are also ascertained via death entries provided by the Office for National Statistics and by the Northern Ireland Statistics and Research Agency, and via laboratory reports to CDSC.

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).*

Since this case definition is relatively non-specific, cases reported from surveillance year (see *Table below*) 1994/95 onwards, whose diagnosis has not been revised, have been allocated a 'Reye-score.'" (reference 1 below)

Study duration

The BPSU involvement with this study began in June 1986; it has been granted a further one year extension to July 1998.

Analysis

Between August 1981 and July 1996 a total of 598 suspected cases of Reye's syndrome were reported to the surveillance unit (see *table*), but the diagnosis was subsequently revised in 148 cases (25%). Nearly half (47%) of the revisions were to one of the Reye-like inherited metabolic disorders. In the year to July 1996, 18 reports of new cases were received and follow up was complete on 17 of these at time of writing. Two of the 17 diagnoses had subsequently been revised, leaving 15 cases whose clinical and pathological features were compatible with Reye's syndrome. All cases except one were reported via the BPSU. One patient was ascertained via a death entry alone. This was an 11 year old male who died suddenly at home.

One further case was ascertained via death entry in 1995/96. This was a 14 year old male who had an illness diagnosed as Reye's syndrome in 1982 at age 5 months; he was not reported to the surveillance scheme at the time. He was left with severe neurological damage and died from bronchopneumonia in 1996.

Cases compatible with a diagnosis of Reye's syndrome (N=15): year to July 1996

There were eight males and seven females; the ages ranged between three months and 15 years with a median of 38 months. Ten lived in England, three in Scotland and two in the Republic of Ireland. Four were ill between August and November; eight had their onsets between December and March, and three between April and July. All of the eight survivors were reported to have made a full recovery with no neurological sequelae. Of thirteen patients with information on preadmission medication, four had received none; three had received paracetamol alone; two had been given paracetamol and aspirin, one had had aspirin alone; another, aspirin plus inderal; one, an antibiotic and one, a benzodiazepine.

Two patients were reported to have had no prodromal illness; nine had had upper respiratory tract or 'flu-like' symptoms; two had vomiting and diarrhoea and two had had non-specific preadmission symptoms – lethargy with pallor and headache with photophobia. A rota virus was recovered from faeces in one patient, an adenovirus from the nasopharynx of another, and in one patient there was a serological evidence of influenza A infection; none of the others had microbiological confirmation of infection. Eleven patients were reported to have been investigated for inherited metabolic disorders; four (aged 3 months, 27 months and 11 years) had not. The 'Reye Score' (possible range; 1-25) ranged between 6 and 17 with a median of 12 and mean of 12.5.



Revised diagnosis cases (N=2)

One who survived was a 14 month old female found subsequently to have medium chain acyl coA dehydrogenase deficiency. The other, who died, was a nine year old male already on sodium valproate before admission, in whom the liver histology showed not only Reye-like fatty infiltration, but also numerous eosinophils. It was considered that his illness was a drug induced hypersensitivity reaction.

Comment

Two of the trends observed in 1994/95 continued in 1995/96, namely the persisting low annual total reports compared to those seen in the 1980's, and the declining proportion (12% compared with 21% in 1994/95) of cases in whom the diagnosis is later revised. The latter trend is expected as it probably reflects increasing awareness of Reye-like inherited metabolic disorders. In keeping with this, nearly three quarters of the patients were reported to have been investigated for those conditions, a similar proportion to last year.

Although details of the investigations are not sought on our questionnaire, (so the rigorousness with which an inherited metabolic disorder has been excluded as the cause of the child's illness is unknown), they were volunteered by the reporting clinician in three cases: a male aged 13 years and two females aged 12 months and 19 months. These patients are of interest because all were atypical for 'classic' Reye's syndrome (the boy because of presentation as sudden unexpected death and the girls because of their young age and some unusual biochemical and histological features), yet extensive investigation at centres of excellence for inherited metabolic disorders did not yield an alternative diagnosis.

These cases illustrate the difficulty in diagnosing 'classic' Reye's syndrome, because the case definition is so non-specific and because there may still be 'Reye-like' inherited metabolic disorders as yet undiscovered. Thus, unlike many other conditions surveyed by the BPSU, a case of 'Reye's syndrome' can rarely, if ever, be described as 'confirmed'. Cases are better designated '*compatible with the diagnosis*'.

Although the proportion of cases investigated for an inherited metabolic disorder was encouraging, there is nevertheless still cause for concern. It was unchanged from last year and four patients (27%) including three who, by virtue of their young age, should have aroused diagnostic suspicion, were not investigated. Furthermore, the preliminary findings of the follow up study of seven cases between 1993 and 1995 ascertained by death entry only (mentioned in last year's report) suggest that in only two were investigations for an inherited metabolic disorder undertaken. All presented as sudden unexpected death, six were aged two years or under and the diagnosis of Reye's syndrome was made solely on the basis of the macroscopic or microscopic appearance of the liver. There is clear need for continuing education of both clinicians and pathologists in the recognition and diagnosis of Reye-like inherited metabolic disorders, many of which may present as sudden death.

There were a number of epidemiological features of reported cases in 1995/96 which differed from previous years; the median age, case fatality rate and number and proportion reporting pre-admission aspirin exposure.

The median age, 3 years 2 months was the highest since surveillance began; in the 1980's it was around 14 months and this fell to 10 months in the early nineties, though it rose again to 14 months last year. Seven of the 15 1995/96 cases were over 5 years,



a more typical age for 'classic Reye's syndrome than younger children. Their mean Reye score was 14.1 (compared to 12.5 among the cases as a whole) and all four who had taken aspirin (mean score 15.8) were in this group. The three patients who had not taken aspirin (mean score 12.0) all manifested some unusual clinical and pathological features, including two who presented with sudden unexpected death.

There were seven deaths in 1995/96, the highest number since 1989/90. All seven had atypical clinical and/or pathological features.

The number (four) and proportion (30% of those with information on preadmission medication) of cases reporting pre-admission aspirin exposure was the highest since 1986/87, the year of the public and professional warnings about the use of aspirin in children under 12. It is also noteworthy that, of the total 14 aspirin associated cases since 1986/87, six have been over the age of 12 years. This compares with eight of 34 such cases between 1984/85 and 1985/86. These data suggest that there may be a need both for a renewed public and professional education campaign and for reconsideration of the justification for 12 years as the upper age limit on the warning. In the United States such labels are required to refer to "children and teenagers".

The investigators thank all BPSU respondents who have kindly reported cases, completed proformas and sent further information.

Table *Reye's Syndrome Surveillance 1981/82 – 1995/96*

Reporting period (August-July)	Total reports from the British Isles	Revised diagnosis (inherited metabolic disorder in brackets)		Cases of Reye's syndrome*	No. of deaths (of cases)
1981/82	47	7	(3)	40	26
1982/83	70	10	(6)	59	34
1983/84	93	12	(3)	81	36
1984/85	64	8	(2)	56	32
1985/86	53	13	(4)	40	22
1986/87	47	21	(11)	26	13
1987/88	44	12	(3)	32	19
1988/89	31 ¹	12	(6)	18	9
1989/90	24 ¹	8	(5)	15	7
1990/91	25	12	(7)	13	5
1991/92	24 ²	6	(5)	16	6
1992/93	21 ³	10	(6)	7	4
1993/94	20 ⁴	12	(6)	3	3
1994/95	17 ⁵	3	(2)	11	3
1995/96	18 ¹	2	(1)	15	7
TOTAL	598	148	(70)	432	226

1. Follow up not received for one case
2. Follow up not received for two cases
3. Follow up not received for four cases and one case did not meet the case definition

4. Follow up not received for five cases
5. Follow up not received for three cases

* Compatible with the diagnosis (see text)



**National Reyes Syndrome
Foundation UK**

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Reference

1 Hardie RM, Newton LH, Bruce JC, Glasgow JFT, Mowat AP, Stephenson JBP, Hall SM. The Changing Clinical Pattern of Reye's Syndrome 1982-1990. Arch.Dis.Child. 1996; 74; 400-405

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